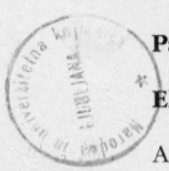
Zdravniški vestnik

JOURNAL OF SLOVENE MEDICAL SOCIETY, ZDRAV VESTN, YEAR 62, SEPTEMBER 1993, Page 1-109, SUPPL I

NEUROPHYSIOLOGICAL ASPECTS OF THE VISUAL SYSTEM

CONTENTS



Zdravniški vestnik

Naslov uredništva in uprave/
Address of the Editorial Office and Administration:
61000 Ljubljana, Komenskega 4, tel. (061) 317-868

Tekoči račun pri/Current Account with
LB 50101-678-48620

UDK 61+614.258(061.1)=863=20
CODEN:ZDVEEB ISSN 1318-0347

To revijo redno indeksirajo in/ali abstrahirajo:
Biological Abstracts, Biomedicina Slovenica,
Excerpta Medica, Medlars

Zdravniški vestnik izhaja praviloma vsak mesec.
Letna naročnina za člane SZD je vključena v članarino,
ki znaša 4.800,00 SIT, za študente 1.200,00 SIT, za ustanove 30.000,00 SIT,
za tujino 300 US $, posamezna številka stane 1.000,00 SIT.
To številko sta financirali:
Ministrstvo za znanost in tehnologijo
in Ministrstvo za zdravstvo
- Tisk Tiskarna »Jože Moškrič«, Ljubljana - Naklada 1000 izvodov

The Journal appears regulary every month.
Yearly subscription for members of the Slovene Medical Society
is included in the membership amounting to 4.800,00 SIT,
for students 1.200,00 SIT, for institutions 30.000,00 SIT, for foreign
countries 300 US$; single number costs 1.000,00 SIT.
The issue is subsidized by Ministry for Research and Technology
and Ministry for Health
- Printed by Tiskarna »Jože Moškrič«, Ljubljana - Printed in 1.000 copies

On the place of leading article

Dr. Janez Faganel Memorial Lectures

Neurology, still a young discipline, seems to enjoy one of its most active and productive periods. Dealing with the complexities of the brain and mind it also attracts broader interest. The dramatic advances in molecular genetics, imaging techniques, neurochemistry, neurobiology, neuropharmacology, and neuroimmunology, have improved our understanding of normal and abnormal neural structure and function, as well as the outcome of many neurological diseases.

Slovenia is a rather small country with limited resources and it would be unrealistic to expect significant activities in each of the many clinical and basic disciplines of neurosciences. With this in mind we were honoured when Vivian L. Smith Foundation for Restorative Medicine, headed by Prof. M. R. Dimitrijević, offered to support us in organising Memorial Dr. Janez Faganel Lectures. These are dedicated to our late colleague and friend, who was also one of the closest and most devoted collaborators of Prof. Dimitrijević. The main concept of these memorial lectures was to stimulate further development in the different clinical neurological disciplines. Each year's lecture is followed by a symposium on the related topics. Now that we are close to the 10th anniversary of this project, it may be appropriate to recapitulate what has been done so far and to consider plans for the coming years. The following is a list of the past Dr. Janez Faganel Memorial Lectures and the *Symposia,* including also the one of this year.

1985 P. D. Wall (London, Great Britain): Pain mechanisms. *Brain Injury Satellite Symposium - BISS '85*

1986 K.-G. Henriksson (Linköping, Sweden): Muscle pain in neuromuscular disorders and primary fibromyalgia. *Diagnostics in Neuromuscular Disorders*

1987 J. K. Light (Houston, Texas, U.S.A.): Neurogenic bladder in patients with spinal cord injury. *2nd Yugoslav Symposium on Neurourology and Urodynamics*

1988 E. Stålberg (Uppsala, Sweden): Electromyography - reflection of motor unit's physiology in health and disease. *Symposium on Quantitative Electromyography*

1989 A. M. Halliday (London, Great Britain): The widening role of evoked potentials in clinical practice. *International Symposium on Sensory Encephalography*

1990 A. M. Sherwood (Houston, Texas, U.S.A.): Brain motor control assessment. *Symposium on Assessment of the Upper Motor Neuron Functions*

1991 V. Deletis (New York, N.Y., U.S.A.): Intraoperative monitoring of evoked potentials - current status and perspective. *Symposium on Neurophysiological Monitoring*

1992 E. Rumpl (Klagenfurt, Austria): Neurophysiological evaluation of severe head injury patients. *International Symposium on Evaluation and Treatment of Severe Head Injury*

1993 H. Ikeda (London, Great Britain): Mammalian retinal neurotransmitters - as seen through the eyes of a neurophysiologist. *Symposium on Neurophysiological Evaluation of the Visual System.*

We are proud of having been able to host so many distinguished neuroscientists and we certainly appreciate their kind willingness to be our guests. We are also happy that Dr. Janez Faganel Memorial Lectures have become a tradition and that they have contributed their part to the development of neurological thinking in this country. The past lectures covered rather diverse topics and such is also our future orientation.

The current and future breakthroughs in the neurosciences can be expected to eventually enable the clinical neurologist to effectively treat the identified biochemical defects by gene transfer, to stimulate nerve regeneration, to more effectively protect the diseased nervous tissue and to compensate for its dysfunction. We look forward to future lectures when we may indeed hear more on the applications of the promising achievements in basic neurosciences to clinical neurology.

This is therefore an invitation to all who are willing to contribute their ideas and endeavours to the success of the future symposia.

Dr. Janez Faganel Memorial Lecture Scientific Committee
Janez Zidar, Chairman

Na mestu uvodnika

Spominska predavanja dr. Janez Faganel

Za nevrologijo, še vedno razmeroma mlado vedo, se zdi, da je v enem od najaktivnejših in najbolj produktivnih obdobij. Zaradi tega in pa zaradi predmeta svojega proučevanja, to je sestava in delovanje možganov in človekovega duha, je deležna tudi splošne pozornosti. Dramatični napredek genetike, tehnik slikanja možganov, nevrokemije, nevrobiologije, nevrofarmakologije in nevroimunologije je pripomogel k boljšemu razumevanju sestave in delovanja zdravega in bolnega živčevja ter izboljšal prognozo mnogih nevroloških bolezni.

Slovenija je majhna država z omejenimi sredstvi. Zato bi bilo nerealistično pričakovati pomembno aktivnost prav v vsaki od številnih kliničnih in bazičnih vej nevroloških znanosti. Zavedajoč se tega smo z veseljem sprejeli pobudo in pomoč za organizacijo spominskih predavanj dr. Janez Faganel, ki jo je v imenu Sklada za restavrativno nevrologijo Vivian L. Smith dal njegov predsednik prof. dr. Milan R. Dimitrijević. Predavanja so posvečena našemu umrlemu kolegu in prijatelju, ki je bil tudi eden najbližjih sodelavcev profesorja Dimitrijevića. Glavni namen spominskih predavanj je bil spodbuditi nadaljnji razvoj različnih kliničnih nevroloških disciplin. Vsakoletno predavanje je vedno spremljal simpozij s sorodno temo. Bližamo se že desetemu spominskemu predavanju, zato je morda čas, da pregledamo opravljeno delo in da se ozremo naprej. Dosedanja spominska predavanja in *simpoziji*, skupaj z letošnjim, so bila sledeča:

1985 P. D. Wall (London, Velika Britanija): Mehanizmi bolečine. *Satelitski simpozij o poškodbi glave - BISS '85*

1986 K.-G. Henriksson (Linköping, Švedska): Mišična bolečina pri živčno-mišičnih boleznih in pri primarni fibromialgiji. *Diagnostika živčno-mišičnih bolezni*

1987 J. K. Light (Houston, Teksas, ZDA): Nevrogeni mehur pri bolnikih s prečno poškodbo hrbtenjače. *2. jugoslovanski simpozij o nevrourologiji in urodinamiki*

1988 E. Stålberg (Uppsala, Švedska): Elektromiografija - pogled na fiziologijo zdrave in bolne motorične enote. *Simpozij o kvantitativni elektromiografiji*

1989 A. M. Halliday (London, Velika Britanija): Rastoči pomen evociranih potencialov v klinični praksi. *Mednarodni simpozij o senzorični encefalografiji*

1990 A. M. Sherwood (Houston, Teksas, ZDA): Ocenjevanje možganske funkcije kontrole gibanja. *Simpozij o ocenjevanju funkcij zgornjega motoričnega nevrona*

1991 V. Deletis (New York, N.Y., ZDA): Medoperativni nadzor evociranih potencialov - sedanjost in perspektive. *Simpozij o nevrofiziološkem nadzoru*

1992 E. Rumpl (Celovec, Avstrija): Nevrofiziološka ocena bolnikov s hudo poškodbo glave. *Mednarodni simpozij o ocenjevanju in zdravljenju hude poškodbe možganov.*

1993 H. Ikeda (London, Velika Britanija): Kemični prenašalci v mrežnici sesalcev - pogled nevrofiziologa. *Simpozij o nevrofiziološkem ocenjevanju vidnega sistema.*

Ponosni smo, da smo lahko gostili toliko pomembnih znanstvenikov nevrologov, in cenimo njihovo pripravljenost na sodelovanje. Z zadovoljsvom ugotavljamo, da so Spominska predavanja dr. Janez Faganel postala tradicionalna in da so po svoje prispevala k oblikovanju slovenske nevrološke misli. Želimo pa si še bolj živega sodelovanja vseh naših nevrološko usmerjenih strokovnjakov. Teme preteklih predavanj so bile raznolike in takšna naj bi bila tudi prihodnja usmeritev Odbora za pripravo predavanj.

Naša in naših bolnikov pričakovanja in želje vsekakor so, da bi zdajšnja in prihodnja znanstvena odkritja omogočila učinkovito zdravljenje biokemično pojasnjenih okvar s pomočjo presajanja genov, pospeševanje regeneracije živčevja, učinkovito zaščito obolelega živčevja pred dodatnimi okvarami in kompenzacijo že okrnjenih funkcij. Z zanimanjem pričakujemo prihodnja predavanja, v katerih bomo morda lahko izvedeli več o klinični uporabnosti sedanjih obetajočih odkritij.

Zaključujemo s povabilom vsem, ki so voljni s svojimi idejami in z delom pripomoči k uspehu prihodnjih predavanj in simpozijev.

Znanstveni odbor Spominskega predavanja dr. Janez Faganel
Janez Zidar, predsednik

NEUROPHYSIOLOGICAL ASPECTS OF THE VISUAL SYSTEM

A: THE ROLE OF DOPAMINE IN THE VISUAL PATHWAY
B: ELECTROPHYSIOLOGICAL EVALUATION OF THE VISUAL SYSTEM

FOREWORD

The 9th Janez Faganel memorial lecture and accompanying symposium in 1993 are dedicated to the visual system with special emphasis on the role of dopamine and other neurotransmitters in the visual pathway, and on electrophysiological evaluation of the visual system.

Visual system undoubtedly holds the central position in human sensory neurophysiology. This judgment arises not only from the fact that man is primarily a visual being, but also from the vast research on large areas of central nervous system that are dedicated to processing and interpretation of visual signals. For this reason, study and evaluation of visual system function combines rather large number of different scientific disciplines and specialties within the field of neuroophthalmology. It was, therefore, our prime intention, while conceptualising this symposium, to put emphasise on this multidisciplinary approach to the visual system. The symposium with its accompanying Proceedings was therefore an attempt to combine/unite two major approaches to the research of visual system. In the first part of the symposium, basic findings were reviewed in the field of neuropharmacology of the chemical neurotransmission of the signals within visual system that ultimately reflect themselves in electrophysiological phenomena. These phenomena can be monitored in health and disease and provide the basis for clinical evaluation of the visual pathway, to which the second part of the symposium has been devoted. It was a great honour for us that the 9th Faganel memorial lecture was accepted and given by Professor Hisako Ikeda from London, a researcher who has, throughout her outstanding career, in many ways succeeded to unite both basic and clinical aspects of vision research. It has been her lifetime belief that thorough understanding of basic aspects of normal function of the visual system will eventually bring answers to clinical questions. The Memorial Lecture is an excellent review of the function of the neurotransmitters within the retina, the topic to which she has herself contributed numerous original findings. Her lecture is followed by contributions which outline the rapidly growing awareness of the role of dopamine in the visual system, especially of its role in receptive field regulation, and its antagonistic interaction with retinal melatonin in renewal and degenerative processes of the retina.

Professor Ikeda also contributed to the second part of the symposium by presenting electrophysiological insight into variety of diseases, which arises from her data on several thousands of patients she saw during her long career. Other valuable contributions outline general anatomical, physiological and technical aspects of electrophysiological testing and its rational application in various clinical situations. There is also a number of clinical reviews including interesting studies in children, and papers dealing with topics such as optic neuritis, optic nerve coloboma and drusen of the optic nerve.

These Proceedings were not intended to be a complete review of the subject, but to provide researchers and clinicians with the up-to-date information on the use of electrophysiological methods and to present some new findings that still await clinical confirmation.

We are grateful to the authors who contributed to this volume and to Mr. Tone Žakelj, Mr. Miloš Kogej and Mr. Nacek Zidar for their help in preparation of the Proceedings. We do hope that the readers and our distinguished guests will find this volume interesting and helpful in their practice and research.

Martin Štrucl,
Jelka Brecelj,
Marko Hawlina

NEVROFIZIOLOŠKI VIDIKI VIDNEGA SISTEMA

A: VLOGA DOPAMINA V VIDNI POTI
B: ELEKTROFIZIOLOŠKO OCENJEVANJE VIDNEGA SISTEMA

PREDGOVOR

Deveto spominsko predavanje dr. Janez Faganel in simpozij sta posvečena vidnemu sistemu s posebnim poudarkom na vlogi dopamina in drugih nevrotransmiterjev v vidni progi ter na elektrofiziološkem ocenjevanju vidnega sistema.

Vidni sistem ima brez dvoma osrednje mesto v senzorični nevrofiziologiji pri človeku. Ta ugotovitev ne izhaja samo iz dejstva, da je človek predvsem vizualno bitje, temveč tudi iz podatkov o obsežnih predelih osrednjega živčevja, ki je namenjeno obdelavi vidnih podatkov. Zato preučevanje in ocenjevanje vidnega sistema združuje kar nekaj specialnosti in disciplin v okviru nevrooftalmologije. Multidisciplinarni pogled na vidni sistem smo hoteli poudariti tudi pri organizaciji simpozija in snovanju pričujočega zbornika, ki sta poskus sinteze dveh različnih pristopov v raziskovanju in ocenjevanju vidnega sistema. Prvi del simpozija povzema nevrofarmakološka spoznanja o mehanizmih kemičnega prenosa vzburjenja pri zdravem in okvarjenem sistemu, kakor se odražajo v elektrofizioloških pojavih. Le-ti se lahko posnamejo pri zdravem ali bolnem organizmu in so tako osnova za klinično ocenjevanje vidne poti, kar je vsebina drugega dela simpozija.

V posebno čast nam je, da je spominsko predavanje sprejela prof. Hisako Ikeda iz Londona, raziskovalka vidnega sistema, katere obsežno delo je pravzaprav posvečeno sintezi osnovnih in kliničnih spoznanj. Vse njeno obsežno življenjsko raziskovalno delo je prežeto s prepričanjem, da bo razumevanje osnovnih vidikov delovanja vidnega sistema prej ali slej omogočilo odgovore na klinična vprašanja. Spominsko predavanje je odličen pregled delovanja nevrotransmiterjev v mrežnici, kjer je tudi sama prispevala veliko relevantnih spoznanj. Njenemu predavanju sledijo prispevki, ki poudarjajo vlogo dopamina v vidnem sistemu predvsem pri nadzoru receptivnih polj in njegovo zaviralno vlogo v sočinkovanju z melatoninom na obnovitvene in degenerativne pojave v mrežnici.

S predstavitvijo svojih izkušenj pri elektrofiziološkem testiranju vidnega sistema pri več tisoč bolnikih je prof. Ikeda pomembno prispevala tudi k drugemu delu simpozija. Ostali prispevki obravnavajo anatomske, fiziološke in tehnične vidike elektrofiziološkega testiranja in njegovo smotrno uporabo pri različnih kliničnih stanjih. Poleg tega je v tem tematskem sklopu tudi nekaj kliničnih pregledov, ki vključujejo elektrofiziološke preiskave pri otrocih ter obravnavajo aktualne teme, kot sta kolobom in druze optičnega živca.

Zbornik seveda ne more biti splošen pregled področja, temveč podaja raziskovalcem in klinikom nekaj aktualnih sporočil o uporabi elektrofizioloških metod, hkrati pa predstavlja nekaj novih spoznanj, ki še čakajo klinične potrditve.

Želimo se zahvaliti predvsem avtorjem tega zbornika, uredništvu Zdravniškega vestnika, ki je ljubeznivo sprejelo ponudbo za objavo, ter ne nazadnje tudi Tonetu Žaklju, Milošu Kogeju in Nacku Zidarju za pomoč pri pripravi zbornika. Upamo, da bodo naši ugledni gostje in predvsem bodoči bralci našli v prispevkih koristna sporočila in pobude za nadaljnje raziskave in klinično uporabo elektrofizioloških metod za ocenjevanje vida.

Martin Štrucl,
Jelka Brecelj,
Marko Hawlina

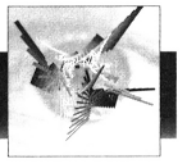
The 9th Dr. Janez Faganel Memorial Lecture

9. spominsko predavanje dr. Janez Faganel

KRKA V OFTALMOLOGIJI

BLEPHAMIDE® N Liquifilm

(sulfacetamid in prednizolon) kapljice za oči



kombinacija sulfacetamida in prednizolona v idealni podlagi — Liquifilmu (umetne solze), kar zagotavlja dobro prodiranje zdravila, učinkovitost in dobro prenašanje

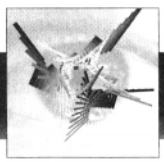
EFFLUMIDEX® Liquifilm

(fluorometolon) kapljice za oči 0,1 %

sintetični kortikosteroid z močnim protivnetnim delovanjem in šibkim vplivom na intraokularni tlak

d EPIFRIN®

(dipivefrin) kapljice za oči 0,1 %



za začetno ali dodatno zdravljenje kroničnega glavkoma z odprtim zakotjem in očesne hipertenzije — učinkovito znižuje intraokularni tlak brez mioze in spazma akomodacije

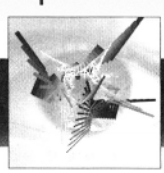
VISTAGAN® Liquifilm

(levobunolol) kapljice za oči 0,5 %

blokator beta adrenergičnih receptorjev za zdravljenje kroničnega glavkoma z odprtim zakotjem in očesne hipertenzije

OCUFLUR® Liquifilm

(flurbiprofen) kapljice za oči



nesteroidno protivnetno zdravilo za zdravljenje vnetij sprednjega očesnega segmenta po očesnih operacijah in za preprečevanje intraoperativne mioze

Podrobnejše informacije in literaturo dobite pri proizvajalcu.

KRKA

tovarna zdravil, p. o., Novo mesto, Slovenija
s sodelovanjem ALLERGAN Westport
Allergan (Ireland) Ltd., Castlebar Road, Westport, Co. Mayo, Irska

MAMMALIAN RETINAL NEUROTRANSMITTERS

AS SEEN THROUGH THE EYES OF A NEUROPHYSIOLOGIST

NEVROTANSMITERJI V MREŽNICI SESALCEV

PRIKAZ Z NEVROFIZIOLOŠKEGA STALIŠČA

Hisako Ikeda

Vision Research Unit of Sherrington School, UMDS, The Rayne Institute, St. Thomas' Hospital, London SE1 7EH, Great Britain

Key words: *benzodiazepine; dopamine; γ-aminobutyric acid; glutamate; glycine*

Abstract - *The lecture considers the functional role of endogenous neurotransmitters in the mammalian retina, elucidated by the use of selective transmitter receptor antagonists in electrophysiological experiments. Firstly, the glutamatergic pathway which relays the visually-evoked excitation of the photoreceptors to the bipolar and the ganglion cells is discussed. Consideration is also given to an important role of NMDA receptors on the ganglion cells which are silent under normal physiological conditions, but become active in the presence of excessive glutamate, e.g. under ischaemic conditions. Secondly, the functional significance of GABAergic and glycinergic pathways which mediate visual inhibition of ON- and OFF-ganglion cells respectively, is considered. Reference is also made to the clinical relevance of benzodiazepine receptors linked with $GABA_A$ receptors. Thirdly, the dopaminergic pathways acting at different levels in the retina are reviewed. Finally, emphasis is placed on the interdependence and interactions between all these neurotransmitters, and on how normal retinal function depends upon a delicate balance, which is maintained by these neurochemical controls.*

Introduction

I became interested in retinal neurotransmitters through observation of patients coming to our electrodiagnostic clinic. I noticed that many systemic diseases or diseases of other parts of the body, as well as a variety of drugs used for treating them, affect retinal function. As a first step in understanding the problem, we began to ask the question what are the chemical substances which are essential for retinal neurones to function normally? Since we are neurophysiologists, our question was directed towards neurotransmitters. Thus, which neurotransmitters initiate visual excitation and inhibition of different classes of retinal cells? The list of neuroactive substances localized in the retinal cells indeed consists of all those substances which are found in different parts of the body as well as in other parts of the nervous system. It includes acetylcholine, all known excitatory and inhibitory amino acids, as well as different amines and a long list of peptides. It is interesting that whenever new peptides are found in other parts of the body, they are also found in the retina. However, in order that a substance may be considered as a neurotransmitter, it must at least satisfy the following seven criteria:

1. Localization in cells
2. Release following visual stimulation
3. Evidence for deactivation following stimulation
4. The presence of synthetic and degradative enzymes
5. Specific receptor binding
6. Agonist action
7. Selective receptor antagonist action.

The last two concern the functional role of the transmitter, therefore evidence must come from neurophysiological experiments. This is indeed the primary subject of this 9th Janez Faganel lecture. The title of the lecture which I am greatly honoured to give today, in memory of the eminent Slovenian neurophysiologist, is thus "Mammalian retinal neurotransmitters - as seen through the eyes of a neurophysiologist".

Methods of elucidation of neurotransmitter action in the retina

To elucidate the action of a neurotransmitter in the retina, two types of experiments must be performed (listed as 6th and 7th of the criteria for neurotransmitters above). The first is to study the effect of applied transmitter agonists, and the second, to study the transmitter receptor antagonists on electrical responses of the retinal neurone concerned. Of the two, the antagonist study is more important than the agonist study. This is because, whilst applied agonists activate their receptors whether the transmitter candidate is released on them or not, selective receptor antagonists block the action of naturally released transmitter on the particular receptor. In this lecture, I have put emphasis upon the studies of antagonists, since these are essential for understanding the functional role of a particular endogenous transmitter in the retina.

Abbreviations: *APB, amino-4-phosphonobutyrate; CNQX, 6-cyano-2, 3 dihydroxy-7-nitroquinoxaline; CPP, (+) -2, 3-carboxypiperazin-4-yl propyl-l-phosphonate; DNQX, 6-7-dinitroquinoxaline-2, 3-dione; LGN, lateral geniculate nucleus; NBQX, 2, 3 dihydro-6-nitro-7-sulfanoyl-benzo (F) quinoxaline; NMDA, N-methyl-D-aspartate; NPC 12626, 2-amino-4, 5-(1, 2-cyclohexyl)-7-phosphonoheptanate.*

How can actions of transmitter agonists and antagonists on specific retinal neurones be studied? The retina, which is part of the CNS, is a thin tissue of less than 0.4 mm thick but it is packed with many different classes of cells. It consists of three hierarchically organized cell layers, the photoreceptors (rods and cones), the bipolar cells and the ganglion cells. There are two synaptic layers: the outerplexiform layer between the photoreceptor and the bipolar cell layers, and the innerplexiform layer between the bipolar and the ganglion cell layers. In addition, there are two principal types of retinal interneurones: the horizontal cells at the outerplexiform layer and the amacrine cells at the innerplexiform layer. There is a third type of retinal interneurone called the interplexiform cells, which have the cell bodies in the innerplexiform layer, and send their processes to the outerplexiform layer. The electrical responses of each of the different classes of the retinal cells are complex.

When drugs are applied to the whole retina by intravenous or intravitreal injection, we cannot determine which cells the drugs are acting upon, or via which synapse they change the electrical response of retinal cells under recording. To study the transmitter actions at the horizontal cells, we have, therefore, used intracellular recording from the horizontal cells in isolated retinae where drugs are introduced into the fluid perfusing the retina (1). This method still cannot distinguish between direct or indirect transmitter actions mediated via other synapses, such as horizontal/horizontal or interplexiform/horizontal synapse, but permits the study of photoreceptor/horizontal synaptic transmission with some degree of certainty, since they receive major inputs from the photoreceptors. However, a similar perfusing method cannot be used to study drug actions on retinal ganglion cells or amacrine cells, since many synapses are involved in mediating excitation or inhibition of these cells.

Transmitter actions at the retinal ganglion cells were thus studied with microiontophoretic techniques using multi-barrelled electrodes in optically intact eyes of anaesthetized cats as previously described (2). A multi-barrelled electrode consists of several pipettes twisted and pulled together. One records somatic spikes of ganglion cells, one balances the current at the tip, and others carry agonists and antagonists of the transmitter for highly localized application. Following isolation and classification of the cell under recording, each of the drugs is iontophoretically applied onto the cell to analyse its effects on visually-evoked response as well as spontaneous firing of the cell.

Excitatory transmitter, glutamate and its receptors

Although acetylcholine qualifies as an excitatory transmitter released from cholinergic amacrine cells in the mammalian retina (3), and its action on the ganglion cells via nicotinic receptors has been demonstrated (4), it is now clear that glutamate is the main excitatory neurotransmitter in the retina. All the hierarchically organized retinal cells, i.e. photoreceptors, bipolar and ganglion cells, which constitute about 80 % of retinal neurones, contain glutamate (5, 6). Available evidence is that the photoreceptors, when depolarized, release glutamate to the bipolar cells and the horizontal cells, and similarly, the bipolar cells release glutamate to the ganglion and amacrine cells.

Glutamate action is mediated by different receptors, the number of which seems to be increasing (7). However, if one considers only those receptors whose endogenous actions are testable, using selective antagonists, they may be classified into two main types: the NMDA and the non-NMDA receptors, which includes classical kainate and quisqualate receptors (8). Competitive and non-competitive antagonists for NMDA and non-NMDA receptors are listed in Table 1 (see the list of abbreviations for full names). The competitive antagonists block the receptor binding sites, whilst non-competitive antagonists block ion-channels which are activated following synaptic transmission. CPP and NPC are competitive antagonists, while Ketamine and MK801 are non-competitive antagonists for NMDA receptors. Selective antagonists for non-NMDA receptors, CNQX, DNQX and NBQX have only become available recently (9, 10).

Glutamatergic synaptic transmission from the photoreceptors to the horizontal and the bipolar cells

The photoreceptors are depolarized and release glutamate in the dark to the horizontal and bipolar cells. They are hyperpolarized by light, which reduces the release of glutamate (11). The light-evoked reduction of glutamate release from the photoreceptor causes transient hyperpolarization of the horizontal cells and the so-called OFF-bipolar cells. The term "OFF" is applied since these cells respond (depolarize) when a light stimulus is switched "off".

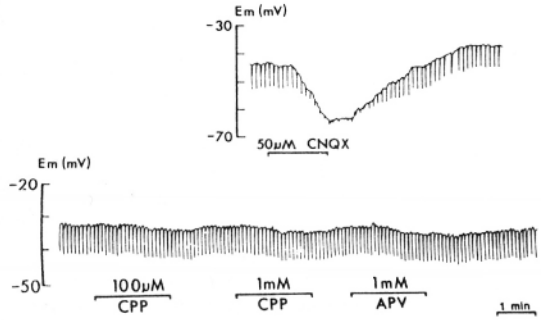


Fig. 1. *Effects of NMDA receptor antagonists (CPP, and APB) and a non-NMDA receptor antagonist (CNQX) on the dark resting membrane potential and light-evoked hyperpolarizations (each of the down beats on the membrane potential) of a rat horizontal cell. Note that CNQX at 50 μM hyperpolarizes the horizontal cell and abolishes the light-evoked responses, whilst higher concentrations of CPP and APB caused no effects, indicating that glutamatergic transmission from the photoreceptors to the horizontal cell is mediated by non-NMDA receptors.*

Sl. 1. *Učinki receptorskih antagonistov NMDA (CPP, in APB) in ne-NMDA receptorskih antagonistov (CNQX) na mirujoči membranski potencial v temi in svetlobno izzvanih hiperpolarizacij (vsak odklon navzdol od membranskega potenciala) pri horizontalnih celicah podgane. Razvidno je, da 50 μM CNQX hiperpolarizira horizontalne celice in zavre odziv na svetlobno draženje. Višje koncentracije CPP in APB niso imele učinka, kar potrjuje, da je glutamatergični prenos od fotoreceptorjev do horizontalnih celic posredovan prek ne-NMDA receptorjev.*

Figure 1 illustrates the response of a rod-driven rat horizontal cell to different glutamate receptor antagonists. Intracellular recordings were made in an isolated retina and drugs perfused in the media whose temperature was maintained at 35.5 °C. In dark, the resting potential of the horizontal cells is about -30 to -40 mV, i.e. they are like the photoreceptors, relatively depolarized. Each of the down beats that appears in the records is a light-evoked hyperpolarization of the cell. A selective non-NMDA antagonist, DNQX at 50 μM, rapidly hyperpolarized the cell membrane and abolished the light response, whilst the NMDA antagonists, CPP and APB at much higher concentrations failed to affect the response of the horizontal cell. This observation suggests that the photoreceptors release glutamate as transmitter to the horizontal cells, and that their light-evoked responses are mediated by non-

NMDA receptors. Similar electrophysiological evidence for the OFF-bipolar cells has only been demonstrated in non-mammalian retinae (12).

How does then the glutamatergic transmission from dark depolarizing photoreceptors to the light-depolarizing ON-bipolar cell come about? At the receptor/ON-bipolar synapse, *glutamate closes ion-channels* (sign inverting), instead of opening them, as at the conventional (sign conserving) synapse, to the horizontal or to the OFF-bipolar cells (see Fig. 2). APB is an analogue (agonist) of glutamate, thus mimicking glutamate action. APB, at a high concentration, has been shown to block the light-evoked depolarization of the ON-bipolar cells in non-mammalian retinae (13), as well as in recently isolated rat bipolar cells (14). APB indeed abolishes the ERG b-wave which is generated by the ON-bipolar cells (15). At the APB-sensitive synapse of the ON-bipolar cells, the light-evoked *reduction of glutamate* from photoreceptors *opens channels*, as shown in Fig. 2. The effects of glutamate or APB on the ON-bipolar cells involve unique biochemical cascades, which accounts for their actions (13).

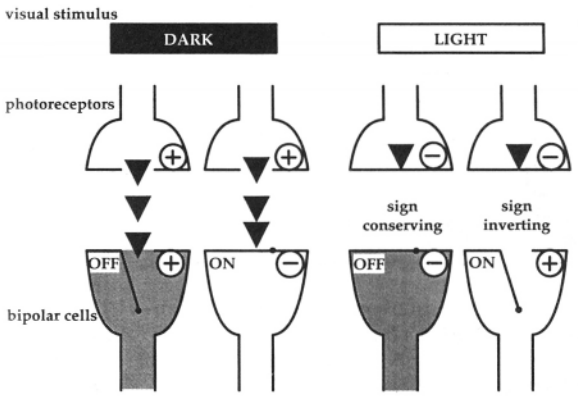


Fig. 2. *Schematic diagrams illustrating the conventional glutamatergic (sign conserving) synapse between the photoreceptors and the OFF-bipolar cells and the unique "sign- inverting" synapse between the photoreceptors and the ON-bipolar cells. The + signs indicate depolarization of cells and - signs, hyperpolarization. The photoreceptors release glutamate in dark, whereas light stops the release. Glutamate , opens ion-channels (shown by a gate sign) of the OFF-bipolar cells, but closes ion-channels of the ON-bipolar cells. The depolarization of the ON-bipolar cells is blocked by APB (see text).*

Sl. 2. *Shematski diagrami ilustrirajo konvencionalno glutamatergično (sign conserving) sinapso med fotoreceptorji in OFF-bipolarnimi celicami in izredno "sign inverting" sinapso med fotoreceptorji in ON-bipolarnimi celicami. Znaki + označujejo depolarizacijo celic, znaki - pa njihovo hiperpolarizacijo. Fotoreceptorji sproščajo glutamat v temi, svetloba sproščanje zavre. Glutamat (označen kot črn trikotnik) odpira ionske kanale (označene z znakom vratic) OFF-bipolarnih celic, istočasno pa zapira ionske kanale ON-bipolarnih celic. Depolarizacijo ON-bipolarnih celic blokira APB (glej tekst).*

Glutamatergic transmitters from the bipolar cells to the ganglion cells

Figure 3 illustrates actions of iontophoretically applied CPP, an NMDA receptor antagonist, and CNQX and DNQX, non-NMDA receptor antagonists, on ON- and OFF-type retinal ganglion cells. These drugs are applied to antagonize endogenously released glutamate on these cells. The ON-cell is responding to a white spot, whilst the OFF-cell to a black spot, presented at the receptive field centre. Each upward deflection of the pen is the spike count during the spot "on", whilst the downward deflection, during the spot "off". When the spot is "off", the firing of cells in all cases is inhibited to virtually zero. CPP (50 mM in a pipette) at an ejection current of 100 nA failed to antagonize the visually evoked responses of both the ON- and OFF-ganglion cells. The selective non-NMDA antagonists (5 mM in a pipette) at 50 nA, on the other hand, blocked the visual responses of both ganglion cells. The cell responses slowly returned to their pre-ejection level.

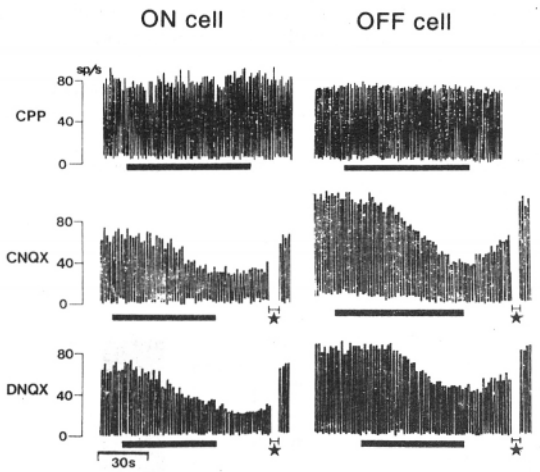


Fig. 3. *Effects of iontophoretically applied NMDA receptor antagonist (CPP) and non-NMDA receptor antagonists (CNQX and DNQX) on visually-driven response of the cat retinal ganglion cells. The cells are firing to an optimal spot (bright spot for the ON- and black spot for the OFF-cell) presented at 1 Hz in the centre of the receptive field. The period of iontophoretic application of each drug is indicated by the bar under each trace. The recovery phase of the histograms showing the effects of CNQX and DNQX is broken by *, which corresponds to a period of 30-60 s. Note that CPP (100 nA) caused no effect, whilst CNQX and DNQX (20-50 nA) suppressed the visual responses of both ON- and OFF-cells, indicating that glutamatergic transmission from the bipolar cells to the ganglion cells is mediated by non-NMDA receptors.*

Sl. 3. *Učinki iontoforetične aplikacije receptorskega antagonista NMDA (CPP) in ne-NMDA receptorskega antagonista (CNQX in DNQX) na odzive vizualnega draženja ganglijskih celic mačke. Celice se vzdražijo po draženju z optimalnim dražljajem (svetla pega za ON-celice in temna pega za OFF-celice), ki ga prikazujemo s frekvenco 1 Hz v središču receptivnega polja. Čas iontoforetične aplikacije vsakega od farmakov je označen s črto pod posnetkom. Faza povrnitve na izhodiščne vrednosti je na histogramih, ki kažejo učinke CNQX in DNQX, prekinjena z znakom *, ki ustreza času 30-60 sekund. Razvidno je, da CPP (100 nA) ni imel nikakršnega učinka, medtem ko sta CNQX in DNQX (20-50 nA) zavrla vidne odzive pri obeh, ON- in OFF-celicah, kar pomeni, da je glutaminergični prenos z bipolarnih na ganglijske celice posredovan prek ne-NMDA receptorjev.*

These experiments on the ganglion cells are consistent with both ON- and OFF-bipolar cells which upon depolarization release glutamate to the ON- and OFF-ganglion cells respectively. Furthermore, glutamatergic synaptic transmission from the bipolar cells to the ganglion cells is mediated by non-NMDA receptors. The results of the study have been described in detail elsewhere (16).

Presence of NMDA receptors on the ganglion cells and their functional role in retinal ischaemia

In the previous section, we have shown that NMDA receptors are not involved in the transmission of the visually-evoked responses from the photoreceptors, either to the horizontal or to the bipolar cells, or from the bipolar cells to the ganglion cells. However, our studies on glutamate agonists suggested that NMDA receptors are present on the ganglion cells (16). Furthermore, some NMDA receptors are found to be activated in immature cells recorded from kittens of 7-9 weeks of age (17) and in the cells of adult cats which had abnormally high spontaneous firing (18).

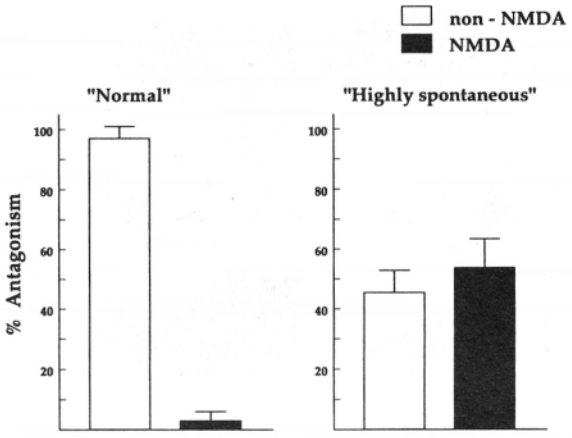


Fig. 4. *Comparison of potency of selective non-NMDA antagonists (CNQX and NBQX) and selective NMDA antagonists (CPP and MK801) in blocking the spontaneous firing of normal cells and cells with abnormally high spontaneous firing. The mean and standard error of the mean potency were determined from % reduction of the firing caused by each drug on each cell. The effects of CPP and MK801 were combined (n = 19) to calculate the NMDA antagonists effect, and those of CNQX and NBQX were combined (n = 12) to determine non-NMDA antagonists effect. Note that NMDA receptor activity is apparent in highly spontaneous cells, but not in normal cells.*

Sl. 4. *Primerjava med učinkovitostjo selektivnih antagonistov non-NMDA (CNQX in NBQX) ter selektivnih antagonistov NMDA (CPP in MK801) na spontano vzdražnost normalnih celic ter celic z abnormno visoko spontano vzdražnostjo. Srednja vrednost in standardna napaka srednje učinkovitosti sta bili določeni na podlagi odstotka znižanja spontane aktivnosti, ki jo je povzročil posamezni antagonist na vsakem od obeh tipov celic. Učinki CPP in MK801 so združeni (n = 19) v izračunu učinka antagonistov NMDA, enako tudi učinki CNQX in NBQX (n = 12) v prikazu učinka antagonistov ne-NMDA. Razvidno je, da je aktivnost receptorjev NMDA očitna pri celicah z visoko spontano vzdražnostjo, ne pa pri normalno vzdražnih celicah.*

Figure 4 compares the potency of selective non-NMDA (CNQX, NBQX) and NMDA (CPP & MK801) antagonists in blocking the spontaneous firing of normal cells and cells with abnormally high spontaneous activity. The selective NMDA antagonists produced little effect on the normal cell, suggesting that normally the NMDA-channels are not active. In contrast, the NMDA antagonists powerfully block the firing of cells with abnormally high spontaneous firing, indicating endogenous glutamate action on the NMDA receptors.

Our next question was, whether the NMDA receptor channels were primarily closed under normal physiological conditions, but open in response to excess glutamate input, as in early cerebral ischaemia (19)? To answer this question, we studied early electrophysiological changes following acute retinal ischaemia by recording single or multi-unit retinal ganglion cells (20). Retinal ischaemia was produced photochemically by platelet aggregation in retinal vessels which had been irradiated with monochromatic green light following an intravenous injection of Rose Bengal dye (21). We found no physiologically active ganglion cells within the irradiated retinal area. However, the ganglion cells in the area 5°-20° away from the lesion, had abnormally high spontaneous firing which was hardly altered by visual stimulus. Indeed, NMDA receptor antagonists had a powerful blocking effect on such abnormally depolarized cells near the lesion. This is illustrated in Figure 5.

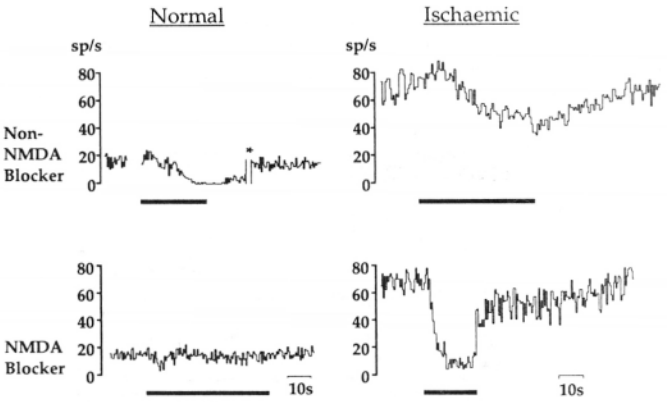


Fig. 5. *Effects of iontophoretically applied non-NMDA antagonist (CNQX) and NMDA channel blocker (MK801) on the moderate spontaneous firing of a normal cell, and on the abnormally raised firing of a cell near an ischaemic lesion. Note that MK801 has little effect on the normal cell but a profound effect on the highly spontaneously active "ischaemic" cell, which suggests that NMDA receptors which are normally silent are activated under ischaemic conditions. The MK801 current used for the normal cell was 80 nA, and that for the ischaemic cell 10 nA. The CNQX current used for both the normal and ischaemic cells was 50 nA and was effective on both cells.*

Sl. 5. *Učinki iontoforetične aplikacije antagonista ne-NMDA (CNQX) in blokatorja kanalov NMDA (MK801) na zmerno spontano aktivnost normalne celice in celice z abnormno zvišano spontano aktivnostjo zaradi ishemične lezije. Razvidno je, da MK801 nima posebnega učinka na normalne celice, medtem ko je očiten njegov močan učinek na zvišano spontano aktivnost "ishemične" celice. Ti rezultati kažejo, da se receptorji NMDA, ki so normalno tihi, aktivirajo ob ishemičnih pogojih.*

Figure 5 shows that an NMDA channel blocker, MK801, had no effect on the normal cell, but reduced the abnormally high firing rate of the ischaemic cell to virtually zero. A non-NMDA receptor antagonist, CNQX 50 nA, on the other hand, blocked the firing of both the normal and the ischaemic cells. But, of course, the non-NMDA receptor antagonist blocks visually-driven response of all ganglion cells (not shown in Fig. 5, but see Fig. 3). Figure 5 thus presents evidence that normally silent NMDA receptors are activated by naturally released glutamate under ischaemic conditions. Our histological studies revealed that the retinal areas where depolarized cells were localized, showed only minor vacuolation of ganglion cell layers (20).

To create a more clinically relevant condition, we produced thrombosis of several retinal vessels by the photochemical method (21), and recorded the effects of glutamate blockers on mass optic nerve responses using an electrode placed at the optic disc.

Figure 6 shows an example of the result. The top two histograms in Figure 6 are visually-evoked optic nerve responses taken before making the lesion. These show that the intravenously injected ketamine (5 mg/kg) has little effect. Ketamine is a barbiturate, frequently used for inducing anaesthesia, but it is a well-known NMDA channel blocker. As the lower left histogram in Figure 6 shows, the lesion resulted in an increase in the spontaneous firing and masking of the VEP. Ketamine which previously had little effect now dramatically suppressed the spontaneous firing, and unmasked the transient component of the visual firing. This suggests that the NMDA blocker, ketamine, had some therapeutic action on early retinal ischaemia. Our neurophysiological results are consistent with previous histological studies of cerebral or retinal ischaemia in animals, showing that pathological damage caused by ischaemia is reduced, if the retina or the brain had been pretreated with MK801, another NMDA channel blocker (19).

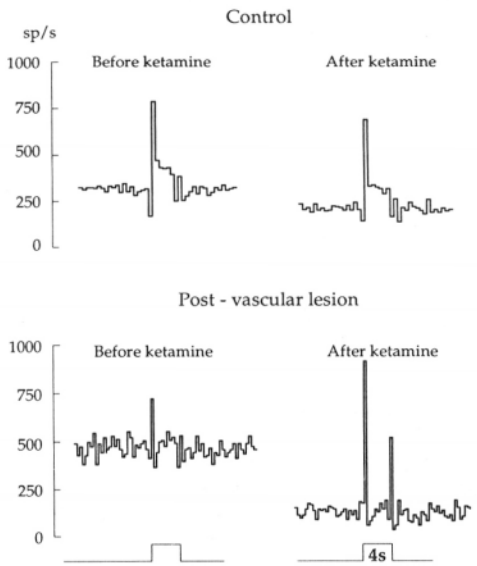


Fig. 6. *Comparison of the effect of intravenously injected NMDA channel blocker, ketamine (5 mg/kg), on mass optic nerve firing to a black spot (25 cd/m², size 10°) present on a screen of 100 cd/m² determined before, and 5 hours after, a photochemically-induced retinal vascular lesion. Timing of the visual stimulation is shown at the bottom. Note that 1) ketamine had no effect on the optic nerve firing before the production of the vascular lesion, 2) the vascular lesion resulted in a significant increase of spontaneous firing, hence masking the visually-driven response and 3) ketamine at the same dose has profound action on the lesion-induced change in the firing: it suppressed the abnormally high spontaneous firing and unmasked the visually-evoked transient firing. The experiment suggests NMDA receptor activation in the ischaemic retina with the possible therapeutic value of NMDA antagonists in combating ischaemic insults.*

Sl. 6. *Primerjava učinkov intravensko injiciranega blokerja kanalov NMDA, ketamina (5 mg/kg) na skupno vzdraženje, registrirano z vidnega živca, po draženju s temno pego (25 cd/m², velikost 10°) na zaslonu s svetilnostjo 100 cd/m², izmerjeno pred fotokemično povzročeno ishemično lezijo in pet ur po njej. Potek svetlobne stimulacije je prikazan na dnu slike. Razvidno je, da 1) ketamin ni učinkoval na vzdražnost vidnega živca pred okvaro, 2) da je lezija povzročila močan porast spontane aktivnosti, ki je tako prekrivala odzive na vidno draženje, in 3) ketamin je v enaki dozi kot pred lezijo močno znižal porast spontane aktivnosti po ishemični leziji in demaskiral vidno vzdraženje. Ti rezultati kažejo, da pride pri ishemični okvari mrežnice do aktivacije receptorjev NMDA, in nakazujejo možnost terapevtske uporabe antagonistov NMDA pri obtočnih motnjah v mrežnici.*

The mechanism through which ischaemic challenge leads to excess glutamate in the retina is not clear. However, a retinal vascular insult is expected to result in a vicious circle of 1) energy depletion of retinal cells causing osmotic damage and glutamate leakage, 2) depolarization of cells causing an increase in glutamate release, and 3) loss of glutamate uptake into Müller cells, causing accumulation of extracellular glutamate. Events following ischaemia-induced glutamate accumulation are shown in Figure 7. A presynaptic cell releases glutamate onto NMDA receptors, as well as onto non-NMDA receptors of a post-synaptic cell. This will lead to increases in intracellular Ca^{2+} and free radicals, as well as to a decrease in intracellular ATP in the post-synaptic cells. As the Na^+ and K^+ pump depend on ATP, the loss of ATP results in a loss of K^+ and an increase of Na^+ in the cell, causing further depolarization, hence further release of glutamate and accumulation of extracellular K^+. At the same time, reduction in the glutamate uptake system leads to accumulation of glutamate in the extracellular space.

There are several ways one can combat this vicious circle of the glutamate toxicity. The possible sites at which we can make therapeutic interventions are also indicated in Figure 7. For example,

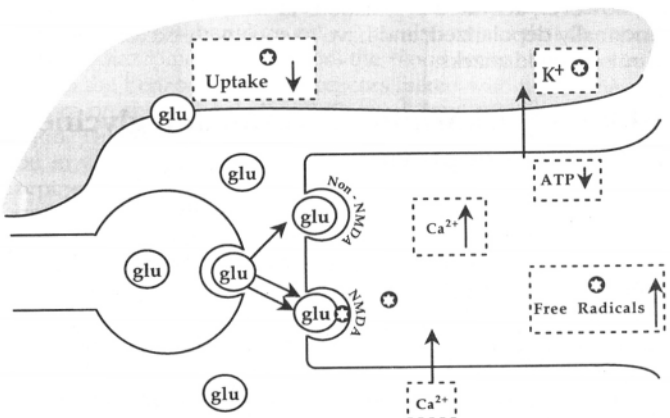


Fig. 7. *Ischaemia-induced depolarization and excess release of glutamate (Glu) of a presynaptic cell, and associated increase in extracellular glutamate due to loss of glutamate uptake resulting from energy depletion and leakage. The chain of events occurs at the post-synaptic cell, including activations of non-NMDA and NMDA receptors which cause increases in the intracellular Ca^{2+} and free radicals, and a loss of ATP. The loss of ATP results in reduced ATP-sensitive K^+ channel activation, accumulation of extracellular K^+ and further increase in glutamate release. The five levels at which the vicious circle of the ischaemia-induced glutamate toxicity may be intercepted, are indicated by *: The blockade of NMDA sites, firstly, at the synapse and, secondly, at the NMDA receptor-mediated ion channels to prevent subsequent glutamate-induced abnormalities, is advantageous, since visually-evoked excitation mediated by non-NMDA receptors would not be affected.*

Sl. 7. *Ishemično sprožena depolarizacija in pretirano sproščanje glutamata (Glu) iz presinaptične celice in s tem povezano zvišanje ekstracelularnega glutamata, do česar pride zaradi ishemije, ki zavre aktivni transport glutamata nazaj v celice. V postsinaptični celici pride do posledične aktivacije receptorjev ne-NMDA in NMDA, ta pa povzroči dvig intracelularnega Ca^{2+} in prostih radikalov in izgubo ATP. Izguba ATP pa prepreči aktivacijo od ATP-odvisnih K^+ kanalov z akumulacijo intracelularnega K^+ in ponovnim zvišanjem sproščanja glutamata.* Circulus vitiosus *ishemične okvare mrežnice bi bilo mogoče prekiniti na petih nivojih, ki so označeni z znakom *: z blokado receptorjev NMDA, najprej na sinapsi in nato na od receptorjev NMDA odvisnih kanalih K^+, kar bi preprečilo nadaljnje kopičenje glutamata. Zmanjšanje kopičenja in s tem povezane toksičnosti bi lahko imelo terapevtski učinek in ob tem ne bi prizadelo vidno pogojenega vzdraženja.*

we can stop the energy depletion by giving O_2, thus increasing the uptake system. But this is not often possible. We may attempt to combat the increase in the free radicals, for example, by the administration of steroids, as used for the treatment of retinal vasculitis/uveitis in the inflammatory eye disease. Alternatively, we may use an ATP-sensitive K^+ channel activator, such as diazoxide, to reduce accumulation of K^+, and in turn to reduce glutamate release. However, we may suggest that the most effective method is to stop the vicious circle at the NMDA sites, using either NMDA receptors or channel blockers. The NMDA antagonists blocked abnormally raised background (spontaneous) firing of ischaemic ganglion cells, without blocking their visually-evoked response which is mediated by the non-NMDA receptors as illustrated in Figure 6.

Summarizing the excitatory transmitter section, we suggest that all the hierarchically organized retinal cells use glutamate as a transmitter mediated by the non-NMDA receptors, except that the transmission from the photoreceptor to the ON-bipolar cells is mediated by the APB sensitive "sign-inverting" receptors (see Fig. 2). However, the NMDA receptors are at least present, though normally silent, on ganglion cells. Such NMDA receptors are, however, activated in situations in which the retinal cells are abnormally depolarized, and have to cope with excess glutamate as in ischaemic attacks.

Inhibitory transmitters, GABA and glycine, and their receptors

As in many other parts of the CNS, best established inhibitory transmitters of the retina are GABA (22) and glycine (23). Both GABA and glycine have selective receptor agonists and antagonists, as listed in Table 1. Glycine has a single well-established receptor and strychnine is a powerful competitive antagonist, although recently strychnine-insensitive glycine sites, linked with the NMDA receptors, have been proposed (24).

In our agonist studies, we found that $GABA_A$ and glycine had a powerful action on the retinal ganglion cells in a selective way (2). GABA and muscimol ($GABA_A$ agonist) inhibited the ON-cell response, whilst glycine inhibited the OFF-cell response. The GABA and glycine actions suggested that $GABA_A$ receptors were on the ON- and glycine receptors on the OFF-ganglion cells. But was endogenous GABA or glycine released onto these receptors? Our studies using the selective $GABA_A$ and glycine receptor antagonists demonstrated that the answer was yes. As shown in Figure 8, bicuculline, a $GABA_A$ receptor antagonist, blocked the post- excitatory inhibition and increased the firing level altogether of the ON-cell, but did not affect the OFF-cell. The opposite was the case with the glycine antagonist, strychnine. Strychnine antagonised the OFF-cell, but not the ON-cell. A receptive field of the ganglion cells consists of an excitatory centre and inhibiting surround which is annulus shaped. We have also shown that the surround inhibition of the ON-cells to bright annulus is blocked by bicuculline, whilst that of the OFF-cells to black annulus, by strychnine (2). These experiments, therefore, suggest that visual inhibition of the ON-cells is mediated by $GABA_A$ receptors, whilst that of the OFF-cells, by glycine receptors.

Tab. 1. *Neurotransmitters, their receptors and selective agonists and antagonists referred to in the text.*

Tab. 1. *Nevrotransmiterji, njihovi receptorji in selektivni agonisti in antagonisti, ki so obravnavani v tekstu.*

Transmitter	Receptor	Agonist	Antagonist
Glutamate	NMDA	NMDA	CPP NPC Ketamine MK 801
	non-NMDA	Kainate Quisqualate	NBQX CNQX DNQX
	"sign-inverting"	APB	
GABA	$GABA_A$ $GABA_B$	Muscimol Baclofen	Bicuculline Phaclofen
Benzodiazepine	Benzodiazepine $GABA_A$	Flurazepam Midazolam	RO 15-1788 (Flumazepil)
Glycine	Glycine	Glycine	Strychnine
Dopamine	D_1	SKF 38393	SCH 23390 L-flupenthixol
	D_2	Bromocriptine LY 141865	L-sulpiride
	D_3 D_4		

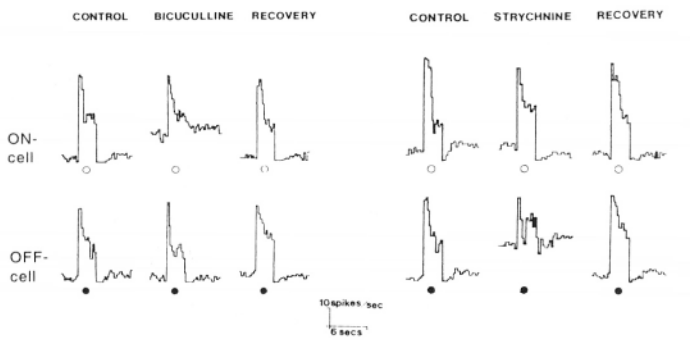


Fig. 8. *Effects of the iontophoretically applied $GABA_A$ receptor antagonist, bicuculline, and glycine receptor antagonist, strychnine, on the response of an ON- and an OFF-cell to an optimal spot (a bright spot to the ON-cell and a black spot to the OFF-cell) at the centre of the receptive field. Note that bicuculline increased firing and abolished post-excitatory inhibition of the ON-cell by antagonizing endogenously released GABA on $GABA_A$ receptors, whilst strychnine had similar effects on the OFF-cell by antagonizing naturally released glycine.*

Sl. 8. *Učinki iontoforetske aplikacije receptorskega antagonista $GABA_A$, bicuculina, in antagonista glicinskih receptorjev, stribnina, na odzive ON- in OFF-celic na optimalno vidno draženje (svetla pega v sredini receptivnega polja za ON- in temna pega za OFF-celice). Razvidno je, da bicuculin zviša vzdražnost in prepreči post-ekscitatorno inhibicijo ON-celic prek inhibicije endogenega sproščanja GABA na receptorje $GABA_A$. Strihnin pa ima podobne učinke na OFF-celicah prek antagoniziranja naravnega sproščanja glicina.*

Consider that a bright object on a dark background excites the ON-cells and inhibits the OFF-cells, whilst a dark object on a bright background excites the OFF-cells and inhibits the ON-cells. Thus, if the ON- and OFF-cells use the same inhibitory transmitter, there would be confusion in contrast detection. Although visual excitation of both ON- and OFF-cells is mediated by glutamatergic transmission, it may be important for contrast vision that the two types of ganglion cells use different inhibitory transmitters. As schematically shown in Figure 9, the ON- and OFF-cells are indeed separated anatomically by the level at which dendritic branching occurs (25), and in keeping with our physiological data, glycine receptors have been localised at the level of OFF-cell stratification (23).

Interestingly, the pharmacological separation of GABA and glycine for ON- and OFF-cell pathways is a distinct feature of ganglion cells in the area centralis (the equivalent of the human

fovea), where important visual contrast detection is made, whilst it is less pronounced in cells in the peripheral retina or (26) immature retinae (27).

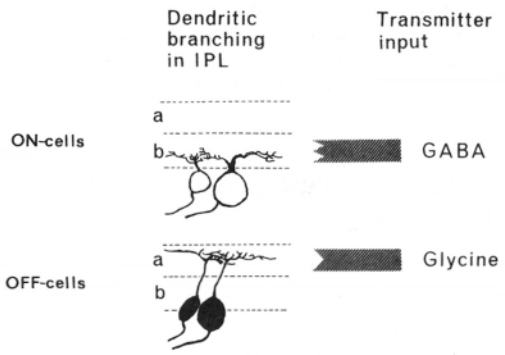


Fig. 9. *Schematic description of the GABA input to the ON-ganglion cells with dendritic branching at the b-sublamina, and the glycine input to the OFF-ganglion cells with dendritic branching at the a-sublamina of the innerplexiform layer. The separate GABA and glycine inputs to the ON- and OFF-ganglion cells respectively is a distinct feature of the area centralis of the cat retina.*

Sl. 9. *Shematični prikaz učinka GABA na ON-ganglijske celice, ki se dendritično razvejijo v b-sublamini mrežnice, ter učinka glicina na OFF-ganglijske celice, ki se razvejujejo v a-sublamini notranje pleksiformne plasti. Ločeni GABA in glicinski receptorji na pripadajočih ON-in OFF-ganglijskih celicah so posebna značilnost središčnega predela mrežnice pri mački.*

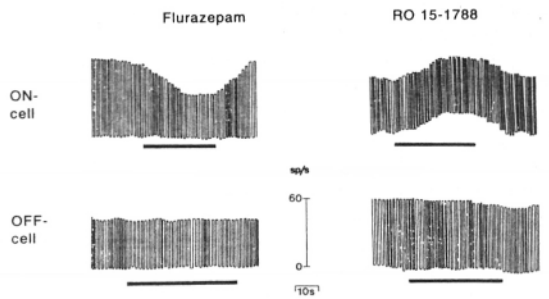


Fig. 10. *Effects of an iontophoretically applied benzodiazepine agonist, flurazepam and its competitive antagonist, RO15-1788, on ON- and OFF-retinal ganglion cell-firing to an optimal spot (a white spot for the ON- and a black spot for the OFF-cell) presented at 1 Hz in the centre of the receptive field. The period of iontophoretic application of each drug is indicated by the bar under each trace. Note that flurazepam (40 nA) suppressed, whilst RO15-1788 (100 nA) increased the firing of the ON-cell, but neither drug had any effect on the OFF- cell. The effect of RO15-1788 suggests the presence of endogenous benzodiazepine ligand on the ON-ganglion cell.*

Sl. 10. *Učinki iontoforetične aplikacije benzodiazepinskega agonista, flurazepama, in njegovega kompetitivnega antagonista, RO15-1788, na vzdražnost ON- in OFF-celic mrežnice po draženju z optimalnim dražljajem, prikazanem s frekvenco 1 Hz, v centru pripadajočega vidnega polja. Razvidno je, da flurazepam (40 nA) zavira, RO15-1788 (100 nA) pa zveča vzdražnost ON-celic, medtem ko nobena od obeh substanc ni imela učinka na OFF-celice. Učinek RO15-1788 kaže na prisotnost endogenega benzodiazepinskega liganda na ON-ganglijskih celicah.*

Are benzodiazepine receptors present in the mammalian retina?

Having found that GABA is an important synaptic transmitter at the retinal ganglion cells, we may ask "Are there any benzodiazepine receptors in the retina?" Benzodiazepine receptors are linked with the $GABA_A$ receptors, and are known to potentiate GABA actions in the CNS (28). Benzodiazepine agonists are flurazepam and Midazolam, and a selective antagonist is RO15 - 1788 (Fluzampil). The details of our studies on retinal benzodiazepine receptors have been described elsewhere (29).
Flurazepam was found to inhibit and the benzodiazepine receptor antagonist, RO15 - 1788, to raise the firing level of the ON-cells but not that of the OFF-cells. This is illustrated in Figure 10. There are, thus, some benzodiazepine receptors upon the ON-ganglion cells which have $GABA_A$ receptors. Furthermore, since the selective benzodiazepine receptor antagonist applied on its own increased the firing of ON-cells, the benzodiazepine receptors on these cells appeared to have endogenous benzodiazepine ligand released on them. This may imply that there are natural tranquillisers in the retina, and that they have inhibitory actions on the ON-ganglion cells. This also means that therapeutic benzodiazepines, which cross the blood retinal barrier, could bind to the benzodiazepine receptors linked with the $GABA_A$ receptors on the ON-ganglion cells, and may exert an inhibitory action. This may be a contributory factor for the reported reduction in visual functions following systemically applied benzodiazepines (30).

Possible functional pathways of the principal excitatory and inhibiting transmitters in the mammalian retina

The previous three sections have considered the glutamatergic pathway from the photoreceptor to the ganglion cells via the bipolar cells, and the inhibitory pathways from the GABAergic and glycinergic amacrine cells to the ganglion cells. The diagram shown in Figure 11 summarizes the principal neurotransmitters and their post-synaptic receptors on different classes of cells in the mammalian retina.
The photoreceptors depolarize and release glutamate in the dark, whereas light hyperpolarizes them, and inhibits the release. The actions of glutamate released from the photoreceptors are directly transmitted to the horizontal and the OFF-bipolar cells via a conventional synapse with non-NMDA receptors. The glutamate actions of the photoreceptor to the ON-bipolar cells are, however, mediated by the APB-sensitive (sign-inverting) receptors at which glutamate closes ion-channels, making the ON-bipolar cells depolarize to light (Fig. 2). The dark depolarizing OFF-bipolar and the light depolarizing ON-bipolar cells release glutamate to the non-NMDA receptors of the OFF-and ON-ganglion cells respectively, to elicit visually-evoked action potentials. The NMDA receptors on the ganglion cells, which are activated under excess glutamate accumulation, are also indicated in Figure 11. Both the OFF- and ON-ganglion cells also contain glutamate as a neurotransmitter (5), and their glutamatergic transmission to the OFF- and ON-LGN (lateral geniculate nucleus) cells has been studied using microiontophoretic technique in the LGN (31, 32). It appears that the LGN cells possess both NMDA and non-NMDA receptors.
The inhibitory pathways arise from the GABAergic and the glycinergic amacrine cells. But their release of transmitter is triggered by the bipolar cells. The OFF-bipolar cells release glutamate to depolarize the GABAergic amacrine cells, although it is not known which type of glutamate receptors is on these cells. The GABAergic amacrine cells then exert GABA action on the ON-

ganglion cells via the $GABA_A$ receptors. There are also benzodiazepine receptors, which are linked with the $GABA_A$ receptors on the ON-ganglion cells. The ON-bipolar cells, on the other hand, release glutamate to depolarize the glycinergic amacrine cells (again the receptor type is not known), which exerts glycinergic action on the OFF-ganglion cells via the strychnine-sensitive glycine receptors.

The weak glycine release on the ON-cells and GABA release on the OFF-cells present in the peripheral (26) or immature retinae (27), although their functional significance is not certain, are shown by thinner lines in Figure 11. There is also weak but definite $GABA_B$ input to the OFF-ganglion cells which make the ganglion cell firing more transient (28).

The diagram in Figure 11 does not include the complex interneurone network which may modify and/or regulate the major excitatory and inhibitory pathways. These pathways of the horizontal, amacrine and interplexiform cells may contain amines and peptides, although their physiological functions are still largely undetermined.

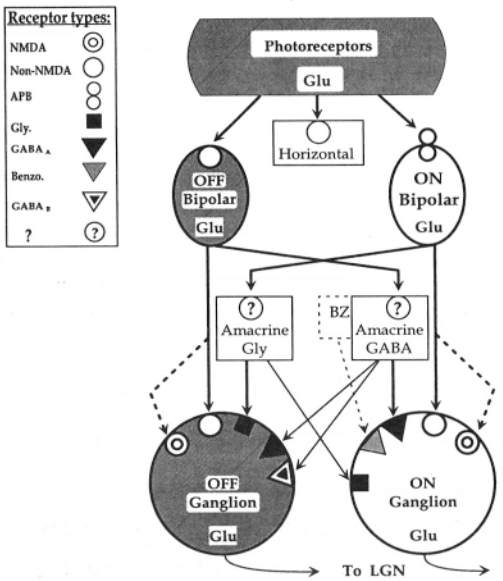


Fig. 11. *Possible functional pathways of the principal excitatory and inhibitory transmitters from the photoreceptors to the ON- and OFF-retinal ganglion cells. The transmitter released, and the types of receptors upon each type of retinal cells are indicated. Note that all glutamatergic transmission, except at the ON-bipolar cell, is mediated by non-NMDA receptors, whilst the ON-bipolar cell has the APB-sensitive "sign-inverting" receptor. Glutamate inputs to NMDA receptors, which possibly function under excess glutamate, are shown in dashed lines. The glycinergic amacrine cell receives glutamate from the ON-bipolar cell, and releases glycine to the OFF-ganglion cell, whilst the GABAergic amacrine cell receives glutamate from the OFF-bipolar cell, and releases GABA to the ON-ganglion cell. Weak $GABA_A$ and $GABA_B$ inputs to OFF-ganglion cells in peripheral retinae are shown in thin lines. Possible benzodiazepine (Benzo) ligand released onto benzodiazepine receptors linked with $GABA_A$ receptors on the ON-cell is shown in a thin dashed line.*

Sl. 11. *Slika prikazuje možne funkcijske poti glavnih ekscitatornih in inhibitornih nevrotransmiterjev od fotoreceptorjev do ON- in OFF-ganglijskih celic mrežnice. Prikazani so posamezni transmiterji in tipi ustreznih receptorjev na posameznih tipih celic v mrežnici sesalcev. Razvidno je, da vsa glutamatergična pot, razen na ON-bipolarnih celicah, poteka prek ne-NMDA receptorjev, medtem ko ON-bipolarne celice delujejo prek na APB-občutljivega "sign-inverting" receptorja. Mesta delovanja glutamata na receptorjih NMDA, ki se verjetno aktivirajo ob stanjih s prebitkom glutamata, so prikazana s črtkano črto. Glicinergične amakrine celice dobivajo glutamat od ON-bipolarnih celic in sproščajo glicin na OFF-ganglijske celice. GABAergične amakrine celice pa sprejemajo glutamat od OFF-bipolarnih celic in sproščajo GABA na ON-ganglijske celice. Šibki vplivi $GABA_A$ in $GABA_B$ na OFF-ganglijske celice v periferiji mrežnice so prikazani s tanko črto. Možni benzodiazepinski (Benzo) ligand, sproščen na benzodiazepinske receptorje, ki so vezani na receptorje $GABA_A$ na ON-celicah, so prikazani s tanko črtkano črto.*

Possible dopaminergic pathways in the mammalian retina

As mentioned above, Figure 11 ignored pathways of the amacrine or the interplexiform cells containing other transmitters than the excitatory and inhibitory amino acids. An important neuroactive substance, which cannot be ignored in the retina, however, is dopamine. Dopamine has satisfied all the criteria for being a retinal neurotransmitter for some time (33), and it is perhaps the most studied substance in the retina. Dopamine is of no exception for its multiplicity of receptors as listed in Table 1. D_1 and D_2 receptors are well established, and their selective agonists and antagonists are available, although D_3 and D_4 with their different affinity to D_2 agonists are proposed (34), which makes dopamine researchers busy for the next decade. D_4 receptors are particularly interesting for the retina, as their presence was demonstrated in the photoreceptors using RNA probes. No selective antagonists for D_3 and D_4 to study their endogenous actions are available at present.

Figure 12 summarizes possible dopaminergic pathways. Dopamine is contained in a class of the amacrine and the interplexiform cells located in the innerplexiform layer. For many years dopaminergic amacrine cells were believed not to make direct synaptic contact either with the bipolar cells or with the ganglion cells (33). However, recent anatomical studies of the mammalian retina (35) indicate that the dopaminergic cells receive inputs from cone-driven bipolar cells, and a physiological study using APB (36) suggests that these cells are ON-bipolars in the mud puppy retina. (I, therefore, entered the input from the ON-bipolar cell to the dopaminergic cell with a question mark in Fig. 12). Intracellular recordings from the dopaminergic amacrine or the interplexiform cells are still required in order to determine if glutamate is the transmitter which depolarizes the dopaminergic cells. The dopaminergic interplexiform cells provide inputs not only to the horizontal cells but also to the photoreceptors (37).

Physiological and biochemical evidence also suggests that dopamine together with melatonin (synthesized in the photoreceptor) have a reciprocal role in the promotion of the photoreceptor renewal processes (38), as well as in dark and light adaptive modulations (39) at these outermost retinal layers. Thus the dopaminergic pathway to the photoreceptor outer segments and pigment epithelium are shown by dotted lines in Figure 12. Anatomical studies also suggest that the dopaminergic amacrine cells are pre-synaptic to the glycinergic as well as to the GABAergic amacrine cells (40, 41).

Dopaminergic actions have been demonstrated at different levels of the retina (42). We have also studied the D_1 receptor-mediated dopamine action on the horizontal cells of the rat (43), and the D_2 receptor-mediated action of dopamine in relation to melatonin at the pigment epithelium (44). These studies will be reported at the dopamine section of this symposium.

A striking factor of the dopaminergic pathway is that, although the dopaminergic cells are only found in the inner plexiform layer, the D_1 and D_2 receptors are scattered throughout the retina, from the pigment epithelium to the ganglion cells (45). In this respect, I wish to draw your attention to the fact that the presence of widespread distribution of the dopamine receptors in

the retina, whether or not natural dopamine release is there, has clinical relevance, because the dopamine receptors can be activated by all dopaminergic drugs which cross the blood/retinal barrier. The evidence for this is apparent from our study which showed that iontophoretically applied dopamine depressed all types of retinal ganglion cells, whilst its receptor antagonists applied alone had no effects on them (46), which suggests that there is no endogenous dopamine. Thus, therapeutic dopaminergic agonists, such as bromocriptine, lysuride, and apomorphine, could activate the dopamine receptors throughout the retina, whether or not they are normally active. Many of the anti-psychotic drugs, such as phenothiazine, on the other hand, inhibit endogenous dopamine actions in the retina.

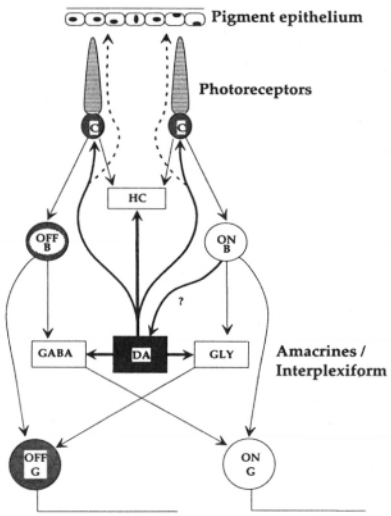


Fig. 12. *Possible dopaminergic pathway in the mammalian retina. The dopaminergic, interplexiform and amacrine cells receive inputs, probably from the ON-bipolar cells. A question mark was added to the pathway, since the evidence is not available for the mammalian retina. The dopaminergic cells feed the horizontal cells, the photoreceptors and possibly the pigment epithelium. They also feed the GABAergic and the glycinergic amacrine cells. The principal excitatory and inhibitory pathways to the ON-and OFF-ganglion cells (as shown in Fig. 10) are drawn in thin lines. The horizontal cell outputs to the photoreceptors and to the bipolar cells are omitted for clarity.*

Sl. 12. *Možne dopaminske poti v mrežnici sesalcev. Dopaminergične, interpleksiformne in amakrine celice sprejemajo signale verjetno od ON-bipolarnih celic. Znak vprašaj je dodan, ker dokazi o tem za mrežnico sesalcev še niso na voljo. Dopaminergične celice kontaktirajo horizontalne celice, fotoreceptorje in morda še pigmentni epitelij. Prav tako so v stiku z GABAergičnimi in glicinergičnimi amakrinimi celicami. Najvažnejše ekscitatorne in inhibitorne poti na ON- in OFF-ganglijskih celicah (kot je prikazano v sliki 10) so označene s tankimi črtami. Eferentni stiki horizontalnih celic s fotoreceptorji so zaradi preglednosti izpuščeni.*

All neurotransmitter and neuromodulator systems interact

In this lecture I have discussed the actions of glutamate, GABA, benzodiazepine, glycine and dopamine separately so far. But *the final point* which I wish to emphasize is that no neurotransmitter in the intact nervous system acts independently, and that neurotransmitters and neuromodulators interact in a complex manner to maintain a delicate balance.

For example, if the amount of glutamate increases or decreases in the retina, the levels of all transmitters released from the interneurones, i.e. horizontal and amacrine cells which receive inputs from the photoreceptors and/or the bipolar cells, would alter accordingly. Thus glutamate interacts with GABA, acetylcholine, glycine and dopamine. Similarly, the dopaminergic actions should interact with the glutamatergic, as well as with the GABAergic and glycinergic transmitter pathways. The dopaminergic amacrine cells innervate the glycinergic and the GABAergic amacrine cells which synapse with the glutamatergic ganglion cells (Fig. 11). The dopaminergic interplexiform cells feed the horizontal cells, which in turn contact both the glutamatergic photoreceptors and the bipolar cells (Fig. 11). In addition, the reciprocal relationships between dopamine and melatonin have been shown to play a significant role in the process of the photoreceptor renewal as mentioned above (38). Thus, the normal retinal function is dependent upon this delicate neurochemical balance. Any drugs applied exogenously to the normal retinae may upset this balance, and hence impair retinal function, although such drugs can have therapeutic effects on abnormal retinae.

Conclusions

At the beginning of the lecture, I have listed neuroactive substances found in the mammalian retina. Of these, acetylcholine, glutamate, GABA, glycine and dopamine are now qualified retinal neurotransmitters, therefore I described the functional role of glutamate, GABA, and glycine in detail, and referred briefly to benzodiazepine, which is linked to $GABA_A$ receptors, and to the possible multiple function of the dopamine pathway. Finally, importance was placed upon the interdependence of all these retinal transmitters.

The substances which are only partially qualified as neurotransmitters include aspartate, taurine, adrenaline, noradrenaline, serotonin and, to this category, substance P and somatostatin from the long list of peptides may now be added (47, 48). For all other peptides, their localization in the amacrine cells still appears to be the only factor by which they qualify, at this time, as a possible retinal transmitter. Future electrophysiological studies on amacrine cells using selective receptor antagonists will throw light on their functional role.

Acknowledgements. The experiments described in this lecture were carried out with Drs. Malcolm Sheardown (1980 - 84), Jonathan Robbins (1982 - 1988), Christine Kay (1986 - 1989), Mark Hankins (1988 - 1993), Toshimichi Asai (1990 - 1991) and Mrs. Elizabeth Dawes (1990 - 1993). I thank warmly Mr. Peter de Villiers and Miss Gail Turner for technical assistance and Mrs. Janet Gladwell for secretarial assistance. The work was supported throughout by the Medical Research Council and The Special Trustees of St. Thomas' Hospital.

References

1. Hankins MW, Ikeda H. Non-NMDA type excitatory amino acid receptors mediate rod input to horizontal cells in the isolated rat retina. Vision Res 1991; 31: 609-17.
2. Ikeda H. Transmitter action at the cat retinal ganglion cells. In: Osborne NN, Chader G eds. Progress in retinal research. Oxford: Pergamon Press, 1985: 4: 1-32.
3. Neal MJ. Cholinergic mechanisms in the vertebrate retina. In: Osborne NN, Chader GJ eds. Progress in retinal research. Oxford: Pergamon Press, 1983: 2: 191-212.
4. Ikeda H, Sheardown MJ. Acetylcholine may be an excitatory transmitter mediating visual excitation of transient cells with the periphery effect in the cat retina: Iontophoretic studies *in vivo*. Neurosci 1982; 7: 1299-308.
5. Ehinger B. Glutamate as a retinal neurotransmitter. In: Weiler R, Osborne NN eds. Neurobiology of the inner retina, NATO ASI series. Berlin: Springer- Verlag, 1987: 1-14.
6. Massey SC. Cell types using glutamate as a neurotransmitter in the vertebrate retina. In: Osborne NN, Chader G eds. Progress in retinal research. Oxford: Pergamon Press 1990: 9: 399-425.
7. Gasic GP, Hollmann M. Molecular neurobiology of glutamate receptors. Ann Rev Physiol 1992; 54: 507-36.

8. Watkins JC, Evans RH. Excitatory amino acid transmitters. Ann Rev Pharmacol Toxicol 1981; 21: 165-204.
9. Drejer J, Honoré T. New quinoxalinediones show potent antagonism of quisqualate response in cultured mouse cortical neurons. Neurosci Lett 1988; 87: 104-8.
10. Sheardown MJ, Nielson EO, Hanson EJ, Jacobsen P, Honoré T. 2,3-Dihydroxy-6-nitro-7-sulfamoyl-benzo (F) quinoxaline. A neuroprotectant for cerebral ischaemia. Science 1990; 247: 571-74.
11. Trifonov YA. Study of synaptic transmission between the photoreceptor and the horizontal cell using electrical stimulation of the retina. Biofizika 1968; 10: 673- 80.
12. Slaughter MM, Miller RF. Bipolar cells in the mudpuppy retina use an excitatory amino acid neurotransmitter. Nature 1983; 303: 537-8.
13. Shiells RA, Falk G, Nagahshineh EH. Action of glutamate and aspartate analogs on rod horizontal and bipolar cells. Nature 1981; 294: 592-4.
14. Yamashita M, Wässle H. Responses of Rod Bipolar cells isolated from the rat retina to the glutamate agonist 2-amino-4-phosphonobutyric acid (APB). J Neurosci 1991; 11: 2372-82.
15. Massey SC, Redburn DA, Crawford MLJ. The effects of 2-amino-4-phosphonobutyric acid (APB) on the ERG and ganglion cell discharge of rabbit retina. Vision Res 1983; 23: 1607-13.
16. Ikeda H, Kay CD, Robbins J. Properties of excitatory amino acid receptors on sustained ganglion cells in the cat retina. Neurosci 1989; 32: 27-38.
17. Ikeda H, Robbins J, Kay CD. Excitatory amino acid receptors on sustained retinal ganglion cells in the kitten during the critical period of development. Dev Brain Res 1990; 51: 85-91.
18. Ikeda H, Dawes E, Hankins MW. Spontaneous firing level distinguishes the effects of NMDA and non-NMDA receptor antagonists on the ganglion cells in the cat retina. Eur J Pharmacol 1992; 210: 53-9.
19. Woodruff GN, Foster AC, Wong EHF, Gill R, Kemp JA, Iversen LL. Excitatory amino acids and neurodegenerative disorders: possible therapeutic indications. In: Excitatory amino acids in health and diseases. Lodge D ed. Chichester: John Wiley & Sons, 1988: 379-89.
20. Ikeda H, Hankins MW, Asai T, Dawes EA. Electrophysiological properties of neurones following mild and acute retinal ischaemia. Exp Eye Res 1992; 58: 435-42.
21. Nanda SK, Hatchell DL, Tiedeman JS, Dutton JJ, Hatchell MC, McAdoo TA. New method for vascular occlusion: photochemical initiation of thrombosis. Arch Ophthalmol 1987; 105: 1121-4.
22. Yazulla S. GABAergic mechanism in the retina. In: Osborne NN, Chader G eds. Progress in retinal research. Oxford: Pergamon Press, 1986; 5: 1-52.
23. Marc RE. The role of glycine in the mammalian retina. In: Osborne NN, Chader G eds. Progress in retinal research. Oxford: Pergamon Press, 1988; 8: 67-108.
24. Johnson JW, Ascher P. Glycine potentiates the NMDA response in cultured mouse brain neurones. Nature 1987; 325: 529-31.
25. Nelson R, Famglietti EV, Kolb H. Intracellular staining reveals different levels of stratification for on-center and off-center ganglion cells in the cat retina. J Neurophysiol 1978; 41: 472-83.
26. Priest TD, Robbins J, Ikeda H. The action of inhibitory transmitters, γ-aminobutyric acid and glycine may distinguish between the area centralis and the peripheral retina in cats. Vision Res 1985; 25: 1761-70.
27. Ikeda H, Robbins J. Postnatal development of GABA and glycine-mediated inhibition of feline retinal ganglion cells in the area centralis. Dev Brain Res 1985; 23: 1-17.
28. Ikeda H, Hankins MW, Kay CD. Actions of baclofen and phaclofen upon ON- and OFF-ganglion cells in the cat retina. Eur J Pharmacol 1990; 190: 1-9.
29. Tallman JF, Gallager DW. The GABAergic system: a locus of benzodiazepine action. Ann Rev Neurosci 1985; 8: 21-44.
30. Robbins J, Ikeda H. Benzodiazepines and the mammalian retina II. Actions on retinal ganglion cells. Brain Res 1989; 479: 323-33.
31. MacNab MW, Foltz EL, Sweizer J. Evaluation of signal detection theory on the effects of psychotropic drugs on critical flicker-fusion frequency in normal subjects. Psychopharmacol 1985; 85: 431-5.
32. Sillito AM, Murphy PC, Salt TE. The contribution of the non-N-methyl-D-aspartate group of excitatory amino acid receptors to retino-geniculate transmission in the cat. Neurosci 1990; 34: 273-80.
33. Ehinger B. Functional role of dopamine in the retina. In: Osborne NN, Chader GJ eds. Progress in retinal research. Oxford: Pergamon Press, 1983; 2: 213-32.
34. Cohen AI, Todd RD, Harmon S, O'Malley L. Photoreceptors of mouse retinas possess D_4 receptors coupled to adenylate cyclase. Proc Natl Acad Sci USA 1992; 39: 12093-7.
35. Hokoc JN, Mariani AP. Synapses from bipolar cells onto dopaminergic amacrine cells in the cat and rabbit retina. Brain Res 1988; 461: 17-26.
36. Wong CJ, McReynolds JS. APB increases apparent coupling between horizontal cells in mudpuppy retina. Vision Res 1989; 29: 541-4.
37. Nguyen-Legros J, Moussafi F, Simon A. Sclerally directed processes of dopaminergic interplexiform cells reach the outer nuclear layer in rat and monkey retina. Vis Neurosci 1990; 4: 547-53.
38. Dubocovich ML. Role of melatonin in retina. In: Osborne NN, Chader GJ eds. Progress in retinal research. Oxford: Pergamon Press, 1988; 8: 129-51.
39. Beharse J C, Iuvone PM. Is dopamine a light adaptive or a dark adaptive modulator in the retina? Neurochem Int 1992; 20: 193-9.
40. Voigt T, Wässle H. Dopaminergic innervation of AII amacrine cells in mammalian retina. J Neurosci 1987; 7: 4115-28.
41. Kolb H, Cuinca N, Wang HH, Dekorver L. The synaptic organisation of the dopaminergic amacrine cell in the cat retina. J Neurocytol 1990; 19: 343-66.
42. Witkovsky P, Dearry A. Functional roles of dopamine in the vertebrate retina. In: Osborne NN, Chader GJ eds. Progress in retinal research. Oxford: Pergamon Press, 1991; 11: 247-92.
43. Hankins MW, Ikeda H. The role of dopaminergic pathways at the outer plexiform layer of the mammalian retina. Clin Vis Sci 1991; 6: 87-93.
44. Hawlina M, Jenkins HG, Ikeda H. Diurnal variations in the ERG c-wave and retinal melatonin content in rats with inherited retinal dystrophy. Doc Ophthalmol 1992; 79: 141-50.
45. Zarbin MA, Wamsley JK, Palacios JM, Kuhar M. Autoradiographic localization of high affinity GABA, benzodiazepine, dopaminergic, adrenergic and muscarinic cholinergic receptors in the rat, monkey and human retina. Brain Res 1986; 374: 75-92.
46. Ikeda H, Robbins J. Dopamine-less D2 receptor on feline retinal ganglion cells. In: Bodis-Wollner ed. Dopaminergic mechanisms in vision. New York: Alan R. Liss Inc, 1988: 179-91.
47. Zalutsky R, Miller RF. The physiology of somatostatin in the rabbit retina. J Neurosci 1990; 10: 383-93.
48. Zalutsky R, Miller RF. The physiology of substance P in the rabbit retina. J Neurosci 1990; 10: 394-402.

NEVROTANSMITERJI V MREŽNICI SESALCEV. PRIKAZ Z NEVROFIZIOLOŠKEGA STALIŠČA

Hisako Ikeda

Izvleček - *Prispevek obravnava vlogo endogenih nevrotransmiterjev v mrežnici sesalcev, prikazanih z uporabo selektivnih receptorskih antagonistov v elektrofizioloških poskusih. Najprej je prikazana glutamatna pot, po kateri se prenaša vidno vzdraženje s fotoreceptorskih na bipolarne in ganglijske celice. Pri slednjih je posebej izpostavljen pomen receptorjev NMDA, ki so v normalnih okoliščinah neaktivni. Aktivira jih šele čezmerna količina glutamata, ki se sprošča ob nekaterih patoloških procesih, kot npr. ob ishemičnih stanjih mrežnice. Nato prispevek obravnava pomen GABA-ergičnih in glicinergičnih poti, ki posredujejo inhibicijske signale na ganglijske celice tipa ON in OFF. Pri tem je omenjen tudi klinični pomen benzodiazepinskih receptorjev, povezanih z receptorji $GABA_A$. V tretjem delu prispevka je prikazana vloga dopamina na različnih celičnih nivojih v mrežnici, posebej pri aktivaciji receptorjev D1 na horizontalnih in amakrinih celicah v regulaciji velikosti receptivnih polj in s tem kontrastne senzitivnosti ter regulaciji svetlobnega vzdraženja vidnega sistema. Prikazan je pomen delovanja dopamina na receptorje D_2 pri ritmičnih procesih obnavljanja fotoreceptorskih celic. Našteti so možni klinični učinki aktivacije obeh tipov receptorjev ter učinki dopaminergičnih zdravil. V zaključku je podan pregled medsebojnih učinkov in interakcij med vsemi obravnavanimi nevrotransmiterji. Pravilno ravnovesje med njimi je pogoj normalnega delovanja mrežnice.*

Ključne besede: *benzodiazepini; dopamin; gama amino-maslena kislina; glicin; glutamat*

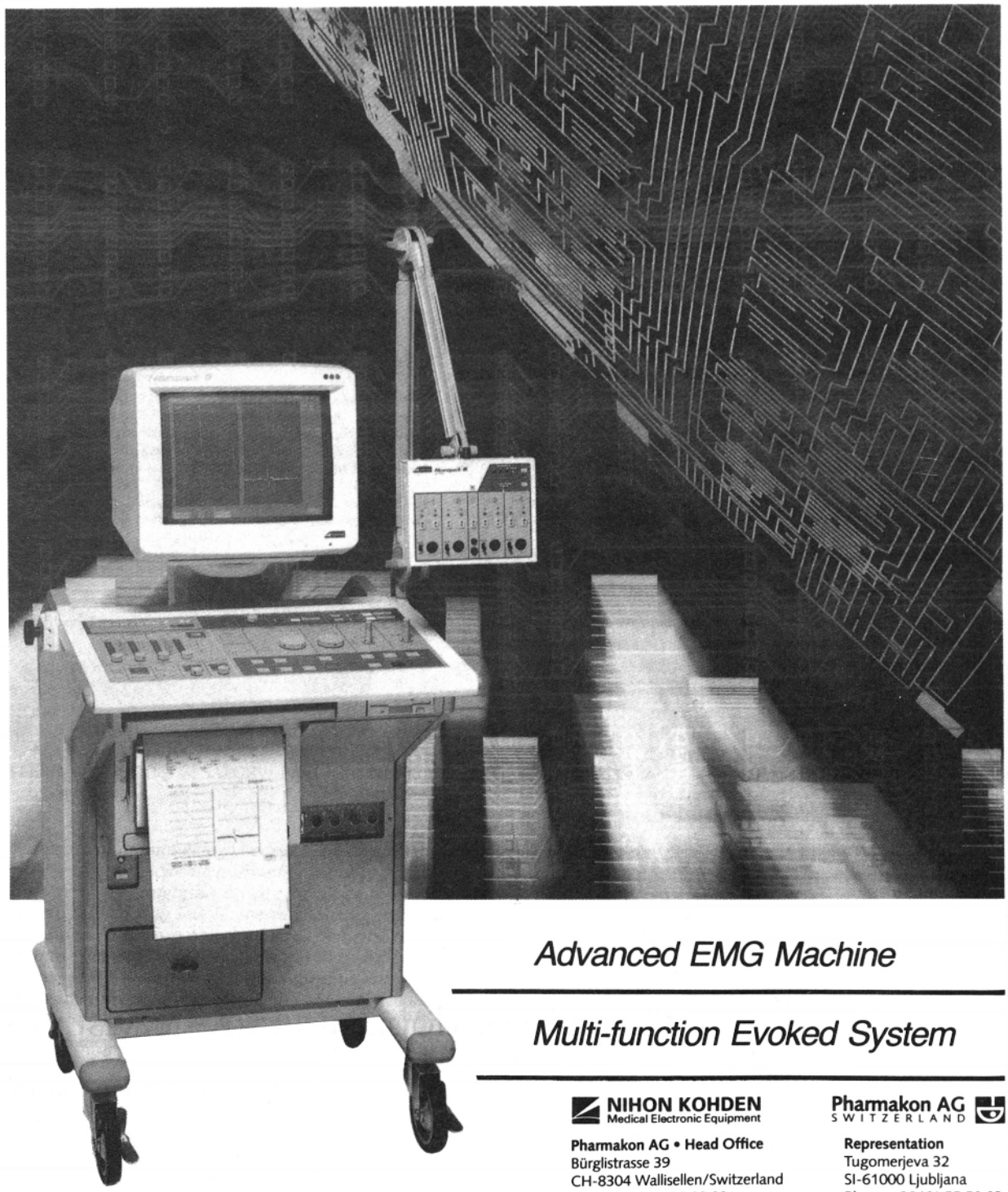
The role of dopamine in the visual system

Vloga dopamina v vidni poti

New Neuropack8

MEM-4204•4208
MEB-4204•4208

Evoked Potential/EMG Systems



Advanced EMG Machine

Multi-function Evoked System

NIHON KOHDEN
Medical Electronic Equipment

Pharmakon AG
SWITZERLAND

Pharmakon AG • Head Office
Bürglistrasse 39
CH-8304 Wallisellen/Switzerland
Phone +41/1 830 02 93
Fax +41/1 830 22 48

Representation
Tugomerjeva 32
SI-61000 Ljubljana
Phone +38/61 55 50 03
Fax +38/61 55 50 03

THIRTY-FIVE YEARS OF DOPAMINE RESEARCH

PETINTRIDESET LET RAZISKOVANJA DOPAMINA

Dušan Sket

Institute of Pathophysiology, University of Ljubljana School of Medicine, Zaloška c. 4, 61105 Ljubljana, Slovenia

Key words: *dopamine; history of medicine; receptors*

Abstract - *The fascinating progress made in 35-year history of dopamine is reviewed in brief. The milestones of dopamine research are: determination of dopamine content in the brain structures (1957-58); discovery of low concentrations of dopamine in basal ganglia of parkinsonian patients (1960); introduction of histochemical fluorescence methods for demonstration of catecholamines in nerve cells (1962-64), followed by localization and morphological characterization of dopamine-containing nerve cells; first single unit recordings of dopamine-innervated neurons in mammalian brain (1965-67); first steps in development of dopamine-dependent behavioural models (1967-71); dopamine-stimulated adenylate cyclase assay (1971-72); introduction of radioactive ligands into studies of dopamine receptor binding* in vitro *(1975); classification of dopamine receptors as D_1 and D_2 receptors (1979); the first clinical positron emmission tomographic study of 11C-chlorpromazine binding (1979); first functionally active transplants of fetal dopamine cells in animals (1979); implantation of human fetal dopaminergic cells to parkinsonian patients, with limited clinical improvement (1988-1990); studies of dopamine regulation of gene expression started in the eighties; molecular biology of dopamine receptors (1988-93): cloning studies have identified two subtypes of D_1 and four subtypes of D_2 receptors. Progress in dopamine research improved our understanding of brain functions and opened up new therapeutic possibilities for several neurological and psychiatric illnesses.*

The dopamine story began in 1957 with a suggestion given by Blaschko (1), an eminent biochemist, who already in 1939 postulated the sequence of enzymatic steps in the synthesis of catecholamines from their aminoacid precursor tyrosine. He assumed that dopamine, a chemical precursor of noradrenalin and adrenalin, might have physiological function in the brain. His assumption was supported by the discovery of high dopamine concentrations in the basal ganglia, reported in the same year (2, 3, 4). After it became evident that dopamine, not noradrenalin, was highly concentrated in certain regions of the basal ganglia (5), the question arose, whether dopamine could have specific neurotransmitter function in the brain. The report on low dopamine concentrations in basal ganglia in the brains of patients with Parkinson's disease, written by Ehringer and Hornykiewicz in 1960 (6), suggested that the changes in dopamine concentrations in the brains might have caused the disease.

However, in order to prove the role of dopamine in physiological functions, as well as in disease, several important steps had to be made. First, dopaminergic neurons had to be visualized, their biochemical and physiological functions discovered and, finally, dopamine receptors recognized as specific entities.

The visualization of dopaminergic neurons became possible with the discovery of histofluorescent methods for demonstration of monoaminergic cell bodies, nerve fibers and nerve terminals in the central nervous system (formaldehyde fluorescence method by Falck et al. 1962 (7); glyoxylic acid fluorescence method by Lindvall and Björklund in 1974 (8)). In 1963, the first dopamine containing neurons in mammals were visualized in the retina of rabbits (9) and rats (10). The dopamine-containing nerve bodies in the mesencephalon were first demonstrated by Dahlström and Fuxe (11). Progress in electron microscopy, immunohistochemistry and immunocytochemistry markedly supported the advances in knowledge about dopamine systems. Soon it has been shown that the brain contains several distinct dopaminergic neuronal systems. They have been classified as:

1. Ultrashort systems (among them are the above mentioned dopaminergic interneurons of the retina, represented by interplexiform amacrine-like neurons).
2. Intermediate-length systems include the tuberohypophysial dopamine neurons, the incertohypothalamic neurons and the medullary periventricular group.
3. Long-length systems, including the nigrostriatal, mesocortical and mesolimbic dopamine projections (12, 13).

First ideas about dopamine receptor mechanisms were formed after the discovery of dopamine-stimulated adenylate-cyclase system. Kebabian and Greengard (14) and Kebabian et al. (15) showed that dopamine increased the adenylate cyclase activity in homogenates of nervous tissue. Brown and Makman (16) described the adenylate cyclase stimulated by dopamine in homogenates of calf and rat retinas. The adenylate-cyclase stimulating activity was attributed to the dopamine receptors (17). The

Abbreviations: *D receptor, dopamine receptor; PET, positron emission tomography*

dopamine-sensitive-adenylate-cyclase model of synaptic receptors allowed speculation about the biochemical mechanisms of dopamine action in the brain. The adenylate cyclase in rat striatal homogenates, or in the calf retina, became an important model for studies of mechanisms of action of dopaminergic agonists and antagonists. It became apparent that a whole class of antipsychotic agents competitively inhibited the dopamine-stimulated adenylate cyclase in a dose-dependent manner (17). However, it soon became clear that the correlation between clinical potency of antipsychotic agents and the inhibition of dopamine-stimulated adenylate-cyclase activity was rather weak. For example, haloperidol, a very potent antipsychotic drug, only weakly inhibited this enzyme (17).

The anomalous behaviour of haloperidol was the keystone in the elaboration of the new idea about two kinds of dopamine receptors (18, 19).

Few years after the discovery of dopamine-stimulated adenylate cyclase, the radioligand binding methods were developed and introduced into the studies of dopamine receptors as well (20, 21). Antipsychotic drugs inhibited the binding of ^{3}H-haloperidol to striatal nerve cell membranes in direct relation to their clinical potencies (22). In these assays the anomaly of haloperidol disappeared. Soon it became clear that some effects of dopamine or of dopaminergic drugs cannot be explained by their binding to the adenylate-cyclase-coupled receptor. The need to give a name to the two types of dopamine receptors was stressed by Spano (23), and both were finally named by Kebabian and Calne (24): the adenylate-cyclase-linked receptor as D_1 receptor, and pituitary dopamine and haloperidol binding site, not linked to the stimulation of adenylate cyclase, as D_2 receptor. Both receptors were later found to be widely distributed in different parts of the brain, and were discovered also in the retina (25).

As mentioned above, the D_2 receptor first seemed not to be connected with adenylate cyclase. But as soon as the selective D_1 antagonist benzazepine SCH23390 was synthesized (26), it was possible to demonstrate that D_2 receptor stimulation in fact decreased the adenylate-cyclase activity. In homogenates where both receptors were present, this effect was overridden by stronger D_1 receptor mediated stimulation of adenylate cyclase (27). Autoreceptors have important role in regulation of dopamine turnover. The presynaptically localized dopamine autoreceptors are of the D_2 type, and were first described by Carlsson (28). They regulate the release and synthesis of dopamine by a negative feedback mechanism (13). The presence of autoreceptors on soma and dendrites of dopaminergic neurons was demonstrated by Aghajanian and Bunney (29).

The electrophysiological studies on dopamine-innervated mammalian neurons in the brain started in mid-sixties (30, 31, 32). The electrophysiological responses of postsynaptic dopamine-target neurons have been studied after iontophoretic application of dopamine, or after stimulation of dopaminergic nuclei. The single unit extra- or intracellular recordings of dopamine-innervated neurons demonstrated inhibition in most cases, but in some cases also facilitation of nerve cell firing (33). However, the electrophysiological data may not reflect the actual physiological function of dopamine released from dopamine neurons. The prevailing hypothesis suggests that the role of dopamine is neuromodulatory, i.e. modulating the effects of other neurotransmitters on target cells (33). The electrophysiological properties of dopamine neurons were to be explored later (34). The new patch clamp technique introduced by Neher and Sakmann (35) became an important tool in studies of dopamine-receptor-regulated ionic channel permeability. D_2 receptors may, in parallel with inhibiting adenylate cyclase and modulating the inositol phosphate production, inhibit the Ca^{2+} entry through voltage-sensitive Ca^{2+} channels and enhance potassium conductance (13, 36). D_1 receptors may, on the other hand, activate the facilitation calcium channels via a cAMP-dependent mechanism (37).

In parallel with biochemical and electrophysiological research, behavioural pharmacology of the dopamine system yielded important information about physiological role of dopamine receptors in the brain. Randrup et al. (38) first described the amphetamine-induced stereotyped behavior in rats. Soon it became clear that the amphetamine-induced behavior depended on the intact function of dopaminergic neurons in basal ganglia and that it could be interrupted by antipsychotic drugs (39). Ernst (40) was the first to suggest that D-amphetamine induced stereotyped behavior by causing a release of endogenous dopamine, and that apomorphine acted as an agonist on the dopamine receptors. The introduction of new behavioural models (for example cycling behavior induced by dopaminergic agents after unilateral lesion of the median forebrain bundle (41)) helped to understand better the functioning of long length dopamine systems. Already in 1979, the first clinical PET study in psychiatry was published by Comar and coworkers (42). They showed images obtained with ^{11}C-chlorpromazine in schizophrenic patients, and thus demonstrated *in vivo* the distribution of the radioligands bound to the dopamine receptors in the human brain. This technique was significantly improved during the past decade, and today different subtypes of dopamine receptors, their gross distribution, total number of binding sites and affinity can be determined in precisely localized regions of the living human brain (43). Up to now, most PET-scan studies of dopamine receptors have been performed for patients with schizophrenia.

The first transplants of fetal nigral cells which survived and produced behavioural dopaminergic effects in rats and monkeys were described by Björklund and Stenevi (44) and by Perlow et al. (45). First case reports on therapeutic effects of human fetal nigral cells transplanted into the brain of parkinsonian patients were published in late 1980's (46, 47, 48). In these early trials, the clinical improvement was modest. Moreover, important ethical questions related to neural transplantation of fetal tissue emerged (49).

With the introduction of radioligand binding methods and the synthesis of specific D_1 and D_2 receptor agonists and antagonists, with the introduction of receptor autoradiography, with the development of more sophisticated behavioural analyses, with the introduction of *in situ* microperfusion techniques, and with the development of PET studies of neuroreceptors in humans, the knowledge about the dopamine systems and receptors increased considerably.

In the late eighties, new important steps were made in the studies of dopamine receptors. New methods, allowing identification and localization of receptor subtypes, appeared with cDNA cloning and *in situ* hybridization. The dopaminergic receptors were found to be members of the large family of G protein coupled receptors (13). Recent cloning studies produced classification of dopaminergic receptors into D_1 family with D_1 and D_5 subtypes, and D_2 family with D_{2S}, D_{2L}, D_3 and D_4 subtypes (50, 51, 52, 53, 54, 55, 56). The receptors of the D_1 family still represent a class of receptors with adenylate-cyclase-stimulating properties but they differ in their affinity for dopamine (D_5 receptor having ten times higher affinity for dopamine than D_1 receptor), as well as in the polypeptide chain length. The receptors of D_2 family do not stimulate adenylate-cyclase activity, some of them even inhibit it. They have different polypeptide chain lengths and different characteristics regarding their affinities for dopamine, haloperidol and clozapine, as well as different aminoacid sequence homology in membrane-spanning domains compared to D_{2L} receptor (13, 57, 58). An alternative classification has been proposed too (59): D_1 receptor family with D_{1A}, D_{1B} and D_{1C} subtypes and D_2 receptor family with D_{2A}, D_{2B} and D_{2C} subtypes. Four subtypes express GTP sensitivity of agonist binding and two subtypes (D_{1C} and D_{2C}) are GTP insensitive/non-cyclase coupled, and apparently linked to a signal-transduction mechanism, which is independent of coupling with G-protein (59).

The functional importance and distribution of different receptor subtypes in different brain regions are fast-moving fields, and great interest has been paid to the molecular genetic studies of psychiatric illnesses. Studies of genetic varieties of D_4 receptors in the human population (60) revealed at least seven polymorphic forms of the D_4. It is possible that the genetic disposition to schizophrenia is linked to the presence of particular subtypes of dopamine receptors in susceptible individuals (61). The genetic polymorphism of receptors may be linked to different responses to neuroleptic drugs (62).

Decades of research have been devoted to the study of short-term signalling events involved in dopamine neurotransmission. In the recent years, rapid expansion of studies of gene expression controlled by dopamine receptors turned the attention of researchers towards the mechanisms through which dopamine exerts its long term effects in the nervous system. Dopaminergic receptors regulate, via the second messengers, the induction of immediate-early genes (for example c-fos). The products of immediate-early genes (for example Fos) regulate transcription of the target genes (63). Dopamine receptors regulate the following peptide and peptide mRNA levels in the striatum: enkephalin (mRNA for proenkephalin), substance P (mRNA for preprotachykinin), dynorphin, substance K (neurokinin A), neurokinin B, neurotensin, somatostatin (64). Dopamine receptors also regulate the synthesis of glutamate decarboxylase in GABAergic neurons of the striatum (65) and of dopamine receptors themselves (66).

The clinical significance of dopamine studies is based on the involvement of this neurotransmitter in severe neurological and psychiatric illnesses. Future research of dopaminergic mechanisms should lead to better understanding of patho(physio)logical processes, as well as to the efficient prophylactic measures and to the development of treatments and drugs with more specific effects.

References

1. Blaschko H. Metabolism and storage of biogenic amines. Experientia 1957; 13: 9-12.
2. Montagu KA. Catechol compounds in rat tissues and in brains of different animals. Nature 1957; 180: 244-5.
3. Weil-Malherbe H, Bone AD. Intracellular distribution of catecholamines in the brain. Nature 1957; 180: 1050-1.
4. Carlsson A, Lindquist M, Magnusson T, Waldeck B. On the presence of 3-hydroxytyramine in brain. Science 1958; 127: 471.
5. Bertler A, Rosengren E. Occurence and distribution of dopamine in brain and other tissues. Experientia 1959; 15: 10-1.
6. Ehringer H, Hornykiewicz O. Verteilung von Noradrenalin und Dopamin (ß-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. Klin Wochenschr 1960; 38: 1236-9.
7. Falck B, Hillarp NA, Thieme G, Torp A. Fluorescence of catecholamines and related compounds condensed with formaldehyde. J Histochem Cytochem 1962; 10: 348-54.
8. Lindvall O, Björklund A. The glyoxylic acid fluorescence histochemical method: A detailed account of the methodology for the visualization of central catecholamine neurons. Histochemistry 1974; 39: 97-127.
9. Häggendal J, Malmfors T. Evidence of dopamine containing neurons in the retina of rabbits. Acta Physiol Scand 1963; 59: 295-6.
10. Malmfors T. Evidence of adrenergic neurons with synaptic terminals in the retina of rats demonstrated with fluorescence and electron microscopy. Acta Physiol Scand 1963; 58: 99-100.
11. Dahlström A, Fuxe K. Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta Physiol Scand 1964; 62: Suppl 232, 1-55.
12. Lindvall O, Björklund A. Anatomy of the dopaminergic neuron systems in the rat brain. Adv Biochem Psychopharmacol 1978; 19: 1-23.
13. Cooper JR, Bloom FE, Roth RH. The biochemical basis of neuropharmacology. Oxford: Oxford University Press, 1991: 285-337.
14. Kebabian JW, Greengard P. Dopamine-sensitive adenyl cyclase: possible role in synaptic transmission. Science 1971; 174: 1346-9.
15. Kebabian JW, Petzold GL, Greengard P. Dopamine-sensitive adenylate cyclase in caudate nucleus of rat brain, and its similarity to "dopamine receptor". Proc Natl Acad Sci USA 1972; 69: 2145-9.
16. Brown JN, Makman MH. Stimulation by dopamine of adenylate cyclase in retinal homogenates and of adenosine 3',5'-cyclic AMP formation in intact retina. Proc Natl Acad Sci USA 1972; 69: 539-43.
17. Iversen LL. Dopamine receptors in the brain. Science 1975; 188: 1084-9.
18. Creese I. Biochemical properties of CNS dopamine receptors. In: Meltzer HY ed. Psychopharmacology: The third generation of progress. New York: Raven Press, 1987: 257-64.
19. Kebabian JW. Brain dopamine receptors: 20 years of progress. Neurochem Res 1993; 18: 101-4.
20. Seeman P, Chau-Wong M, Tedesco J, Wong K. Brain receptors for antipsychotic drugs and dopamine: Direct binding assays. Proc Natl Acad Sci USA 1975; 72: 4376-80.
21. Creese I, Burt DR, Snyder SH. Dopamine receptor binding: differential agonist and antagonist states with ^{3}H-dopamine and ^{3}H-haloperidol. Life Sci 1975; 17: 993-1002.
22. Seeman P, Lee T, Chau-Wong M, Wong K. Antipsychotic drug doses and neuroleptic/dopamine receptors. Nature 1976; 261: 717-9.
23. Spano PF, Govoni S, Trabucchi M. Studies on the pharmacological properties of dopamine receptors in various areas of the central nervous system. Adv Biochem Psychopharmacol 1978; 19: 155-65.
24. Kebabian JW, Calne DB. Multiple receptors for dopamine. Nature 1979; 277: 93-6.
25. Rogawski MA. New directions in neurotransmitter action: dopamine provides some important clues. Trends Neurosci 1987; 10: 200-5.
26. Hyttel J. SCH 23390. The first selective dopamine D-1 antagonist. Eur J Pharmacol 1983; 91: 153-4.
27. Onali P, Olinas MC, Gessa GL. Selective blockade of dopamine D-1 receptors by SCH 23390 discloses striatal dopamine D-2 receptors mediating the inhibition of adenylate cyclase in rats. Eur J Pharmacol 1984; 99: 127-8.
28. Carlsson A. Receptor mediated control of dopamine metabolism. In: Usdin E, Bunney WE Jr. eds. Pre- and postsynaptic receptors. New York: Marcel Dekker, 1975: 49-65.
29. Aghajanian GK, Bunney BS. Dopamine "autoreceptors". Pharmacological characterization by microiontophoretic single cell recording studies. Naunyn Schmiedebergs Arch Pharmacol 1977; 297: 1-7.
30. Bloom FE, Costa E, Salmoiraghi GC. Anesthesia and the responsiveness of individual neurons of the cat's caudate nucleus to acetylcholine, norepinephrine and dopamine administered by microelectrophoresis. J Pharmacol Exp Ther 1965; 150: 244-52.
31. Herz A, Zieglgängsberger W. Synaptic excitation in the corpus striatum inhibited by microelectrophoretically administered dopamine. Experientia 1966; 22: 839-40.
32. Frigyesi TL, Purpura DP. Electrophysiological analysis of reciprocal caudate-nigral relations. Brain Res 1967; 6: 440-56.
33. Bunney BS, Sesack SR, Silva NL. Midbrain dopaminergic systems: Neurophysiology and electrophysiological pharmacology. In: Meltzer HY ed. Psychopharmacology: The third generation of progress. New York: Raven Press, 1987: 113-26.
34. Bunney BS, Walters JR, Aghajanian GK, Roth RH. Dopaminergic neurons: Effect of antipsychotic drugs and amphetamine on single cell activity. J Pharmacol Exp Ther 1973; 185: 560-71.
35. Neher E, Sakmann B. Single-channel currents recorded from membrane of denervated frog muscle fibers. Nature 1976; 260: 799-802.
36. North RA. Drug receptors and the inhibition of nerve cells. Br J Pharmacol 1989; 98: 13-28.
37. Artalejo CR, Ariano MA, Perlman RL, Fox AP. Activation of facilitation calcium channels in chromaffin cells by D_1 dopamine receptors through a cAMP/protein kinase A-dependent mechanism. Nature 1990; 348: 239-42.
38. Randrup A, Munkvad I, Udsen P. Adrenergic mechanism and amphetamine induced abnormal behaviour. Acta Pharmacol Toxicol 1963; 20: 145-57.
39. Cooper SJ, Dourish CT. An introduction to the concept of stereotypy and a historical perspective on the role of brain dopamine. In: Cooper JR, Dourish CT eds. Neurobiology of stereotyped behaviour. Oxford: Clarendon Press, 1990: 1- 24.
40. Ernst AM. Mode of action of apomorphine and dexamphetamine on gnawing compulsion in rats. Psychopharmacologia 1967; 10: 316-23.
41. Ungerstedt U. Postsynaptic supersensitivity after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. Acta Physiol Scand 1971; 83: Suppl 367, 69-93.
42. Comar D, Zarifian E, Verhas M et al. Brain distribution and kinetics of ^{11}C-chlorpromazine in schizophrenics: positron emission tomography studies. Psychiatry Res 1979; 1: 23-9.
43. Sedvall G. PET imaging of dopamine receptors in human basal ganglia: relevance to mental illness. Trends Neurosci 1990; 13: 302-8.
44. Björklund A, Stenevi U. Reconstruction of the nigrostriatal dopamine pathway by intracerebral nigral transplants. Brain Res 1979; 177: 555-60.
45. Perlow MJ, Freed WJ, Hoffer BJ, Seiger A, Olson L, Wyatt RJ. Brain grafts reduce motor abnormalities produced by destruction of nigrostriatal dopamine system. Science 1979; 204: 643-7.
46. Freed CR, Breeze RE, Rosenberg NL et al. Therapeutic effects of human fetal dopamine cells transplanted in a patient with Parkinson's disease. Progr Brain Res 1990; 82: 715-21.
47. Hitchcock ER, Kenny BG, Clough CG, Hughes RC, Henderson BTH, Detta A. Stereotactic implantation of foetal mesencephalon (STIM) in UK experience. Progr Brain Res 1990; 82: 723-8.
48. Lindvall O, Rehncrona S, Brundin P, Gustavii B et al. Neural transplantation in Parkinson's disease: the Swedish experience. Progr Brain Res 1990; 82: 729-34.
49. Hoffer BJ, Olson L. Ethical issues in brain-cell transplantation. Trends Neurosci 1991; 14: 384-8.

50. Bunzow JR, Van Tol HHM, Grandy DK et al. Cloning and expression of a rat D_2 dopamine receptor cDNA. Nature 1988; 336: 783-7.
51. Chio CL, Hess GF, Graham RS, Huff RM. A second molecular form of D_2 dopamine receptor in rat and bovine caudate nucleus. Nature 1990; 343: 266-9.
52. Dearry A, Gingrich JA, Falardeu P, Fremeau RT Jr, Bates MD, Caron MG. Molecular cloning and expression of the gene for a human D_1 dopamine receptor. Nature 1990; 347: 72-6.
53. Sokoloff P, Giros B, Martres M-P, Bouthenet M-L, Schwartz J-C. Molecular cloning and characterization of a novel dopamine receptor (D_3) as a target for neuroleptics. Nature 1990; 347: 146-51.
54. Sunahara RK, Guan H-C, O'Dowd BF et al. Cloning of the gene for a human dopamine D_5 receptor with higher affinity for dopamine than D_1. Nature 1991; 350: 614-9.
55. Van Tol HHM, Bunzow JR, Guan H-C et al. Cloning of the gene for a human dopamine D_4 receptor with high affinity for the antipsychotic clozapine. Nature 1991; 350: 610-4.
56. O'Dowd BF. Structures of dopamine receptors. J Neurochem 1993; 60: 804-16.
57. Schwartz J-C, Giros B, Martres M-P, Sokoloff P. The dopamine receptor family: molecular biology and pharmacology. Semin Neurosci 1992; 4: 99-108.
58. Strange PG. New insights into dopamine receptors in the central nervous system. Neurochem Int 1993; 22: 223-36.
59. De Keyser J. Subtypes and localization of dopamine receptors in human brain. Neurochem Int 1993; 32: 83-93.
60. Van Tol HHM, Wu CM, Guan H-C et al. Multiple dopamine D_4 receptor variants in the human population. Nature 1992; 358: 149-52.
61. Iversen LL. Which D_4 do you have? Nature 1992; 358: 109.
62. Shaikh S, Collier D, Kerwin RW et al. Dopamine D_4 receptor subtypes and response to clozapine. Lancet 1993; 341: 116.
63. Esterle TM, Sanders-Bush E. From neurotransmitter to gene: identifying the missing links. Trends Pharmacol Sci 1991; 12: 375-9.
64. Graybiel AM. Neurotransmitters and neuromodulators in the basal ganglia. Trends Neurosci 1990; 13: 244-54.
65. Segovia J, Tillakarante NJKT, Whealan K, Tobin AJ, Gale K. Parallel increase in striatal glutamic acid decarboxylase activity and mRNA levels in rats with lesions of the nigrostriatal pathway. Brain Res 1990; 529: 345-8.
66. Gerfen CR, Engber TM, Mahan LC, Susel Z, Chase TN, Monsma FJ Jr, Sibley DR. D_1 and D_2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science 1990; 250: 1429-32.

PETINTRIDESET LET RAZISKOVANJA DOPAMINA

Dušan Sket

Izvleček - *Na kratko je prikazan izreden napredek v preteklih 35 letih zgodovine dopamina. Mejniki raziskovanja dopamina so: določitev koncentracije dopamina v posameznih delih možganov (1957-58); odkritje znižane koncentracije dopamina v bazalnih ganglijih bolnikov s Parkinsonovo boleznijo (1960); vpeljava histokemičnih fluorescenčnih metod za prikazovanje kateholaminov v živčnih celicah; prvo odvajanje potencialov s posameznih, z dopaminskimi končiči oživčenih živčnih celic v možganih sesalcev (1965-67); prvi koraki v razvoju od dopamina odvisnih vedenjskih modelov na živalih (1967-71); odkritje od dopamina odvisne adenilatne ciklaze (1971- 72); uvedba radioaktivno označenih spojin v* in vitro *vezavne študije na dopaminskih receptorjih (1975); razdelitev dopaminskih receptorjev na tipa D_1 in D_2 (1979); prva klinična raziskava s pozitronsko emisijsko tomografijo glede vezave 11C-klorpromazina (1979); prvi funkcionalno aktivni presadki fetalnih dopaminskih celic pri živalih (1979); začetek presajanja človeških fetalnih dopaminergičnih celic bolnikom s Parkinsonovo boleznijo, z razmeroma majhnim kliničnim izboljšanjem (1988-1990); študije dopaminske regulacije izražanja genov so se začele v osemdesetih letih; molekularna biologija dopaminskih receptorjev (1988-93): z genskim kloniranjem so ugotovili dva podtipa receptorjev D_1 in štiri podtipe receptorjev D_2. Napredek v raziskovanju dopamina je prispeval k boljšemu razumevanju možganskih funkcij in k možnostim zdravljenja pri nekaterih nevroloških in psihiatričnih boleznih.*

Ključne besede: *dopamin; receptorji; zgodovina medicine*

THE ROLE OF MELATONIN AND DOPAMINE IN RETINAL RENEWAL AND DEGENERATION

VLOGA MELATONINA IN DOPAMINA PRI OBNAVLJANJU IN DEGENERACIJI MREŽNICE

Marko Hawlina[1,2] *Hisako Ikeda*[2]

[1] University Eye Clinic, Medical Centre, Zaloška c. 2, 61105 Ljubljana, Slovenia
[2] Vision Research Unit of Sherrington School, UMDS, The Rayne Institute, St. Thomas' Hospital, London SE1 7EH, Great Britain

Key words: *disc shedding; diurnal rhythm; dopamine; electroretinography; hereditary retinal degeneration; melatonin*

Abstract - *The outer segments of the photoreceptors of the retina are renewed daily by the phagocytosis of discarded outermost discs by the retinal pigment epithelium, whilst new discs are being formed at the inner segments. This process is regulated by retinal melatonin and dopamine. Derangement in phagocytosis by the retinal pigment epithelium causes retinal degeneration in one of the most studied animal model of retinitis pigmentosa, the RCS rat. Similar mechanisms are also proposed as a possible cause of some other clinical conditions, such as Best's vitelliform dystrophy and some drug related retinopathies. This paper reviews studies on photoreceptor renewal process with emphasis on the role of melatonin and dopamine. It also presents our work on the electroretinography which reflects the diurnal rhythmicity of the photoreceptor renewal process. Abnormally high level of retinal melatonin content that we found in RCS rats is discussed as a possible causative factor of degeneration. Finally, our results from electroretinography after long-term application of a dopamine D2 agonist, bromocriptine, are presented in an attempt of therapeutic approach to this type of retinal degeneration.*

Renewal of photoreceptor cells by the retinal pigment epithelium

Young and Bok (1) were the first to present unequivocal autoradiographic evidence that the discarded photoreceptor outer segments are phagocytosed by the retinal pigment epithelium (RPE). The authors used the term *phagosomes* for the inclusion bodies with disc material. During the process of 'disc shedding', the outer segments of rods and cones are ensheathed at their distal ends by the villous projections, derived by the RPE apical membrane. The packets of detached outermost discs are then engulfed and metabolized by the RPE cell (2). Young (3) estimated that in the monkey retina, each rod manufactured 80-90 new outer segment discs every 24 hours, and that the number of discs phagocytosed by an RPE cell daily was about 2,000 in the para-fovea, 3,500 in the peri-fovea and about 4,000 in the periphery. In the rat, each rod outer segment contains on the order of 950 discs. These discs are renewed every 9 to 10 days, representing a daily disc output of roughly 100 discs per rod. Single epithelial cell is in contact with some 250 to 300 rods. Therefore as much as 25,000 to 30,000 discs are phagocytosed daily by a single RPE cell (4).

Rhythmicity of the RPE phagocytosis

The phagocytosis of the shed outer segment discs of the photoreceptors has been shown to occur in bursts, according to an entrained diurnal rhythm that is synchronized by light (5, 6). Although the cellular mechanisms of rod and cone disc shedding appear to be similar, they occur at the opposite times of the day. The rods shed 1-3 hours after light onset, whilst the cones, soon after light offset (7, 8). Interestingly, it appears that the pigment epithelium 'sweeps up' the retina when the respective type of photoreceptors are least used: namely rods in the brightness of the morning, and cones in the dusk of the evening.

The normal rhythm of disc shedding requires alternating periods of light and darkness (9, 10). Constant light blocks disc shedding, but it can be followed in an entrained rhythmic fashion for at least three days in constant darkness (5, 9, 10). Since the discovery that photoreceptor disc shedding is a circadian process (5), substantial attention has been devoted to understanding the regulatory mechanisms that underlie rhythmic events in the photoreceptor-pigment epithelial complex (8).

Melatonin and biological clock in the eye

It has been shown that retinal amines melatonin and dopamine mediate circadian light signals in the retina and play the modulatory role in regulation of outer segment disc shedding (8). The observation that disc shedding is blocked by reserpine, a drug which interferes with the pineal circadian rhythm, was the first suggestion that the pineal hormone melatonin may influence disc shedding (5). However, subsequent studies have indicated that pinealectomy has no effect on disc shedding, suggesting that

Abbreviations: *DA, dopamine; EOG, electrooculogram; ERG, electroretinogram; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NAT, N-acetyl transferaze; RCS, Royal College of Surgeons; RPE, retinal pigment epithelium;*

retinal melatonin may be responsible for regulation of disc shedding (11, 12).

The pineal indoleamine, melatonin (5-methoxy-N-acetyltryptamine), has been implicated in the regulation of various neural and endocrine processes which are cued by the daily change of photoperiod (13). Besides in the pineal gland, autonomous melatonin synthesis has also been shown in the retinal photoreceptors (13). In both pineal gland and the retina, melatonin is synthesized from its precursor serotonin and secreted in a diurnal rhythm with peak levels during the dark period (14). Diurnal rhythms of melatonin synthesis in the presence of light cycles results from a combination of direct effects of light and darkness and regulation by a circadian clock (8, 15, 16). A circadian clock is functionally defined as an oscillator system with the capacity of persistent rhythmicity, with a period of approximately 24 hours in the absence of external timing cues (17). In other words, the phasing of rhythmicity with daily changes will remain the same as that established by cyclic light and dark, even if the cycle is removed (e.g. when subjects are kept in constant darkness).

Day-night differences in retinal melatonin content result from cycling of activity of the rate-limiting enzyme in melatonin synthesis, N-acetyl transferase (NAT), which is elevated during the night and lowered during the daytime (14, 16). The increase of NAT activity in darkness involves a cyclic AMP-mediated increase in protein synthesis (18). In *Xenopus* frog retina, a rhythm of NAT activity persists in eye cups maintained *in vitro*, indicating the presence of a circadian clock in the eye (19). Recently it has been shown in *Xenopus laevis* that the biological clock in the retina, that controls NAT activity, is located within the photoreceptor cells (20). Besides cycling of NAT activity, photoreceptor terminals of rat retinas have been shown to accumulate 3H-serotonin in the light, but not in the dark, while newly synthesized N-acetylserotonin and melatonin are released from retina exposed to dark (21).

The synthesis of retinal melatonin, moreover, appears to be influenced by dopamine. Activation of D2 dopamine receptors suppresses the dark-dependent increase in retinal NAT activity (22). Interestingly, dopamine seems to have no effect on melatonin synthesis in the pineal gland, where its synthesis is regulated by norepinephrine release on sympathic beta-adrenergic receptors (23). Since norepinephrine has no effect on retinal melatonin synthesis (22), the control of melatonin synthesis in the pineal gland and that in the retina appear to be neuropharmacologically separated.

Retinal dopamine

Malmfors (24) was the first to identify catecholamine neurons in the rat retina and found that dopamine (DA) is the predominant retinal catecholamine. The intraretinal synthesis of dopamine has been ascertained by identifying and localizing the enzymes involved in its metabolism (25).

The retinal DA neurons in most species including man are amacrine cells and interplexiform cells with their cell bodies situated in the inner nuclear layer. Amacrine cell dendrites mostly extend horizontally, whilst interplexiform cell dendrites traverse the retina vertically reaching outer retinal layers. In the rat, as well as in humans, overall density of dopaminergic neurons is 20-25 cells/mm^2, out of which up to 50 % are interplexiform (26, 27). It has recently been shown (27) that human dopamine-containing cells form two plexuses with five concentric zones around the macula, which indicates specific importance of DA in modulation of retinal function.

Actions of dopamine in the retina are diverse and depend on activation of different types of dopamine receptors. Kebabian and Calne (28) were the first to demonstrate two types of DA receptors, D1 and D2: D1 receptor has relatively low affinity (micromolar range) for the ligand, and its activation is stimulating adenylate cyclase. D2 receptor, on the other hand, has high affinity for ligand (nanomolar range), and has either no effect or actual inhibitory action on adenylate cyclase. Autoradiographic studies show that D1 receptors are located predominantly in the inner retina and in horizontal cells (29, 30), while D2 type receptors have been predominantly shown in the photoreceptor layer (30, 31) and retinal pigment epithelium (32, 33). Recent cloning studies revealed new subtypes of these receptors, and classified them into D1 family, with D1 and D5 subtypes, and D2 family, with D2, D3 and D4 subtypes (34).

The discovery of the new subtypes of receptors offers an interpretation to the disagreement in the literature regarding the distribution of D2 receptors, detected by mRNA hybridization and that by ligand binding. Whilst binding data indicated high concentration of D2 receptors on photoreceptors in various mammals, including man (30, 31), molecular cloning of D2 receptors in human retina by *in situ* hybridization method failed to show any labelling to the photoreceptor layers (35). Cohen et al. (36) have recently shown by *in situ* hybridization that D2-like dopamine D4 receptor, linked to the inhibition of adenylate cyclase, is located on the photoreceptors of the mouse retina. Thus the D4 receptor may be the one responsible for D2-like ligand binding and related effects at the photoreceptors and perhaps on the RPE.

Another controversy is related to the mode of action of dopamine on photoreceptors and RPE in regulation of rhythmic metabolic processes, since dopaminergic neurons do not synapse on photoreceptors or RPE. Recently, Nguyen-Legros et al. (26) described sclerally directed processes of dopaminergic interplexiform cells that reach the photoreceptor cells in rat and monkey retina. It has been suggested that dopamine, released from these processess can diffuse in paracrine fashion through 75-100 µm to reach the outer segments of photoreceptors and the RPE cells (26). An alternative pathway has been proposed recently which suggests that dopaminergic influences on disc shedding and RPE metabolism are mediated by the processes arising from the ciliary nerves that reach the RPE from the choroidal side (37).

Dopamine synthesis, release and turnover in the retina are influenced by diurnal changes in illumination in opposite manner to those of melatonin (8). The activity of tyrosine hydroxylase, the rate limiting enzyme involved in the biosynthesis of dopamine, and the rates of dopamine release and turnover are higher during the light period (38).

Interactions between the retinal melatonin and dopamine

Retinal dopamine and melatonin, regarded as chemical analogues of day and night (8), exhibit direct mutual inhibitory interaction between them. Functional feedback between retinal dopamine and melatonin is apparent from the following observations:

1. Melatonin, which is synthesized and secreted during the dark period (8, 21), mediates changes in retinal dopaminergic activity through the ability to effectively inhibit dopamine release in picomolar concentrations (39).
2. Dopamine, which is synthesized and released during the light period, acts as a feedback neuromodulator of the retinal melatonin synthesis, since activation of D2-like dopamine receptors reduces NAT activity and the synthesis of melatonin (8, 22).

Role of melatonin and dopamine in regulation of RPE phagocytosis

It has been suggested that the mode of action of melatonin and dopamine is to act as paracrine neuromodulators regulating intracellular second messenger cAMP levels in their target cells (8).

Cyclic changes of melatonin and dopamine in diurnal light transitions convey extracellular signals on respective melatonin and dopamine receptors on photoreceptors and the RPE to cause change in cAMP level within these cells, necessary to initiate phagocytosis (7, 8).

Melatonin has been shown to increase cAMP level (40), while dopamine and D2 agonists reduce it (41). It has been shown that sustained high or low levels of cAMP inhibit phagocytosis by the RPE, and that the change in cAMP level is necessary for the phagocytosis to be triggered (42). Thus, rhythmic variation of cAMP level, caused by change in melatonin and dopamine from night to day levels and vice versa, may be responsible for bursts of disc shedding which occur only at light-transition periods (8, 42) (Fig. 1). Since precise interaction between melatonin and dopamine in modulation of intracellular cAMP levels appears to be essential in regulation of disc shedding and phagocytosis, we investigated some aspects of these mechanisms in the inbred strain of rats with defective RPE phagocytosis.

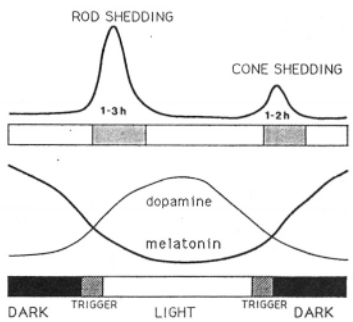


Fig. 1. *Schematic presentation of diurnal bursts of disc shedding with larger peak representing rod shedding approximately 1-3 hours after light onset and smaller peak of cone shedding 1-2 hours after light offset. Shedding appears to be triggered by change in melatonin (which is high in the night) and dopamine (which is high in the daytime) levels at the light transition periods. Adapted after La Vail (5) and Besharse et al. (8).*

Sl. 1. *Shematski prikaz dnevnega ritma obnavljanja mrežnice kaže večji vrh fagocitoze vrhnjih diskov paličic (rod shedding) 1-3 ure po prehodu noči v dan. Manjši vrh predstavlja fagocitozo diskov čepkov (cone shedding), 1-2 ure po prehodu dneva v noč. Fagocitozo sproži (trigger) sprememba nivoja melatonina (ki je visok ponoči) in dopamina (ki je visok podnevi). Prirejeno po: La Vail (5) in Besharse s sod. (8).*

Animal model of impaired RPE phagocytosis - the RCS rat

It has been shown that the pigment epithelium in a strain of RCS (Royal College of Surgeons) rats does not phagocytize outer segment discs (43). This autosomal recessively inherited retinal degeneration in pigmented RCS rats occurs approximately 7-10 days later than in albino RCS rats, and proceeds as follows (44): At birth and during the first two weeks the RCS rat retina is histologically normal. Gradually, rod outer segments elongate, and debris composed of detached discs, which was not cleared by the RPE, starts to appear at the surface of the pigment epithelium on about postnatal day 20-22. The outer segment zone becomes thicker and the first pyknotic photoreceptor nuclei appear at about 25-27th day. From this age until about day 60-70, the outer segments progressively disintegrate, and the outer segment zone is replaced entirely by a debris zone composed of whorls of outer segment membranes, pigment epithelial cell processes, and invading RPE cells. Gradually, debris and entire outer nuclear layer is cleared by invading macrophages and migrated melanin-laden RPE cells. Finally, atrophied outer retinal layers, with the inner retinal layers remaining relatively intact show the retinal appearance which is not unlike to the clinical picture seen in patients with advanced retinitis pigmentosa.

Gradual reduction of electroretinogram (ERG) a- and b-wave, presented by the RCS rats, is accompanying retinal degeneration from around 25th postnatal day until 60-70th day until the responses are virtually eliminated (45). However, the pigment epithelial response measured in albino RCS rats by electrooculogram (46) showed transiently supernormal amplitudes around 15-18th day. In agreement with this early study by Arden and Ikeda, we have found that the c-wave amplitude is also supernormal in dystrophic rats between 17-24th day of age, while a- and b-waves show no difference (Fig. 2). We were therefore interested to investigate the rhythm of the ERG c-wave in predegenerate retina during the peak time of disc shedding and RPE phagocytosis.

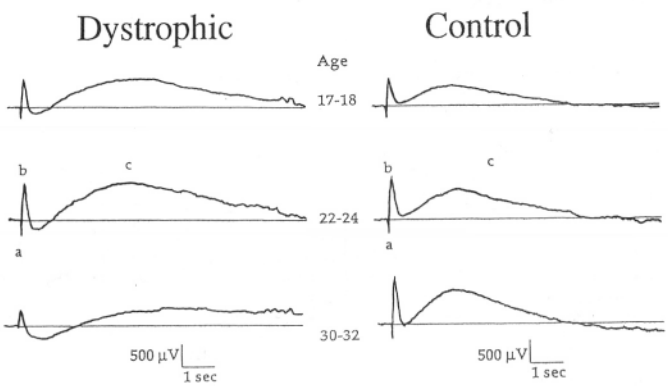


Fig. 2. *Examples of ERGs obtained from dystrophic and control rats of three different age groups (in days). Each trace is an average of responses obtained from three rats. Note that the c-waves of the dystrophic rats aged 17-18 days and 22-24 days are significantly larger and more prolonged than those of their respective controls, while the a- and b-waves of the control and dystrophic rats show no difference. Statistic values: c- wave amplitude between 17-24 days, mean ± standard error of the mean; dystrophic: 720.7 ± 43.3 µV, n = 6; control: 497.3 ± 69.2 µV, n = 6; p < 0.05 (47). Note that the ERG of dystrophic rats 30-32 days old is already greatly reduced compared to that of control rats of the same age. From Hawlina et al. (47), with permission.*

Sl. 2. *Primeri elektroretinogramov pri distrofičnih in kontrolnih podganah v treh starostnih skupinah (v dnevih). Vsak posnetek je povprečje odzivov treh živali. Razvidno je, da je c-val distrofičnih podgan, starih 17-18 dni in 22-24 dni, pomembno višji in podaljšan kot pri kontrolnih živalih, medtem ko se a-val in b-val ne razlikujeta pomembno. Statistične vrednosti: amplituda vala c med 17.-24. dnem, srednja vrednost ± standardna napaka; distrofične živali: 720.7 ± 43.3 µV, n = 6; kontrolne živali: 497.3 ± 69.2 µV, n = 6; p < 0.05 (47). Glej ERG 30-32 dni starih distrofičnih podgan, ki je že močno nižji kot pri kontrolni skupini enake starosti. Iz: Hawlina s sod. (47), z dovoljenjem.*

Rhythm of the ERG c-wave at the peak of rod disc shedding reflects abnormal phagocytosis in RCS rat retinas

Electrically, RPE cells in a single layer, held together by tight junctions, exhibit a high resistance, responsible for generation of the standing potential of the eye and the c-wave of the elec-

troretinogram (48). Since RPE phagocytosis is a process involving dynamic interaction between RPE and photoreceptor outer segments, we investigated how the ERG c-wave (the light-evoked trans-pigment epithelial potential that depends on the integrity of the RPE and photoreceptor outer segments) reflected the circadian rhythmicity of disc shedding and RPE phagocytosis in dystrophic RCS rats and in their heterozygous controls. We therefore developed a method for ERG recording in rats (49) and recorded the ERG during morning transition period, starting 0.5 hours before expected light-on time, and ending 2 hours after it.

We found that, while the ERG c-wave of the control rats showed a distinct amplitude reduction, 1-1.5 hours after expected light-on time (consistent with the peak time of rod disc shedding and phagocytosis), the ERG c-wave of the dystrophic rats was significantly less reduced (Fig. 3 B). In contrast, confirming the finding of Sandberg et al. (50), no difference in the diurnal rhythm of the ERG b-wave was found between the dystrophic and the control rats (Fig. 3 A).

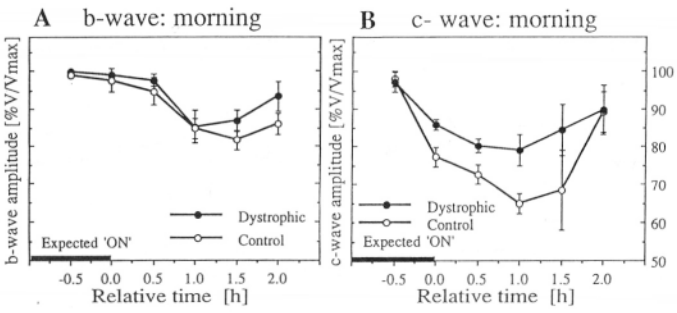


Fig. 3. *Rhythm of ERG b-and c-wave amplitude in dystrophic and control rats during morning transition period, recorded 0.5 hours before expected light onset and 2 hours after it. In (A), transient reduction of b-wave amplitude 1-1.5 hour after expected light onset show no difference between the both strains which indicates that the rhythmicity of disc separation may be preserved in dystrophic rats before degenerative changes occur. In contrast, the ERG c-wave rhythm (B) is significantly less pronounced in dystrophic rats than in controls (Control: 35.1 %; Dystrophic: 21.0 %; $p < 0.05$), which may reflect early defect in phagocytosis. See explanation in Fig. 4. From Hawlina et al. (47), with permission.*

Sl. 3. *Ritem ERG b-vala (A) in c-vala (B) pri distrofičnih in kontrolnih podganah, posnet pol ure pred pričakovanim nastopom svetlobe in dve uri po njem. Slika (A) prikazuje prehodno znižanje amplitude b-vala uro do uro in pol po pričakovanem nastopu svetlobe, ki ne kaže statistično pomembnih razlik med obema skupinama. To kaže na obranjen ritem v ločitvi diskov pred razvojem degenerativnih sprememb. Slika (B) pa kaže statistično pomembno manjše znižanje amplitude c-vala pri distrofičnih živalih, kar lahko odseva zgodnje abnormnosti v fagocitozi. (Kontrolne: 35.1 %; distrofične: 21.0 %; $p < 0.05$). Glej razlago ob sliki 4. Iz ref. 47, z dovoljenjem.*

Our interpretation of results in Figure 3 B is shown in Figure 4: During the process of ingestion of the detached discs, c-wave in control rats is reduced due to a) transient decrease of the RPE apical membrane resistance (and therefore decrease in ratio between apical and basal RPE membrane resistances that decreases c-wave) during the passage of the detached discs into the RPE cells and due to b) photoreceptor membrane disruption during disc detachment. Since in dystrophic retinas ingestion by the RPE does not occur, the RPE apical membrane resistance remains unchanged and does not affect the c-wave. The c-wave may then only be passively reduced due to disruption of the photoreceptor membranes during disc detachment. Since no differences were found in dystrophic and control rats in the rhythm of the b-wave during peak of disc shedding (Fig. 3 A), disc detachment probably occurs alike in both strains before degeneration takes place (47, 50).

Our results are consistent with well known fact that the early abnormality in the RCS rats is located in the RPE rather than in the photoreceptors (43). More importantly, these findings also show that abnormal RPE phagocytosis may be detected at very early stages of degeneration by abnormal rhythm of the ERG c-wave and by its supernormal amplitudes, which may be important for early diagnosis of certain clinical conditions.

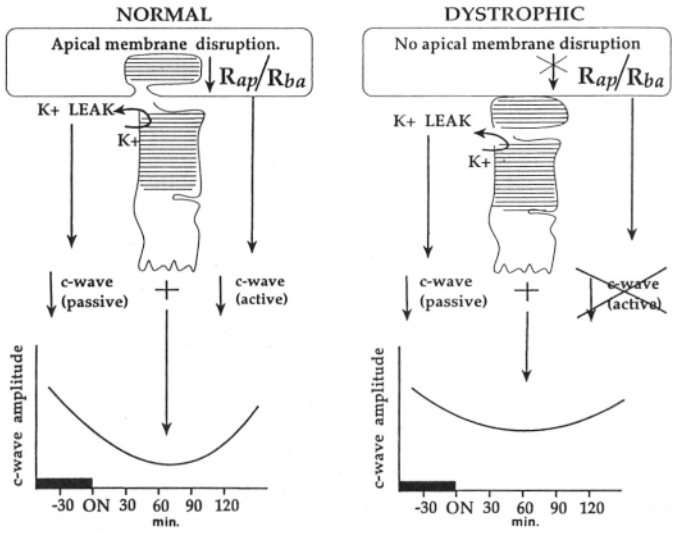


Fig. 4. *Schematic interpretation of the differences in the rhythm of the c-wave amplitude shown in Fig. 3 B. In normal control retinas, c-wave is 'actively' (viewed from the RPE origin) decreased during passage of photoreceptor discs through the RPE apical cell membrane. Disruption of RPE apical membrane transiently decreases the ratio between apical and basal RPE membrane resistances (Rap/Rba), and reduces the c-wave (designated as 'active'). In addition, c-wave is also 'passively' reduced due to photoreceptor membrane disruption and K^+ leak at light stimulation during disc detachment (designated as 'passive'). The sum of both reductions is reflected in larger c-wave reduction of the control rats approximately 60 minutes after expected lights-ON time. In dystrophic retinas, no passage of the discs through the RPE apical membrane occurs, therefore the c-wave may only be 'passively' reduced due to reduced photoreceptor response.*

Sl. 4. *Shematična razlaga razlik v ritmu amplitude ERG c-vala med kontrolno in distrofično mrežnico v sliki 3 B. Pri kontrolni mrežnici (NORMAL) se zaradi prehoda fotoreceptorskih diskov skozi apikalno membrano pigmentnega epitelija zniža razmerje upornosti med apikalno in bazalno membrano (Rap/Rba), zaradi česar se zniža c-val (active). Poleg tega se zaradi disrupcije membrane fotoreceptorjev pri odluščenju diskov in uhajanja K^+ med svetlobnim draženjem c-val tudi 'pasivno' zniža (passive) zaradi znižanja fotoreceptorskega odziva. Vsota obeh znižanj odseva upad amplitude pri kontrolnih podganah. Pri distrofičnih podganah (DYSTROPHIC), kjer do fagocitoze ne pride, ostane upornost apikalne membrane nespremenjena. Upad amplitude c-vala okrog 60 minut po pričakovanem času razsvetlitve (ON) gre tako zgolj na račun znižanja fotoreceptorskega odziva.*

Abnormally high melatonin content in the dystrophic RCS retinas - a possible causative factor of degeneration?

Since, as discussed previously, retinal melatonin may serve as a prime circadian signal in the regulation of RPE phagocytosis with direct synchronizing effect on dopamine release (8), we wondered if melatonin level in dystrophic RCS rat retinas with defective RPE phagocytosis was different from that in control retinas prior to retinal degeneration.

Retinal melatonin content in dystrophic and heterozygous control RCS rats (aged 20-24 days) was, therefore, determined in dark adapted retinas 3-4 hours after morning and evening light transition times using the radioimmunoassay method (47). We found that retinal melatonin content was almost twice as high in dystrophic RCS rats compared to the age matched heterozygous controls in both time points measured (Fig. 5).

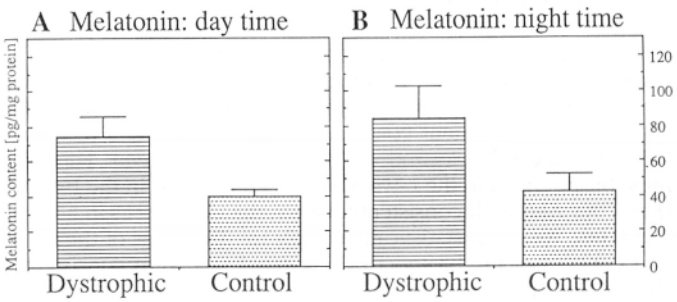


Fig. 5. *Content of melatonin (mean ± standard error of the mean) determined in 10 control and 10 dystrophic rat retinas isolated during subjective daytime (10 AM to noon) (A) and in 10 control and 8 dystrophic retinas isolated during subjective nighttime (10 PM to midnight) (B). Note that the mean melatonin content of the dystrophic retina is significantly higher (Student's t-test: $p < 0.05$) in both A and B. Dystrophic: 74.0 ± 11.5 (A), 84.4 ± 18.5 (B); Control: 39.9 ± 4.0 (A),42.5 ± 9.8 (B). From Hawlina et al. (47), with permission.*

Sl. 5. *Vsebnost melatonina (srednja vrednost ± standardna napaka), izmerjena pri 10 kontrolnih in 10 distrofičnih mrežnicah, odvzetih v temi med subjektivnim dnevom (10h-12h) (A), in 10 kontrolnimi in 8 distrofičnimi mrežnicami, odvzetimi med subjektivno nočjo (22h-24h) (B). Glej pomembno zvišan nivo melatonina v distrofičnih mrežnicah (Studentov t-test: $p < 0.05$) tako v A, kot v B. Distrofične: 74.0 ± 11.5 (A), 84.4 ± 18.5 (B); Kontrolne: 39.9 ± 4.0 (A), 42.5 ± 9.8 (B) Iz: Hawlina s sod. (47), z dovoljenjem.*

This finding opened several questions regarding the possible causes and consequences of excessive retinal melatonin level. Since its synthesis is cAMP dependent (18), melatonin level can be elevated due to conditions that elevate cAMP in the photoreceptors, such as defective phosphodiesterase function (51). Moreover, melatonin itself also elevates cAMP in the photoreceptor-pigment epithelial complex (48). Indeed, an increase in cyclic nucleotides has been universally described in early stages of retinal degenerations in RCS rat and some other species including humans (52, 53).

As described previously, melatonin has been shown to be a potent inhibitor of dopamine release in the retina (39). Thus, excessive melatonin level might block dopamine release on D2-like receptors which would normally reduce cAMP (22, 41). This would abolish the feedback loop for intracellular cAMP homeostasis and result in excessive cAMP formation. In photoreceptors,

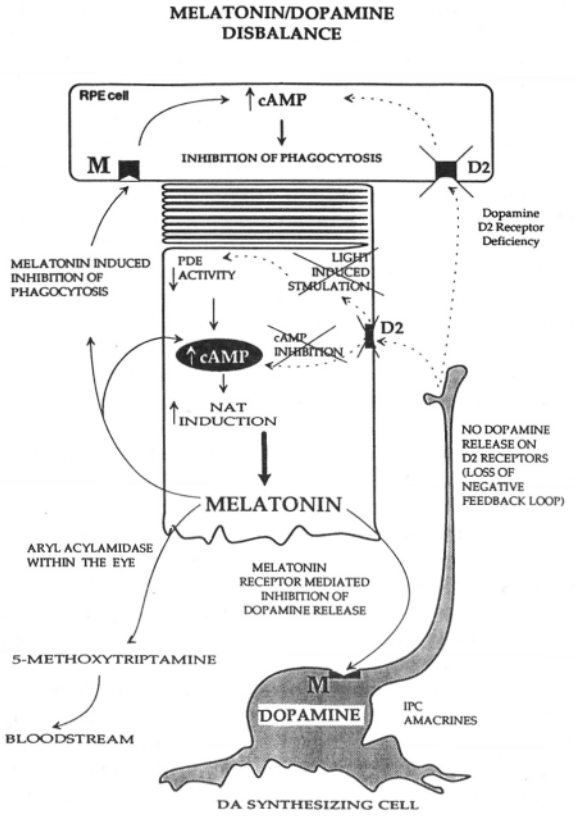


Fig. 6. *Schematic interpretation of possible mechanisms which may cause inhibition of phagocytosis by the RPE cells in the RCS rat. Raised melatonin (47) that diffuses freely to melatonin receptors (M) on DA synthesizing cells (8) inhibits dopamine release on D2 receptors (dysfunction shown by crossed on figure) on the photoreceptor cells (39), causing deficiency in cAMP reducing mechanism (36). This causes a loss of negative feedback loop in the regulation of cAMP. Consequent increase in cAMP formation may in turn activate NAT and melatonin synthesis (18) thus establishing a vicious cycle. On the RPE cells, overactivated melatonin receptors and non-activation of D2 receptors (crossed on figure) causes cAMP accumulation and inhibition of the phagocytosis (40, 42, 57, 58). Some of the potential causes of increased melatonin level may be decreased number of D2 receptors (54) and insufficient PDE activation (crossed on figure) (51, 54), or a defect in enzymatic reduction of melatonin within the eye (55).*

Sl. 6. *Shematična razlaga mehanizmov, ki lahko zavrejo fagocitozo fotoreceptorskih diskov v RPE pri distrofičnih mrežnicah RCS. Zvišan nivo melatonina (47), ki prosto difundira do melatoninskih receptorjev (M) na dopaminergičnih celicah (8) (DA synthesizing cell), inhibira sproščanje dopamina na D2 receptorje (prekrižani na sliki) na fotoreceptorjih (39), s čimer se onemogoči mehanizem za znižanje cAMP (36). S tem pride do funkcionalne izgube negativne povratne zveze v regulaciji cAMP. Posledično zvišanje cAMP zopet aktivira NAT in sproži nadaljnjo sintezo melatonina (18) in s tem vzpostavi* circulus vitiosus. *Čezmerna aktivacija melatoninskih receptorjev in odsotnost aktivacije receptorjev D2 na pigmentnem epiteliju (prekrižani na sliki) sproži čezmerno sintezo cAMP, ki lahko zavre fagocitozo (40, 42, 57, 58). Nekateri možni vzroki za zvišanje nivoja melatonina so znižanje števila receptorjev D2 (54) in nezadostna aktivacija fosfodiesteraze (PDE, na sliki prekrižano) (51, 54), ali okvara v encimski degradaciji melatonina v očesu (55).*

this would, in turn, induce NAT and melatonin synthesis (18) and further inhibit dopamine release, thus creating a vicious circle.
The question here is whether the D2 receptor mediated cAMP reduction is impaired only due to excessive melatonin, or primary abnormality lies in D2 receptors themselves. In keeping with the later possibility, Reading (54) found decreased D2 receptor density and decreased D2 receptor-mediated phosphodiesterase activation in the retina of 2-3 weeks old RCS rats, without change in physical nature of the receptors prior to retinal degeneration. Since reduction of cAMP in photoreceptors is mediated through D2-like receptors (41), abnormally low population of these receptors could indeed cause cAMP increase and induce NAT. Another possibility for genetic defect expression which would increase melatonin level may involve recently described enzymatic pathway for degradation of melatonin within the eye (55). This discussion is summarized in Figure 6.
Following our finding that melatonin content in RCS rat retinas is abnormally elevated (47), Hankins and Ikeda (56) have found that the endogenous dopamine release at horizontal cells was indeed blocked in dystrophic retinas before the onset of retinal degeneration. Furthermore, electrophysiological behaviour of dystrophic retinae showing the lack of endogenous dopamine release was mimicked by application of melatonin in control retinas. This experimental evidence support the hypothesis that in dystrophic retinae, endogenous dopamine release may indeed be blocked by excessive melatonin.
The loss of feedback control in maintenance of rhythmic balance of cAMP level within photoreceptor/RPE complex, caused by elevated melatonin level, may therefore lead to inhibition of phagocytosis. In keeping with this suggestion, it has been shown that melatonin and cAMP inhibited RPE phagocytosis in culture (57). Furthermore, it has recently been shown that photoreceptor disc ingestion is effectively inhibited by nanomolar concentrations of the drugs that increase intracellular cAMP in the RPE, which suggests that phagocytosis may be extremely sensitive to cAMP level (58). We therefore wondered whether pharmacologically induced reduction of melatonin synthesis by the photoreceptors could have some therapeutic effects in RCS rat RPE function.

Dopamine D2 agonist prolongs the survival of RCS rat retinas

Before the interrelation between melatonin and dopamine was discovered, Bubenik and Purtill (59) demonstrated by histology that a dopamine D2 agonist, bromocriptine, slowed-down the progress of degeneration in the RCS rat retinae.
Since recently described melatonin receptor antagonist (60) was not available, and since it has been shown that a D2 agonist, bromocriptine, reduced the activity of the rate limiting enzyme for melatonin synthesis, NAT, by 67 % (22), our question was, whether bromocriptine may also prolong the functional survival of RCS rat retinas, measured by the electroretinography.
To answer this question, we recorded ERGs from dystrophic RCS rats after daily intraperitoneal treatment with bromocriptine, or vehicle, starting at 12th day of age following the same dosage regimen as Bubenik and Purtill (59). We found, that bromocriptine indeed enhanced ERG of dystrophic RCS rat retinas after the 28-31 days of treatment compared to the control rats receiving vehicle solution (measured at the age of 40-43 days). This was most pronounced in the c-wave (Fig. 7 B) and less in the b-wave (Fig. 7 A). Although consistently larger, the differences in a-wave amplitude were not statistically significant. Latencies of the a-, b- and c-waves of the bromocriptine-treated rats were consistently shorter than in vehicle-treated rats, which suggested that retinal function after bromocriptine treatment may be faster, but differences were not statistically significant except in c-wave elicited by maximal light intensity (data not shown).

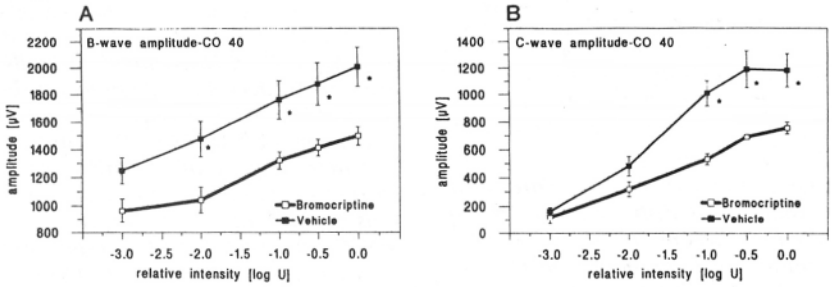


Fig. 7. *ERG b-wave (A) and c-wave (B) (mean ± SEM) in dystrophic retinas after 28-31 days of treatment with bromocriptine recorded at the age of 40-43 days (DY 40). Note significantly higher amplitudes (*, Student's t-test, p < 0.05) comparing to vehicle-treated controls. ERGs were recorded in 10 rats per group with five light intensities, -3.0, -2.0, -1.0, -0.5 and maximal light intensity, -0.0 logarithmic units (log U), corresponding to 13,000 lux. Details on the recording method are described in references 47 and 49.*

Sl. 7. *ERG b-val (A) in c-val (B) (srednja vrednost ± standardna napaka srednje vrednosti) pri distrofičnih mrežnicah po 28-31 dneh dajanja bromokriptina. Glej statistično pomembno višje amplitude v primerjavo s skupino, ki je prejemala nosilno raztopino (*, Studentov t-test, p < 0.05). ERG je bil posnet pri 10 podganah v vsaki skupini s 5 jakosti svetlobe, -3.0, -2.0, -1.0, -0.5 in z maksimalno jakostjo, -0.0 logaritmičnih enot (log U), ki ustreza osvetlitvi 13.000 luksov. Podrobno je metoda opisanav referencah 47 in 49.*

Our electrophysiological results are in agreement with the histological findings of Bubenik and Purtill (59). However, they raise the questions regarding possible mechanisms of bromocriptine action in preserving the RCS rat retinal function, as reflected by the ERG?
Bromocriptine is a predominantly D2-agonist (22). It may be possible that bromocriptine substituted endogenous dopamine action on D2-like receptors on photoreceptor cells to reduce cAMP and melatonin synthesis, and thus disinhibited endogenous dopamine release. Secondly, by activation of D2-like dopamine receptors on the RPE cells, it may have caused change in cAMP level, and thus perhaps triggered phagocytosis by the RPE. This assumption would require electron microscopical confirmation.
The mode of action of bromocriptine may therefore be in restoring the balance between melatonin synthesis and dopamine release. This assumption may be supported by the following findings (8): Inhibition of rate limiting enzyme of melatonin synthesis, NAT, was found to be associated with D2 mediated reduction of cAMP in the NAT containing cells. Accordingly, dopamine blocks the rise in NAT activity, in concentrations far lower than those needed to increase retinal cAMP by D1 receptor activation Pharmacological analysis further showed that NAT activity is suppressed by selective D2 agonists such as bromocriptine, LY 171555 and apomorphine, but not by the D1 selective agonist,

SKF3839-A. Furthermore, the inhibitory effects of dopamine are antagonized by the D2 selective antagonists spiroperidol and metoclopramide, but not by the selective D1 antagonist SCH23390.

Our results suggest that D2 dopamine agonists may have a therapeutic effect in the hereditary retinal degeneration in RCS rats, and open a question, whether the disbalance between retinal dopamine and melatonin may have a causative role also in clinically known conditions of retinal degenerations. In this respect it is interesting to note that the changes observed in the ERGs of Parkinsonian patients and normal subjects receiving dopamine antagonist haloperidol, prompted Cavallacci et al. (61) to speculate, that dopaminergic system may be defective also in patients with retinitis pigmentosa. After treatment with L-DOPA, the authors reported 30 % overall improvement of the visual field in the group of 487 patients. However, these rather sensational results have never been confirmed by any follow-up study. Nevertheless, regarding to above more recent knowledge, this treatment might not have been completely unjustified, although L-DOPA mainly promotes dopamine synthesis and not its release. However, although the degeneration in RCS rats cannot be simply equated with retinitis pigmentosa, it would seem of clinical interest to test the effects of dopamine D2 agonists and melatonin antagonist in very early stages of the disease.

Dopamine and melatonin affect susceptibility to light

Modulation of retinal dopamine and melatonin also seems to have important effects on regulation of light sensitivity of the retina, and may participate in pathophysiology of light-induced retinal damage. Malmfors (24) noted that animals treated with reserpine, a catecholamine depletor, turned from the light and closed their eyes. Photophobia, also observed in psychiatric patients treated with dopamine antagonists (62), may be associated with recently described dopamine D1 receptor-mediated function in regulation of receptive field size by electrotonically coupling of rod-driven horizontal cells in mammalian retina (63).

On the other hand, Bubenik and Purtill (59) also found that exogenous melatonin accelerated retinal degeneration in albino rats exposed to bright light, while treatment with bromocriptine protected the retina from light-induced effects. These results have been recently confirmed (64, 65). In accordance with this, our data in bromocriptine treated control rats show retinal potentials of significantly lower amplitudes (Fig. 8 A and B), mimicking effect of a neutral density filter in the ERG b-wave (Fig. 8 A). In part, this apparent protective effect may be related to the ability of D2 agonists to reverse melatonin-evoked melanosome aggre-

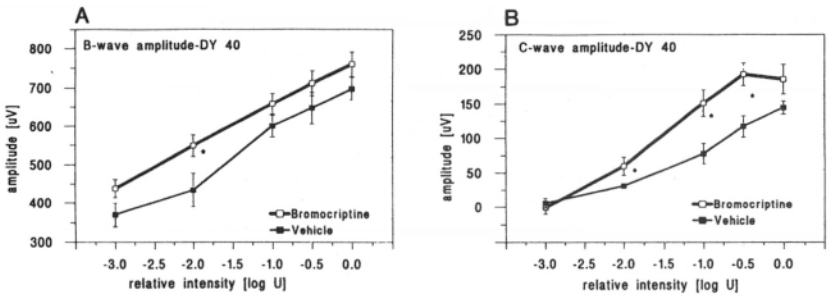


Fig. 8. *ERG b-wave (A) and c-wave (B) (mean ± SEM) in normal heterozygous retinas after 28-31 days of treatment with bromocriptine recorded at the age of 40-43 days (CO 40) with five light intensities as described in Fig. 7. Note that responses are of significantly lower amplitudes than in the vehicle treated group (*, n = 5 per group, Student's t-test, p = 0.02). Parallel slope of reduction of the b-wave (A) in bromocriptine treated group comparing to controls mimicks the effect of a neutral density filter. This may be in agreement with the assumption that D2 mediated mechanisms contribute to long-term light adaptation (8) and that D2 agonists may have protective effect on light-induced damage (59, 64).*

Sl. 8. *ERG b-val (A) in c-val (B) (srednja vrednost ± standardna napaka srednje vrednosti) pri normalnih heterozigotnih mrežnicah po 28-31 dneh dajanja bromokriptina. ERG je bil posnet pri petih podganah v vsaki skupini s petimi jakostmi svetlobe, kot je opisano ob sliki 7. Razvidno je, da so amplitude pomembno nižje kot pri kontrolni skupini, ki je prejemala nosilno raztopino (*, Studentov t-test, p = 0.02). Paralelni potek krivulje znižanja b-vala pri skupini, ki je prejemala bromokriptin, ponazarja učinek filtra nevtralne gostote. To je v soglasju z domnevo, da dopaminski D2 receptorji sodelujejo pri dolgotrajni adaptaciji mrežnice na svetlobo (8) in da utegnejo imeti agonisti D2 zaščitni učinek na mrežnico pred okvarami, povzročenimi s svetlobo (59, 64).*

gation in the RPE and choroid, and make the protective pigment layer thicker or "light-adapted" and thus less susceptible to light (8, 33, 66). These findings suggest that derangement of balance between retinal melatonin and dopamine may be associated with abnormal long-term light adaptation and may participate in light-induced retinal damage.

Dopamine depletion and antagonists cause abnormal retinal function

There is a number of studies showing abnormal retinal function in Parkinson's disease, suggesting that retinal dopamine neurons are also affected (67). Ellis et al. (68) have demonstrated that both rod and cone mediated ERGs are subnormal in patients with Parkinson's disease, but normalized after administration of L-DOPA. Economou and Stefanis (69) have reported abnormal EOG in patients with Parkinson's disease, which indicates that also the function of the RPE is affected. However, the sufficient function of remaining retinal dopaminergic neurons in this disease seem to prevent more severe abnormalities, such as lipofuscin accumulation in the RPE after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, drug that induces a model of Parkinson's disease (70)).

Another body of evidence for the involvement of the dopaminergic metabolism in retinal function comes from the studies of drug-induced retinopathies. Besides chloroquine, thioridazine (Melleril) is the drug that most often causes retinopathy (62, 71). Thioridazine and related phenotiazines are dopamine antagonists which are commonly used for treatment of psychiatric disorders. These drugs bind to melanin in the RPE, and may remain in the cell for prolonged periods after cessation of intake (62, 71). The retinopathy is usually heralded by a complaint of blurred vision. The characteristic pigmentary retinopathy caused

by thioridazine begins with coarse black pigmentary stippling throughout the posterior fundus, while severe retinopathy may be indistinguishable from retinitis pigmentosa (62, 71). Although higher doses are more likely to cause retinopathy, there is no uniform safe dosage limit, suggesting that in some patients the threshold of retinopathy may be lower. Regular fundus and visual field examinations and occasional electrophysiological tests are, therefore, necessary (62, 71). Although the mechanism of this retinopathy has not yet been conclusively determined, the toxic action of dopamine antagonists may involve interference with melatonin synthesis and disregulation of disc shedding and phagocytosis. In keeping with this assumption, it has recently been shown that endogenous dopamine depletion caused by intraocular administration of alpha-methyl-para-tyrosine, a selective inhibitor of the enzyme for biosynthesis of dopamine, increases retinal melatonin level and reduces the electrophysiological responses of the RPE (72). In addition, disturbances of disc shedding have recently been implicated also in some other pathological conditions of the pigment epithelium such as Best's vitelliform dystrophy (73).

In conclusion, recent experimental data on the role of melatonin and dopamine in the retinal function have revealed several potentially important clues to the pathophysiology of inherited and acquired retinal degeneration. In perspective, pharmacological means that will enable effective and accurate cyclic modulation of dopamine and melatonin and their respective second messenger systems within the particular layers of the retina may offer some important therapeutic modalities that await clinical confirmation.

Acknowledgements. Our work reviewed in this article was supported by grants from The British Council, the British Retinitis Pigmentosa Society, Slovene Ministry for Science and Technology, and the Special Trustees of St.Thomas' Hospital. We are most grateful to Peter de Villiers and Gail Turner for technical assistance and to Mark Hankins for valuable comments during preparation of the manuscript.

References

1. Young RW, Bok D. Participation of the retinal pigment epithelium in the rod outer segment renewal process. J Cell Biol 1969; 42: 392-403.
2. Hogan MJ, Wood I, Steinberg RH. Phagocytosis by pigment epithelium of human retinal cones. Nature 1974; 252: 305-7.
3. Young RW. The renewal of photoreceptor outer segments. J Cell Biol 1967; 33: 61-72.
4. Bok D, Young RW. Phagocytic properties of the retinal pigment epithelium. In: Zinn KM, Marmor MF eds. The retinal pigment epithelium. Cambridge, Mass.: Harvard Press, 1979: 148-74.
5. La Vail MM. Rod outer segments disc shedding in rat retina: Relationship to cyclic lighting. Science 1976; 194: 1071-4.
6. Young RW. The daily rhythm of shedding of rod and cone outer segment membranes in the chick retina. Invest Ophthalmol Vis Sci 1978; 17: 105-16.
7. Besharse JC. The daily light-dark cycle and rhythmic metabolism in the photoreceptor-pigment epithelial complex. Prog Retinal Res 1982; 1: 81-124.
8. Besharse JC, Iuvone MP, Pierce ME. Regulation of rhythmic photoreceptor metabolism: A role for post receptoral neurons. Prog Retinal Res 1988; 7: 21-61.
9. Currie JR, Hollyfield JG, Rayborn ME. Rod outer segments elongate in constant light: darkness is required for normal shedding. Vision Res 1978; 18: 995-1003.
10. Goldman A, Tierstein PS, O'Brien P. The role of ambient lighting in circadian disc shedding in the rod outer segment of the rat retina. Invest Ophthalmol Vis Sci 1980; 19: 1257-67.
11. Tamai M, Tierstein P, Goldman A, O'Brien P. The pineal gland does not control rod outer segment disc shedding and phagocytosis in the rat retina and pigment epithelium. Invest Ophthalmol Vis Sci 1978; 17: 558-62.
12. Yu HS, Pang SF, Tang PL. Increase in the level of retinal melatonin and persistence of its diurnal rhythm in rats after pinealectomy. J Endocrinol 1981; 91: 477-81.
13. Wiechmann AF. Melatonin: Parallels in pineal gland and retina. Exp Eye Res 1986; 42: 507-27.
14. Pang SF, Yu HS, Suen HC, Brown GM. Melatonin in the retina of rats: A diurnal rhythm. J Endocr 1980; 87: 89-93.
15. Pang SF, Yu HS, Tang PL. Regulation of melatonin in the retinae of guinea pigs: effects of environmental lighting. J Expl Zool 1982; 222: 11-5.
16. Binkley S. Rhythms in ocular and pineal N-acetyltransferase: A portrait of an enzyme clock. Comp Biochem Physiol 1983; 75A: 123-9.
17. Pittendrigh CS. Circadian systems: General perspective. In: Aschoff J ed. Handbook of behavioral neurobiology. Vol.4. Biological Rhythms. New York: Plenum, 1981: 57-80.
18. Iuvone PM, Besharse JC. Cyclic AMP stimulates serotonin-N-acetyltransferase activity in *Xenopus* retina *in vitro*. J Neurochem 1986; 46: 82-8.
19. Besharse JC, Iuvone PM. Circadian clock in Xenopus eye controlling retinal serotonin N-acetyltransferase. Nature 1983; 305: 133-5.
20. Cahill GM, Besharse JC. Circadian clock functions localized in xenopus retinal photoreceptors. Neuron 1993; 10: 573-7.
21. Redburn DA, Mitchell CK. Darkness stimulates rapid synthesis and release of melatonin in rat retina. Vis Neurosci 1989; 3: 391-403.
22. Iuvone PM, Besharse JC. Dopamine receptor-mediated inhibition of serotonin N-acetyltransferase activity in retina. Brain Res 1986; 369: 168-76.
23. Rohde BH, Chiou GCY. Is ocular melatonin regulated by the adrenergic system? Ophthalmic Res 1987; 19: 178-86.
24. Malmfors T. Evidence of adrenergic neurons with synaptic terminals in the retina of rats demonstrated with fluorescence and electron microscopy. Acta Physiol Scand 1963; 58: 99-100.
25. Da Prada M. Dopamine content and synthesis in retina and *N. accumbens* septi. Pharmacological and light induced modifications. Adv Biochem Psychopharmacol 1977; 16: 311-9.
26. Nguyen-Legros J, Moussafi F, Simon A. Sclerally directed processes of dopaminergic interplexiform cells reach the outer nuclear layer in rat and monkey retina. Vis Neurosci 1990; 4: 547-53.
27. Savy C, Simon A, Nguyen-Legros J. Spatial geometry of the dopamine innervation in the avascular area of the human fovea. Vis Neurosci 1991; 7: 487-98.
28. Kebabian JW, Calne DB. Multiple receptors for dopamine. Nature 1979; 277: 93-6.
29. Zarbin MA, Wamsley JK, Palacios JM, Kuhar M. Autoradiographic localization of high affinity GABA, benzodiazepine, dopaminergic, adrenergic and muscarinic cholinergic receptors in the rat, monkey and human retina. Brain Res 1986; 374: 75-92.
30. Tran VT, Dickman M. Differential localization of dopamine D1 and D2 receptors in rat retina. Invest Ophthalmol Vis Sci 1992; 33: 1620-6.
31. Brann MR, Young WS III. Dopamine receptors are located on rods in bovine retina. Neurosci Lett 1986; 69: 221-2.
32. Bruininck A, Dawis S, Niemeyer G, Lichtensteiger W. Catecholaminergic binding sites in cat retina, pigment epithelium and choroid. Exp Eye Res 1986; 43: 147-51.
33. Dearry A, Burnside B. Dopaminergic regulation of cone retinomotor movement in isolated teleost retinas: I. Introduction of cone contraction is mediated by D2 receptors. J Neurochem 1986; 46: 1006-21.
34. Sket D. Thirty-five years of dopamine research. Zdrav Vestn 1993; 62: Suppl 1: 19-22.
35. Stormann TM, Gdula DC, Wiener DM, Brann MR. Molecular cloning and expression of a dopamine D2 receptor from human retina. Mol Pharmacol 1990; 37: 1-6.
36. Cohen AI, Todd RD, Harmon S, O'Malley L. Photoreceptors of mouse retinas possess D4 receptors coupled to adenylate cyclase. Proc Natl Acad Sci USA 1992; 39: 12093-7.
37. Schütte M, Witkovsky P. Catecholaminergic fibers innervate the retinal pigment epithelium, choroid, sclera and ciliary body in the turtle's eye. Invest Ophthalmol Vis Sci 1991; 32 (Suppl. ARVO): 2891.
38. Iuvone PM, Galli CL, Garrison-Gund CK, Neff NH. Light stimulates tyrosine hydroxylase activity and dopamine synthesis in retinal amacrine neurons. Science 1978; 202: 901-2.
39. Dubocovich ML. Melatonin is a potent modulator of dopamine release in the retina. Nature 1983; 306: 782-4.
40. Blazynski C, Ferrendelli JA, Cohen AI. Indoleamine-sensitive adenylate cyclase in rabbit retina: Characterization and distribution. J Neurochem 1985; 440-7.
41. Cohen AI, Blazynski C. Dopamine and its agonists reduce a light-sensitive pool of cyclic AMP in mouse photoreceptors. Vis Neurosci 1990; 4: 43-52.
42. Edwards RB, Flaherty PM. Association of changes in intracellular cyclic AMP with changes in phagocytosis in cultured rat pigment epithelium. Curr Eye Res 1986; 5: 19-26.
43. Bok D, Hall MO. The role of pigment epithelium in the etiology of inherited retinal dystrophy in the rat. J Cell Biol 1971; 49: 664-82.
44. La Vail MM. The retinal pigment epithelium in rats and mice with inherited retinal degeneration. In: Zinn KM, Marmor MF eds. The retinal pigment epithelium. Cambridge, Mass.: Harvard Press, 1979: 357-80.
45. Dowling JE, Sidman RL. Inherited retinal dystrophy in the rat. J Cell Biol 1962; 14: 73-109.
46. Arden GB, Ikeda H. Effects of hereditary degeneration of the retina on the early receptor potential and the corneo-fundal potential of the rat eye. Vision Res 1966; 6: 171-84.
47. Hawlina M, Jenkins HG, Ikeda H. Diurnal variations in the ERG c-wave and retinal melatonin content in rats with inherited retinal dystrophy. Doc Ophthalmol 1992, 79: 141-50.
48. Steinberg RH, Schmidt R, Brown KT. Intracellular responses to light from cat pigment epithelium: Origin of the electroretinogram c-wave. Nature 1970; 227: 728-30.
49. Hawlina M, De Villiers PLG. Light-emitting diodes and half-cell electrodes in experimental recording of electroretinogram c-wave. Doc Ophthalmol 1992; 81: 227-37.
50. Sandberg MA, Pawlyk BS, Berson EL. Diurnal rhythm in the electroretinogram of the Royal College of Surgeons (RCS) pigmented rat. Exp Eye Res 1988; 46: 929-36.

51. Liu YP, Krishna G, Aguirre G, Chader GJ. Involvement of cyclic GMP phosphodiesterase activator in an hereditary retinal degeneration. Nature 1979; 280: 62-4.
52. Lolley RN, Farber DB. A proposed link between debris accumulation, guanosine 3',5'cyclic monophosphate changes and photoreceptor cell degeneration in retina of RCS rats. Exp Eye Res 1976; 22: 477-86.
53. Sandberg MA, Miller S, Berson EL. Rod electroretinograms in an elevated cyclic guanosine monophosphate-type human retinal degeneration. Comparison with retinitis pigmentosa. Invest Ophthalmol Vis Sci 1990; 31: 2283-9.
54. Reading HW. Dopaminergic hyposensitivity in retinal degeneration. Abstract. Vth ICER Congress Eindhoven 1982.
55. Cahill GM, Besharse JC. Retinal melatonin is metabolized within the eye of *Xenopus laevis*. Proc Natl Acad Sci USA 1989; 86: 1098-102.
56. Hankins MW, Ikeda H. Dopamine pathways in the outer mammalian retina - and abnormalities expressed in hereditary retinal dystrophy. Zdrav Vestn 1993; 62: Suppl 1: 33-38.
57. Ogino N, Matsumura M, Shirakawa H, Tsukuhara I. Phagocytic activity of cultured retinal pigment epithelial cells from chick embryo: Inhibition by melatonin and cyclic AMP, and its reversal by taurine and cyclic GMP. Ophthalmic Res 1983; 15: 72-89.
58. Hall MO, Abrams TA, Mittag TW. The Phagocytosis of rod outer segments is inhibited by drugs linked to cyclic adenosine monophosphate production. Invest Ophthalmol Vis Sci 1993; 34: 2392-401.
59. Bubenik GA, Purtill RA. The role of melatonin and dopamine in retinal physiology. Can J Physiol Pharmacol 1980; 58: 1457-62.
60. Dubocovich ML. Luzindole (N-0774): a novel melatonin receptor antagonist. J Pharmacol Exp Therapeutics 1988, 264: 902-10.
61. Cavallacci G, Genovesi-Ebert F, Mannini A, Marconcini C, Oliva A, Pucci G. Le basi teoriche ed i risultati clinici della terapia con L-DOPA. In: Wirth A, Cavallacci G. eds. Rilazione al LXIV congresso della Societa ophthalmologica Italiana. Roma: Pacini Editore, 1984: 429-42.
62. Botermans CHG. Primary pigmentary retinal degeneration and its association with neurological diseases. In: Vinken PJ, Bruyn GW eds. Neuroretinal degenerations. Amsterdam: North-Holland Publishing Co., 1972: 148-340.
63. Hankins MW, Ikeda H. The role of dopaminergic pathways at the outer plexiform layer of the mammalian retina. Clin Vis Sci 1991; 6: 87-93.
64. Eder DJ, Drake MA, Williams TP. Compression of photoreceptor cell responsivity in the isolated rat retina by physiological concentrations of dopamine: protection against light damage? Invest Ophthalmol Vis Sci 1991; 32 (Suppl. ARVO): 2899.
65. Wiechmann AF, O'Steen KW. Melatonin increases photoreceptor susceptibility to light-induced damage. Invest Ophthalmol Vis Sci 1992; 33: 1894-902.
66. Pang SF, Yew DT. Pigment aggregation by melatonin in the retinal pigment epithelium and choroid of guinea pigs, *Cavia porcellus*. Experientia 1979; 35: 231-3.
67. Nguyen-Legros J. Functional neuroarchitecture of the retina: hypothesis on the dysfunction of retinal dopaminergic circuitry in Parkinson's disease. Surg Radiol Anat 1988; 10: 137-44.
68. Ellis CJK, Allen TG, Marsden CD, Ikeda H. Electroretinographic abnormalities in idiopathic Parkinson's disease and the effect of levodopa administration. Clin Vision Sci 1988; 4: 347-50.
69. Economou SG, Stefanis CN. Changes in electrooculogram (EOG) in Parkinson's disease. Acta Neurol Scand 1978; 58: 44-52.
70. Mariani AP, Neff NH, Hadjiconstantinou M. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment decreases dopamine and increases lipofuscin in the mouse retina. Neurosci Lett 1986; 72: 221-6.
71. Zinn KM, Marmor MF. Toxicology of the human retinal pigment epithelium. In: Zinn KM, Marmor MF eds. The retinal pigment epithelium. Cambridge, Mass.: Harvard Press, 1979: 395-412.
72. Rudolf G, Vivien-Roels B, Pevet B, Kempf E, Wioland N. Dopamine and melatonin interactions in the intact chicken eye. Electrooculographic and biochemical study. Brain Res 1992; 584: 64-70.
73. O'Gorman S, Flaherty WA, Fishman GA, Berson EL. Histopathologic findings in Best's vitelliform macular dystrophy. Arch Ophthalmol 1988, 106; 1261-8.

VLOGA MELATONINA IN DOPAMINA PRI OBNAVLJANJU IN DEGENERACIJI MREŽNICE

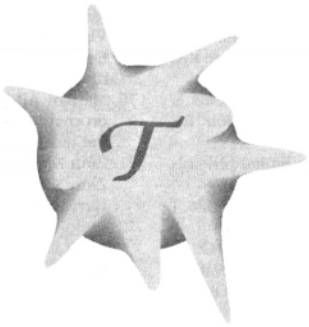
Marko Hawlina, Hisako Ikeda

Izvleček - *Zunanji segmenti fotoreceptorskih celic mrežnice se vsakodnevno obnovijo v procesu fagocitoze odluščenih vrhnjih diskov v pigmentnem epiteliju mrežnice, medtem ko ob vznožju zunanjih segmentov nastajajo novi. Ta proces regulirata melatonin in dopamin. Okvara procesa fagocitoze povzroča eno najbolj raziskanih recesivno podedovanih degeneracij mrežnice pri posebni vrsti podgan tipa RCS, ki jo uvrščajo med eksperimentalne modele pigmentne retinopatije. Podobni vzročni mehanizmi so verjetni tudi pri nekaterih drugih boleznih, kot npr. pri Bestovi viteliformni distrofiji in nekaterih, z medikamenti povzročenih retinopatijah. V prispevku je podan pregled literature o procesu obnavljanja fotoreceptorjev, s poudarkom na vlogi melatonina in dopamina. Predstavljeni so naši izsledki o električnih odzivih pigmentnega epitelija pri podganah RCS, ki odsevajo nenavzočnost fagocitoze in izgubo njene dnevne ritmičnosti še pred razvojem degenerativnih sprememb. Pri tej vrsti živali smo našli tudi abnormno visok nivo melatonina, ki je obravnavan kot možni vzročni dejavnik degeneracije. V zadnjem delu pa so predstavljeni naši rezultati elektroretinografije po dolgotrajnejši aplikaciji dopaminskega D2 agonista, bromokriptina, ki zavira sintezo melatonina, kot poskus terapevtskega pristopa k tej vrsti degeneracije mrežnice.*

Ključne besede: *dedna degeneracija mrežnice; dnevni ritem; dopamin; elektroretinografija; melatonin; obnavljanje fotoreceptorskih diskov*

TAGREN®

tablete *tiklopidin*



- ◇ specifično, učinkovito, novo antiagregacijsko zdravilo
- ◇ nova možnost v preprečevanju posledic aterosklerotičnih žilnih bolezni
- ◇ preprečuje arterijsko trombozo in trombembolične zaplete
- ◇ uspešno varuje pred možgansko kapjo in ponovno možgansko kapjo, srčnim infarktom in umrljivostjo zaradi žilnih bolezni
- ◇ preprečuje ponovno zaporo žile po rekanalizacijskih posegih
- ◇ preprečuje trombozo v dializnih spojih in umetnih dializnih membranah

Doziranje

Običajna doza Tagrena za vse indikacije je 2-krat 1 tableta po 250 mg dnevno med jedjo.

Oprema

30 tablet po 250 mg

Podrobnejše informacije in literaturo dobite pri proizvajalcu.

KRKA

tovarna zdravil, p.o., Novo mesto, Slovenija

DOPAMINE PATHWAYS IN THE OUTER MAMMALIAN RETINA - AND ABNORMALITIES EXPRESSED IN HEREDITARY RETINAL DYSTROPHY

DOPAMINERGIČNI MEHANIZMI V ZUNANJIH PLASTEH MREŽNICE SESALCEV IN OKVARE PRI PRIROJENI DISTROFIJI MREŽNICE

Mark Hankins, Hisako Ikeda

Vision Research Unit of Sherrington School, UMDS, The Rayne Institute, St. Thomas' Hospital, London SE1 7EH, Great Britain*

Key words: *dopamine; horizontal cell; melatonin; neurotransmitter; rat retina*

Abstract - *The dopaminergic pathway affecting rod-driven horizontal cells has been studied, both in the normal pigmented rat and the Royal College of Surgeons (RCS) rat with hereditary retinal dystrophy during the period preceding photoreceptor loss. In the normal retinae, dopamine (2-10 μM) depolarizes horizontal cells and reduces the light response to full-field stimulation, whilst the D1 antagonist, SCH 23390 (10 μM), hyperpolarizes horizontal cells and enhances the full-field light response. These results reveal an endogenous dopamine pathway, mediated by D1 receptors, which regulates horizontal cell response. In the pre-degenerate retina of the RCS rat, SCH 23390 had no effect on the horizontal cells, though they were depolarized by exogenous dopamine. Thus, there appears to be a significant reduction of endogenous dopamine release in these retinae, though the dopamine receptors are normal. Furthermore, SCH 23390 had no effect on horizontal cells in control retinae when applied in the presence of melatonin (200-500 nM). Thus, in the period preceding photoreceptor cell loss, the RCS retina expresses a functional abnormality involving dopaminergic pathways. Since the melatonin content of the RCS retina has been reported to be high, we propose that abnormalities in the dopamine/melatonin system generate a functional deficit in the retina of the RCS rat.*

Introduction

Abnormalities and deficits expressed in retinal dopamine pathways have implications for a number of clinical conditions, which may include Parkinson's disease, age related degeneration and hereditary retinal dystrophy. One clear demonstration of the importance of retinal dopamine pathways is the visual dysfunction expressed in patients with Parkinson's disease. Various visual deficits have been ascribed to Parkinson's patients, including a delay in the visual evoked potential (1). Direct evidence for a retinal involvement came from an electroretinographic study which showed that Parkinson's patients had reduced and delayed ERG b-wave response patterns, which were normalised following L-dopa therapy (2). Indeed, measurements of the post-mortem retinal dopamine content of Parkinson's patients yielded levels which were typically half those found in their age-matched controls (3). However, the precise mechanism and localisation of the deficits at the neuronal level have yet to be resolved. The importance of dopamine pathways in the regulation of retinal function has led us to examine their significance at the outer mammalian retina, using the rat as a model system. The rat retina has been the subject of extensive anatomical and biochemical studies, and has been shown to contain all the cellular dopamine components found in higher primate retinae.

The DA-containing cells have been described in many vertebrate retinae, including human, and appear to be restricted to two anatomical classes of inner retinal neurones, the amacrine cells and the interplexiform cells (4, 5); although the anatomical distinction between the two categories remains unclear (6). Measurements made on the rat retina suggest that there are 18-24 DA-containing cells per mm^2 half of which appear to be of the interplexiform type (7). This sparse, yet apparently influential population of dopaminergic neurones, has a well defined morphology and connectivity, consistent with a role in the regulation of retinal sensitivity (See reviews 5 & 8). In general terms, the DA-interplexiform cells in mammalian retinae receive synaptic inputs at the inner plexiform layer (IPL) from amacrine and bipolar cells. In response to light stimuli, they release dopamine primarily at the outer plexiform layer (OPL) onto horizontal cells and bipolar cells (see 8). However, the most recent studies suggest that they also release dopamine at the IPL onto the AII amacrine cells, whilst the distal processes of the DA-cells reach as far as the photoreceptor outer segments (9, 10).

The effects of DA are mediated by membrane receptors which have been broadly divided into two categories, the D1 and the D2 types (11). Recent receptor cloning studies have, however,

* **Address for correspondence:** Dr. M. W. Hankins, Gunnar Svaetichin Laboratory, Depts. of Biology and Physics, Imperial College at Silwood Park, Ascot, Berks SL5 7PY, Great Britain.

Abbreviations: *DA, dopamine; IPL, inner plexiform layer; L-sulp, L-sulpiride; NAT, N-acetyl transferase; OPL, outer plexiform layer; RCS, Royal College of Surgeons rat; SCH, SCH 23390*

demonstrated that the D2 receptors are a heterogeneous group with sub-classes identified as D2S, D2L, D3, and D4 (12). Dopamine receptors occur on virtually all morphological classes of neurones throughout the retina, and this is reflected in electrophysiological studies on a broad-range of species, primarily non-mammalian, which reveal a multiplicity of DA effects on the light-evoked responses of retinal cells (Recent reviews: 5 & 8). Perhaps the most clearly established of the DA-mediated synaptic mechanisms is the uncoupling of cone- driven horizontal cell gap-junctions (13). Recent studies in our laboratory have therefore examined the principal influence of dopamine upon the rod-driven horizontal cells in the rat retina (14). Here, we will provide an overview of the basic properties of the dopamine system at the OPL of the normal rat retina.

The Royal College of Surgeons (RCS) rat is an extensively studied animal model of hereditary retinal dystrophy, in which an autosomal recessive defect is manifested as an apparent reduction in the phagocytosis of rod outer-segments. In this model, the photoreceptors begin to degenerate in around 24 days, and the animal eventually becomes blind in around 60 days (15). In an anatomical study, Bubenik and Purtill (16) first reported that the photoreceptor degeneration in the case of the RCS rat could be reduced by treatment with dopamine agonists, but was also exacerbated by melatonin. Furthermore, recent studies showed that at the predegenerate stage in the RCS rat retinal melatonin levels are high (17); from which the authors concluded that dopamine pathways may be abnormal in these animals. We have, therefore, examined the dopamine pathway of these animals electrophysiologically, at the horizontal cell level, during the stages preceding retinal degeneration.

Methods

Preparation: Adult pigmented rats (PVG 90 - 120 days), or both homozygous and heterozygous pigmented dystrophic (RCS 17 - 24 days) rats, were dark adapted (1-3 hours) prior to experiments. The animals were anaesthetised with urethane (1.5 g/kg I.P.) prior to enucleation under dim-red light. The eyeball was hemisected, the neural retina separated from the pigment epithelium, and placed photoreceptor side up in a superfusion chamber. The preparation was superfused with a physiological solution of the following composition: NaCl - 124 mM, KCl - 2.6 mM, $MgSO_4$ - 1.3 mM, $CaCl_2$ - 1 mM, $NaHCO_3$ - 26 mM and D-glucose - 15 mM (analar grade reagents). This solution was gassed with 95 % O_2, 5 % CO_2 (titrated to pH 7.8 with NaOH), and delivered to the recording chamber at a rate of 5 $ml.min^{-1}$ and at a temperature of 35.5 ± 0.25 °C. Normal superfusate, or a combination of various drug containing perfusates were selected by a six way valve.

Light Stimulus Parameters: Full-field light or combinations of spots and annuli of various sizes were used to stimulate the retina (520 nm, E_{max} 0.2 $\mu W.cm^{-2}$). The stimuli were focused onto the preparation from above, via the dissecting microscope, and were presented for 100-1000 ms and at intervals of 5-10 s. The stimulus intensity was controlled by neutral density filters.

Electrophysiological Methods: The principal methods have been described previously (14, 18). Glass microelectrodes were produced from 1.2 mm fibre-containing glass using a Livingston puller. These were filled with 3 M KCl, and had resistances in the range 100 - 180 M Ohms. Electrode potential was monitored using an Axoclamp 2A. Rod-driven horizontal cells were identified according to standard light response characteristics including sensitivity and receptive field properties (14).

Drugs: Drugs used in these studies were obtained from the following sources: dopamine, melatonin, ascorbate - Sigma; SCH 23390, L-sulpiride - Research Biochemicals Incorporated (USA). All dopamine containing solutions contained 200 µM ascorbate as an antioxidant. This concentration of ascorbate had no effect on the electrophysiological responses of horizontal cells (n = 12).

Results

Effects of dopamine and selective dopamine antagonists on horizontal cells in the normal adult (PVG) retina

In the course of these studies, recordings were made from a total of 63 rod-driven horizontal cells in normal PVG retinae. The mean dark-resting membrane potential for these cells was -27 ± 3.7 mV (mean ± 1 SEM). The light-driven responses of these cells are characterised by a slow, maintained hyperpolarization known as the S-potential. The S-potential response of these cells represents the light-evoked reduction in glutamate release from photoreceptors (18). When dopamine is applied to these cells (2-10 µM), it evokes a depolarization (2-22 mV), which is accompanied by a clear reduction (10-60 %) in the light evoked response to a full- field stimulus. These effects were observed in 23 of 24 cells examined, and the typical dose dependent effects of dopamine are illustrated in Figure 1A.

The effects of selective dopamine antagonists on horizontal cells were examined in a total of 24 PVG horizontal cells. The D1 antagonist SCH 23390, at 10-100 µM concentrations, hyperpolarized horizontal cells (5-20 mV) and enhanced their light-

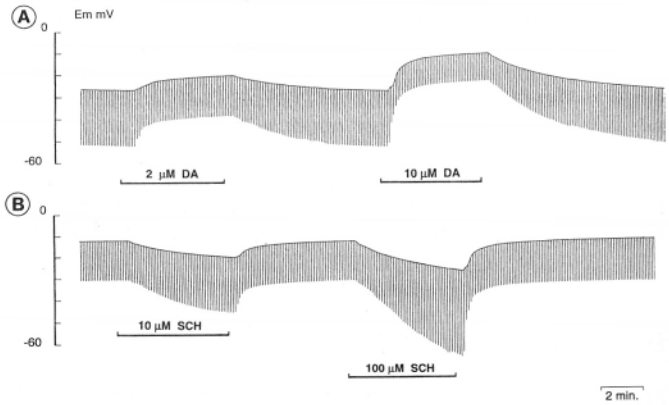


Fig. 1. *The dose-dependent effects of (A) dopamine and (B) the D1 antagonist SCH 23390 upon the dark-resting membrane potential (Em, mV) and light-evoked responses of rod-driven horizontal cells in the rat retina. Each downward deflection on the resting potential is a hyperpolarizing light response to a full-field, 520 nM, light stimulus. Drugs are applied at the times indicated by the bars beneath each recording. (A): 2 µM and 10 µM dopamine (DA) result in dose-dependent depolarizations, accompanied by a reduction in the light response. The effects of dopamine are rapidly reversed following washout. (B): 10 µM and 100 µM SCH 23390 (SCH) evoke dose-dependent hyperpolarizations, accompanied by a marked enhancement of the light response.*

Sl. 1. *Slika prikazuje od doze odvisne učinke dopamina (A) in D1 antagonista SCH 23390 (B) na mirujoči membranski potencial v temi (Em, mV) in na svetlobno izzvane odzive horizontalnih celic v mrežnici podgane. Vsak odklon navzdol od mirujočega potenciala predstavlja hiperpolarizacijo po svetlobnem draženju (520 nM) s celim poljem. Čas aplikacije farmakov je označen pod vsakim posnetkom. (A): Dodatek 2 µM in 10 µM dopamina (DA) povzroči depolarizacijo horizontalnih celic, ki je odvisna od doze. Depolarizacijo spremlja upad amplitude odzivov na svetlobno draženje. Učinki dopamina se po odplaknjenju hitro izgubijo. (B): 10 µM in 100 µM SCH 23390 (SCH) povzroči od doze odvisne hiperpolarizacije, ki jih spremlja povečanje odzivov na svetlobno draženje.*

evoked response to a full-field stimulus in a dose dependent manner (Fig. 1B), and these effects were observed in all 20 cells studied. In contrast, the D2 antagonist L-sulpiride (100 μM) had no effect on either the dark resting potential or the light response of any of the 18 cells studied (not illustrated, though see Fig. 4A). The pharmacology of the exogenous DA-evoked effects was examined by co-application of dopamine and the selective D1 and D2 antagonists. The results of these experiments are illustrated in Figure 2. Both the depolarization and the reduction in light response were reversed by the D1 antagonist SCH 23390 (Fig. 2A; 10 μM; n = 8), but unaffected by the D2 antagonist L-sulpiride (Fig. 2B; 100 μM; n = 7).

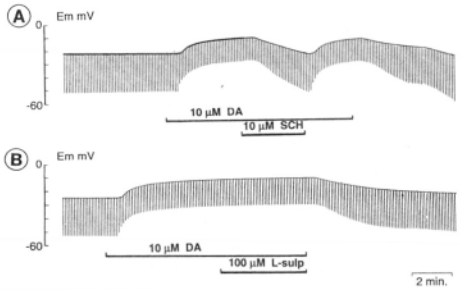


Fig. 2. *Effects of a D1 antagonist, SCH 23390 (A) and the D2 antagonist L-sulpiride (B) on the exogenous DA-evoked effects upon horizontal cells. Note that in (A) the effects of dopamine (DA) are reversed by the subsequent addition of 10 μM SCH 23390 (SCH); whilst in (B) 100 μM L-sulpiride (L-sulp) has no effect upon the DA-evoked response.*

Sl. 2. *Učinki D1 antagonista, SCH 23390 (A) in D2 antagonista, L-sulpirida (B) na horizontalne celice, predhodno izpostavljene dodatku dopamina. Kot je razvidno iz (A) so učinki dopamina (DA) preprečeni z dodatkom 10 μM SCH 23390 (SCH), medtem ko (B) dodatek 100 μM L-sulpirida (L-sulp) ni imel nikakršnega vpliva na odzive, predhodno povzročene z dopaminom.*

Effects of dopamine upon horizontal cell receptive fields

Previous studies in non-mammalian retinae have demonstrated the effect of dopamine on the radial electrotonic coupling between adjacent cone-driven horizontal cells (13, 19). Such effects will modify the receptive field properties of horizontal cells. One method for studying this phenomena is to present the cells with alternating stimuli consisting of a central spot or an annulus surround. Initially, the stimuli are manipulated in intensity, so as to evoke approximately equal amplitude light responses, then dopamine is applied whilst presenting alternate spot and annulus stimuli. One such experiment is illustrated in Figure 3; depolarization of the cell by dopamine was accompanied by a rapid and selective reduction in the annulus response (A), compared to that evoked by a central spot (C) (Fig. 3A). Therefore, when the ratio of A/C response is displayed (Fig. 3B), there is approximately a 50 % reduction during dopamine application. Thus, the cell response to the annulus, namely that to light presented outside the dendritic field, is greatly reduced. We have observed similar responses in all 12 cells examined by this method. Our previous studies (14), using receptive field plots generated by light spots displaced left and right of centre, have also shown that dopamine significantly sharpens the receptive field profile (reduction in cell coupling), whilst D1 antagonists broaden the receptive field (increase cell coupling).

The dopamine pathway in the predegenerate retina of the RCS rat

Having established the properties of the dopamine pathway affecting horizontal cells, we examined these phenomena in the retina of the RCS rat at postnatal days 17-24, namely the period which precedes photoreceptor degeneration. Recordings were made from age-matched groups of control (RCS-rdy$^+$p$^+$) and dystrophic (RCS-p$^+$) progeny which were raised under identical conditions. Dopamine and dopamine antagonists were applied to a total of 24 control and 24 dystrophic retinal horizontal cells. The results of these studies are illustrated by two typical recordings from age-matched animals in Figure 4.

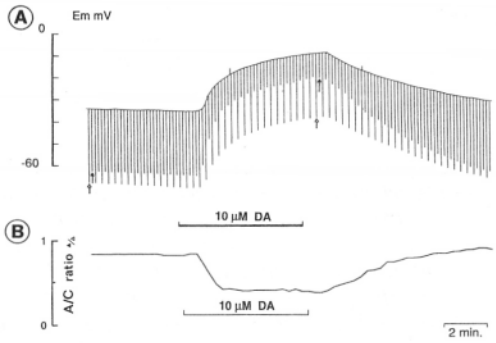


Figure 3. *(A): The differential effect of dopamine on the horizontal cell response to peripheral or central light stimuli. The cell is stimulated alternately by a central spot (100 μm diameter) and an annulus (internal diameter 150 μm, external diameter 4 mm), both centred on the recording electrode. Central spot stimulation C' is denoted by the open arrow and that by the annulus A' by the filled arrow. Note that 10 μM dopamine (DA) depolarizes the cell, and selectively reduces the amplitude of the annulus response. (B): A plot of the concurrent changes in the annulus/central (A/C) ratio, showing the rapid and selective loss of surround sensitivity evoked by dopamine, and its subsequent recovery.*

Sl. 3. *Slika (A) prikazuje različen učinek dopamina na odziv horizontalnih celic na periferno in centralno svetlobno draženje mrežnice. Celice smo dražili izmenjaje z dražljajem v obliki točke (premer 100 μm) ter kolobarja (notranji premer 150 μm, zunanji premer 4 mm), oba dražljaja pa sta bila centrirana na snemalno elektrodo. Centralno točkovno draženje 'C' je prikazano z odprto puščico, draženje s kolobarjem 'A' pa s polno puščico. Razvidno je, da 10 μM dopamin (DA) depolarizira celico in selektivno zniža amplitudo odziva na draženje s kolobarjastim dražljajem, ne pa tudi odzivov na točkovno draženje. (B): Slika prikazuje razlike sočasnih sprememb med draženjem s točkastim in kolobarjastim dražljajem, izraženo kot razmerje (A/C). Viden je selektivni upad občutljivosti okolice centra, ki ga povzroči dodatek dopamina, in povratek na osnovne vrednosti po prenehanju dodajanja.*

Dopamine (10 μM) consistently depolarized horizontal cells in both control (Fig. 4A; n = 23 of 24 cells) and dystrophic (Fig. 4B; n = 24 of 24 cells) retinae. The effects of dopamine, like those in the adult PVG retina, were associated with a reduction in the light-evoked response to full-field stimulation. Thus, dopamine receptors are present in both normal and dystrophic retinae. Horizontal cells from both control and dystrophic animals were, like the PVG retina, unaffected by the D2 antagonist L-sulpiride (100 μM; Fig. 4A & 4B). However, the application of the D1 antagonist SCH 23390 did reveal a significant difference. Whilst cells from the control retinae were hyperpolarized, and the full- field light evoked response enhanced by 10 μM SCH 23390 (10 μM, n = 13 of 14 cells), cells recorded in the dystrophic retinae were unaffected by SCH 23390 at either 10 or 100 μM concentrations (n = 15). This suggests there is a significant reduction in endogenous retinal dopamine release in the dystrophic animals, in which the retinae are destined to degenerate.

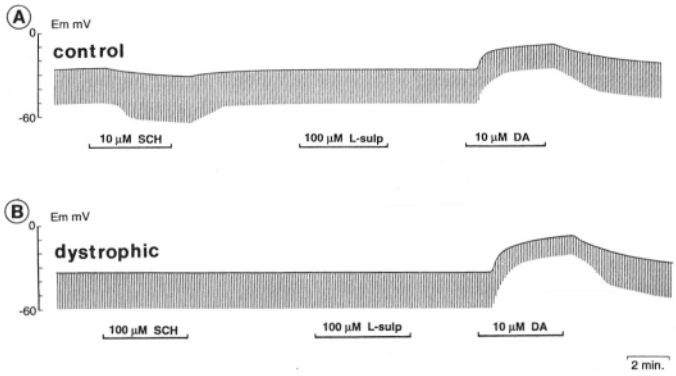


Fig. 4. *A comparison of the effects of dopamine and dopamine antagonists on horizontal cells recorded in retinae isolated from heterozygous control (A) and homozygous dystrophic (B) RCS rats (PD 22). Note that in (A) 10 μM SCH 23390 hyperpolarizes the cell and enhances the full-field light response, 100 μM L-sulpiride has no effect, whilst 10 μM dopamine depolarizes the cell and reduces the light response. In (B) neither 100 μM SCH 23390 nor L-sulpiride has any effect on the cell, whilst 10 μM dopamine depolarizes the cell and reduces the light response.*

Sl. 4. *Primerjava med učinki dopamina in dopaminskih antagonistov na horizontalne celice mrežnic kontrolnih heterozigotnih podgan (A) ter homozigotnih distrofičnih (B) RCS podgan starosti 22 dni. Iz slike (A) je razvidno, da 10 μM SCH 23390 hiperpolarizira celico in ojači odziv na draženje s celim poljem. Dodatek 100 μM L-sulpirida nima učinka, medtem ko 10 μM dopamin depolarizira celico in zniža odziv na svetlobno draženje.*

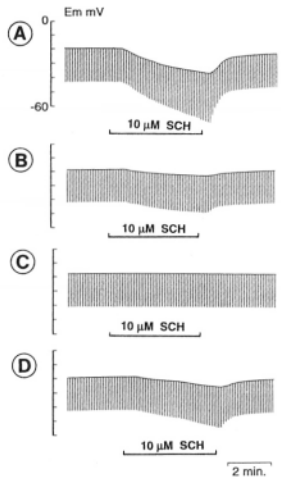


Fig. 5. *Melatonin inhibits the horizontal cell response to SCH 23390 in the heterozygous control RCS retina. This figure is a recording from a single horizontal cell. (A): Shows the control response to 10 μM SCH 23390 (SCH). (B): 5 minutes after the application of 200 nM melatonin, the response to SCH is reduced. (C): 15 minutes after the application of melatonin, the response to SCH is abolished. (D): Note that following 25 minutes of washout, the response to SCH returns.*

Sl. 5. *Melatonin inhibira odziv horizontalnih celic na SCH 23390 v kontrolni mrežnici. Slika (A) prikazuje odziv kontrolne mrežnice na 10 μM SCH 23390 (SCH). Slika (B) kaže znižanje odziva kontrolne mrežnice na SCH 23390 pet minut po dodatku 200 nM melatonina. Slika (C) prikazuje popolno odsotnost odziva mrežnice na SCH 15 minut po dodatku melatonina, ki pa se 25 minut po prenehanju dodajanja melatonina spet povrne.*

Potential involvement of melatonin in the regulation of dopamine release

Given the proposal that retinal dopamine release is modulated by melatonin (20) and that the endogenous retinal melatonin content is abnormally high in the retina of the RCS rat at the predegenerate stage (17), we examined the effect of exogenous melatonin application to heterozygous control RCS retinae in relation to endogenous dopamine release, assessed by the effect of the D1 antagonist, SCH 23390. We found that melatonin (200-500 nM) abolished the response to SCH 23390 in the retinae of the control RCS rat (Fig. 5; n = 6). Thus, in the presence of exogenous melatonin, endogenous dopamine release appears to be significantly reduced, which indicates that the application of excess melatonin mimics the condition found in the dystrophic retina.

Discussion

We have demonstrated the principal effects of dopamine pathways upon horizontal cells in the outer mammalian retina. Dopamine applied to the retina in μM concentrations depolarized rod-driven horizontal cells, an effect which was clearly accompanied by a reduction in the amplitude of the light evoked response to full-field (whole retinal) stimulation. We have also established that endogenous dopamine is released upon horizontal cells, since the D1 antagonist hyperpolarizes horizontal cells and enhances their responses to full-field stimuli. The effects of dopamine on horizontal cells are mediated by D1 and not D2 receptors, since they were antagonised by SCH 23390, not by L-sulpiride.

Retinal horizontal cells summate electrical signals over large areas of the retina, much wider than that of their dendritic (photoreceptor driven) field. This property gives rise to the so called S-space (21), which originates from the extensive electrotonic coupling between adjacent horizontal cells. Previous studies in lower vertebrates have established that the coupling between cone-driven horizontal cells is regulated by dopamine (13, 19). Here we have demonstrated that dopamine clearly affects the coupling between adjacent rod-driven horizontal cells, since our studies using central spot and surround annuli showed that dopamine selectively reduces the response to surround stimuli, which are mediated by photoreceptors outside the horizontal cell dendritic field (Fig. 3). Since horizontal cells provide the surround input to bipolar cells (22), dopamine pathways must have a critical role in the initiation of centre-surround organisation in the mammalian retina, thus deficiencies in retinal dopamine activity should be reflected by a reduction in spatial contrast sensitivity. Consistent with the wide spread distribution of retinal dopamine receptors, it is apparent from recent studies that there exist multiple DA-regulated cellular mechanisms, and therefore numerous sites of action for released dopamine within the retina. In Table 1, we have summarised the currently established sites of action for dopamine in the mammalian neural retina.

DA-antagonists block the activity of endogenous dopamine released onto the particular receptors of cells under study. Thus, our finding in the predegenerate RCS rat, that SCH 23390 failed to affect the horizontal cell response, suggests that there is a significant reduction in the level of endogenous dopamine release in these retinae compared to their age matched heterozygous controls (Fig. 3). Previous studies have shown that retinal dopamine levels in the RCS rat at 14 and 30 days are normal, with no significant differences between the dystrophic and control retina (24). In addition, we have recently examined the dopamine containing cells in these retina, and found them to be normal (Hankins and Ikeda, unpublished observation). This suggests that the pharmacological differences we have observed between control and dystrophic retinae, at the predegenerate stage, can only be explained by a reduction in dopamine release and not by the ab-

sence of DA cells or a reduction in retinal dopamine content. Since horizontal cells generate the receptive field surround of retinal bipolar cells, we can conclude that spatial visual processing will be abnormal in the predegenerate RCS retina. However, given the numerous DA-regulatory mechanisms outlined in Table 1, we would predict there to be other functional abnormalities in these retinae.

Tab. 1. *The established effects and sites of action of dopamine at the cellular level in the mammalian retina.*

Tab. 1. *Učinki in prijemališča delovanja dopamina na celičnem nivoju v mrežnicah sesalcev.*

Site of Action Mesto učinka	Mode of Action Način delovanja
Photoreceptors	Reduction of the light sensitive pool of cAMP; via D4 receptor; (29)
Fotoreceptorji	Znižanje na svetlobo občutljivega poola cAMP; prek D4 receptorjev; (29)
Horizontal cells	Modulates the electrotonic coupling of rod driven horizontal cells; via D1 receptor; (14)
Horizontalne celice	Modulacija elektrotoničnega stika (coupling) horizontalnih celic prek D1 receptorjev; (14)
Amacrine cells	Affects the coupling of AII amacrine Cells; via D1 receptor; (9)
Amakrine celice	Vpliv na stik AII amakrinih celic prek D1 receptorjev; (9)
Ganglion cells	Silent DA-synapses, active in early development; via D2 receptor; (23)
Ganglijske celice	Tihe DA-sinapse, ki so aktivne v zgodnji fazi razvoja; prek D2 receptorjev; (23)

The obvious question arises as to the mechanism which underlies the reduction in endogenous dopamine release in the dystrophic retina. Our finding that exogenous melatonin abolished the response to SCH 23390 in control retinae (Fig. 5) is consistent with melatonin acting as a potent inhibitor of endogenous dopamine release (20). Furthermore, our results provide support for the prediction of a dopamine deficiency in the RCS rat by Hawlina et al. (17), who reported abnormally high retinal melatonin content in these retinae.

It has been suggested recently that retinal DA-release may represent a critical paracrine signal for slow light-adaptation, initiating a number of discrete regulatory processes, and that this mechanism also involves an interaction with melatonin (8, 25). In the retinae of numerous species, including man, melatonin synthesis is confined to photoreceptors and to some cone bipolar cells (26). The level of melatonin synthesis governs the level of release (27), whilst the synthesis of melatonin is clearly linked to the light/dark state of the photoreceptors, since the activity of N-acetyltransferase (NAT), one of the rate limiting synthetic enzymes, is dependent on intracellular calcium and cyclic AMP (28). Whilst melatonin is an inhibitor of retinal dopamine release (20), dopamine, through its action at the D2 or D4 sites on photoreceptors, inhibits melatonin synthesis (28, 29). These observations are consistent with dopamine and melatonin functioning in contra-regulatory roles in slow-light adaptation. It is tempting to speculate that abnormalities in the retinal dopamine/melatonin system may have a role in conditions such as retinitis pigmentosa, where deficits in adaptation are commonly described.

The site of the primary abnormality in the RCS retina appears to be located at the retinal pigment epithelium (30). However, it is possible that early abnormalities in the photoreceptors result in an increase in melatonin synthesis. Assuming that this excess melatonin were released, it would inhibit retinal dopamine release (20). Such an imbalance in the retinal melatonin-dopamine system would be further exaggerated by feedback, since the reduction of retinal dopamine release would disinhibit the synthesis of melatonin, via a reduction in D2 receptor activation at the photoreceptors (28).

Selective melatonin antagonists have been described (31), and clearly it would be of interest to examine whether such agents reverse the abnormalities in dopamine pathways in the dystrophic retina. It remains to be resolved whether the dopamine abnormalities are causative, although they precede the photoreceptor loss in the RCS retina, which may suggest that it is a primary phenomenon. This question would be best resolved by examining whether melatonin antagonists retard or arrest the degenerative process *in vivo*, which may be expected since melatonin itself has been shown to exacerbate photoreceptor cell loss in the RCS rat (16).

Acknowledgements. We are grateful for the support of the Special Trustees of St. Thomas' Hospital, and the Research Endowments Committee. We are also indebted to Mr Peter de Villiers for skilled technical assistance.

References

1. Bodis-Wollner I, Yahr M. Measurement of visual evoked potentials in Parkinson's disease. Brain 1978; 101: 661-71.
2. Ellis CJK, Allen TGJ, Marsden CD, Ikeda H. Electroretinographic abnormalities in idiopathic Parkinson's disease and the effect of levodopa administration. Clin Vision Sci 1987; 1: 347-55.
3. Harnois C, DiPaolo T. Decreased dopamine in the retinas of patients with Parkinson's disease. Invest Ophthalmol & Vis Sci 1990; 31: 2473-5.
4. Dowling JE, Ehinger B. Synaptic organisation of the amine containing interplexiform cells of the goldfish and Cebus monkey retinas. Science 1975; 188: 270-3.
5. Witkovsky P, Dearry A. Functional roles of dopamine in the vertebrate retina. Prog in Retinal Res 1991; 11: 247-92.
6. Dacey DM. Dopamine-accumulating retinal neurones revealed by in vitro fluorescence display a unique morphology. Science 1988; 240: 1196-8.
7. Nguyen-Legros J, Savy C, Martin-Martinelli E, Yelnik J. Distribution and spatial organization of dopaminergic interplexiform cells in the rat retina. In: Weiler R, Osborne NN eds. Neurobiology of the inner retina. Berlin: Springer-Verlag, 1989: 65-75.
8. Djamgoz MBA, Wagner H-J. Localization and function of dopamine in the adult retina. Neurochem Int 1992; 20: 139-91.
9. Hampson ECGM, Vaney DI, Weiler R. Dopaminergic modulation of gap junction permeability between amacrine cells in mammalian retina. J Neurosci 1992; 12: 4911-22.
10. Nguyen-Legros J, Moussafi F, Simon A. Sclerally directed processes of dopaminergic interplexiform cells reach the outer nuclear layer in rat and monkey retina. Visual Neurosci 1990; 4: 547-53.
11. Kebabian JW, Calne DB. Multiple receptors for dopamine. Nature 1979; 277: 93-6.
12. Sibley DR, Monsma FJ. Molecular biology of dopamine receptors. TiPS 1992; 13: 61-9.
13. Negishi K, Drujan BD. Reciprocal changes in centre and surrounding S- potentials of fish retina in response to dopamine. Neurochem Res 1979; 4: 311-34.
14. Hankins MW, Ikeda H. The role of dopaminergic pathways at the outerplexiform layer of the mammalian retina. Clin Vis Sci 1991; 6: 87-93.
15. Dowling JE, Sidman RL. Inherited retinal dystrophy in the rat. J Cell Biol 1962; 14: 73-109.
16. Bubenik GA, Purtill RA. The role of melatonin and dopamine in retinal physiology. Can J Physiol 1980; 58: 1457-62.
17. Hawlina M, Jenkins HG, Ikeda H. Diurnal variations in the electroretinographic c-wave and retinal melatonin content in rats with inherited retinal dystrophy. Doc Ophthalmol 1992; 79: 141-50.
18. Hankins MW, Ikeda H. Non-NMDA type excitatory amino acid receptors mediate rod input to horizontal cells in the isolated rat retina. Vision Res 1991b; 31: 609-17.
19. Piccolino M, Neyton J, Gershenfeld HM. Decrease of gap junction permeability by dopamine and cyclic adenosine 3':5'-monophosphate in horizontal cells of turtle retina. J Neurosci 1984; 4: 2477-88.
20. Dubocovich ML. Melatonin is a potent modulator of dopamine release in the retina. Nature 1983; 306: 782-4.
21. Naka K-I, Rushton WHA. The generation and spread of the S-potentials in fish (cyprinidae). J Physiol 1967; 192: 437-61.
22. Kaneko A. Receptive field organization of bipolar and amacrine cells in the goldfish retina. J Physiol 1973; 235: 133-53.
23. Ikeda H, Priest TD, Robbins J, Wakakuwa K. Silent dopaminergic synapse at feline retinal ganglion cells. Clin Vis Sci 1986; 1: 25-38.
24. Frucht Y, Vidauri J, Melamed E. Light activation of dopaminergic neurones in rat retina is mediated through photoreceptors. Brain Res 1982; 249: 153-6.

25. Besharse JC, Iuvone PM. Is dopamine a light-adaptive or a dark-adaptive modulator in the retina? Neurochem Int 1992; 20: 193-9.
26. Wiechmann AF, Hollyfield JG. HIOMT-like immunoreactivity in the vertebrate retina: A species comparison. Exp Eye Res 1988; 49: 1079-95.
27. Redburn DA, Mitchell CK. Darkness stimulates rapid synthesis and release of melatonin in rat retina. Vis Neurosci 1989; 3: 391-403.
28. Iuvone PM, Besharse JC. Dopamine receptor mediated inhibition of serotonin N-acetyltransferase activity in retina. Brain Res 1986; 369: 168-76.
29. Cohen AI, Todd RD, Harmon S, O'Maley KL. Photoreceptors of mouse retinas possess D4 receptors coupled to adenylate cyclase. P.N.A.S. (USA) 1992; 89: 12093-7.
30. Mullen RJ, La Vail MM. Inherited retinal dystrophy: Primary defect in pigment epithelium determined with experimental rat chimeras. Science 1976; 192: 799-801.
31. Dubocovich ML. Luzindole (N-0774): a novel melatonin receptor antagonist. J Pharmacol Exp Therapeutics 1988; 246: 902-10.

DOPAMINERGIČNI MEHANIZMI V ZUNANJIH PLASTEH MREŽNICE SESALCEV IN OKVARE PRI PRIROJENI DISTROFIJI MREŽNICE

Mark Hankins, Hisako Ikeda

Izvleček - *V prispevku so prikazani dopaminergični mehanizmi, ki so vključeni v delovanje horizontalnih celic med paličnicami pri normalnih pigmentiranih podganah ter pri podganah RCS (Royal College of Surgeons) s prirojeno distrofijo mrežnice, v obdobju še pred razvojem degenerativnih sprememb fotoreceptorskih celic. V normalni mrežnici depolarizira dopamin (2-10 µM) horizontalne celice in zmanjša odziv na svetlobno draženje s celim poljem, medtem ko antagonist D1 SCH 23390 (10 µM) hiperpolarizira horizontalne celice in ojači električni odziv na svetlobno draženje. Ti rezultati odkrivajo endogeno funkcijo, pri kateri dopamin prek dopaminskih receptorjev D1 uravnava medsebojno spajanje horizontalnih celic (coupling) in s tem določa velikost receptivnih polj v mrežnici. Nasprotno pa SCH 23390 v distrofični mrežnici podgan RCS še pred nastopom degenerativnih znakov ni imel nobenega učinka na odziv horizontalnih celic, tudi če so bile le-te predhodno depolarizirane z dodatkom dopamina. Ti rezultati kažejo, da gre v distrofični mrežnici za pomembno zmanjšanje endogenega sproščanja dopamina, čeprav so dopaminski receptorji normalni. Nadalje SCH 23390 ni več učinkoval na normalne, kontrolne mrežnice po dodatku eksogenega melatonina (200-500 nM), kar kaže na to, da melatonin blokira normalno sproščanje dopamina in tako simulira situacijo pri distrofičnih mrežnicah. Ti rezultati kažejo, da gre v času pred nastopom degenerativnih sprememb v distrofični mrežnici za pomembno funkcijsko okvaro v sproščanju dopamina. Ker je nivo melatonina, ki močno zavira sproščanje dopamina, v distrofičnih mrežnicah po poročilih v literaturi zvišan, rezultati te študije potrjujejo domnevo, da gre pri distrofiji mrežnice podgan RCS za funkcijsko okvaro v sproščanju dopamina zaradi blokade z melatoninom.*

Ključne besede: *dopamin; horizontalne celice; melatonin; nevrotransmiter; podganja mrežnica*

SEEING NOT JUST WATCHING: POSTSTRIATE COGNITIVE PROCESSING OF VISUAL SIGNALS

VIDETI, NE LE GLEDATI: KOGNITIVNO PROCESIRANJE VIDNIH SIGNALOV

Zvezdan Pirtošek,[1] Geoff Barrett,[2] Andrew J. Lees[2]

[1] University Institute of Clinical Neurophysiology, Medical Centre, Zaloška c. 7, 61105 Ljubljana, Slovenia
[2] The National Hospital for Neurology & Neurosurgery, Queen Square, London WC1N 3BG, Great Britain

Key words: *attention; event-related potentials; Steele-Richardson-Olszewski syndrome; visual processing*

Abstract - *Visual information leaving the retina travels along the retinotectal and geniculostriate pathways to the primary visual cortex. In post-striate areas visual signals are further processed in the posterior parietal lobe (spatial location and sensorimotor transformations) and in the inferotemporal cortex (perceptual identification of non-spatial features). Relevant signals are selected by attentional mechanisms in these posterior brain areas. More sustained and sophisticated attention activates the anterior attentional modules in right prefrontal areas. Patients with Steele-Richardson-Olszewski syndrome (SRO) present clinically with a prominent attentional disorder. Reaction time studies suggest that covert orienting of visual attention is impaired in the vertical plane in this syndrome, and that the lesion responsible is located in midbrain retinotectal pathways. We used event-related potentials to study orienting of visual and auditory attention in a group of patients with SRO. Inability to switch attention was found in both modalities, and orienting of attention was impaired in the horizontal plane. These data provide evidence that the disorder of attention in SRO is global and associated with anterior attentional modules.*

Central processing of visual information

In this article we will describe how visual signals can be cognitively shaped once they leave the retina, and some of the impairments resulting from localized lesions along the poststriate visual pathways. The electrophysiology of visual selective attention will be briefly outlined, and some findings in the Steele-Richardson-Olszewski syndrome presented to illustrate how an event related potentials (ERPs) paradigm can add to the understanding of this neurological disease.

Visual information leaving the retina travels along the retinotectal and the geniculostriatal pathways to the primary visual cortex. Further processing occurs beyond the striate area, and the brain creates a perfect visual image of the surrounding world. There is some evidence, however, that visual information can be sensibly organized already on the subcortical level. Neurophysiological recordings from the mammalian superior colliculi point to the role of this primitive structure in the early evaluation of visual stimuli, as well as in consequent visuo-motor transformation (1): if the visual stimulus is interpreted as "threatening", an uncrossed descending pathway is used to trigger an avoidance and defence motor behaviour with accompanying autonomic changes. If the visual stimulus is interpreted by the collicular neurons as "non-threatening", a crossed descending pathway activates ocular saccades to pursue and possibly approach the object. Goodin et al. (2) have described a patient with a homonymous hemianopsia after surgical removal of one occipital lobe. The P100 wave (thought to be generated in striate cortex) was absent, but the patient was able to generate a long-latency P300 potential in response to stimuli presented in the blind hemifield; the authors ascribe the visual processing in this patient to the older retinotectal pathways. In a disorder called the Steele-Richardson-Olszewski syndrome (SRO) there is a prominent involvement of subcortical structures, especially in the basal ganglia and in the midbrain. In fully developed disease, patients present with parkinsonism and a conspicuous impairment of vertical gaze. Even before this gaze disorder occurs, the blank expression, staring and lack of reaction to changes in the visual field, observed in the patient by their family, indicate impaired orienting of visual attention. This disorder of attention is said to be due to a severe denervation of the retinotectal pathways in the SRO syndrome (3).

It is the activity of poststriate structures in occipital, parietal, temporal and prefrontal lobe that adds a decisive cognitive perspective to visual information (Fig. 1). Two anatomically separate pathways lead from the primary visual cortex (4): dorsal (to the posterior parietal lobe) and ventral (to the inferotemporal cortex). The former is phylogenetically and ontogenetically older. It informs us about the spatial location of the object, its motion and its structural characteristics in view of our possible interaction with the object. Jumping on a slowly departing train does not need much processing of colours, it does depend however on an exact computation of the position and structure of the moving stairs by the neurons in the parietal lobe. Rich connections of this lobe with the midbrain and the pre-motor regions of the frontal

Abbreviations: *DLPF, dorsolateral prefrontal; EOG, electrooculogram; ERPs, event-related potentials; PET, positron emmission tomography; SRO, Steele-Richardson-Olszewski*

lobe will provide the necessary ocular control, and enable appropriate limb movements. Standing now safely on the departing train, we can gaze at the Slovenian landscape: dark green forests, white churches with baroque copper-beaten cupolas, snowy Alpine peaks, approaching and then sinking again in the mist of an early morning. Neurons in the inferotemporal cortex show striking sensitivity to all these forms, patterns, colours, and they maintain their selective responsiveness across a wide range of optical and perspective transformations, quite independently from the momentary viewpoint. This visual coding is important for learning, recognition, and unlike the coding in parietal lobe, it is not action-oriented. The dorsal and ventral pathways may differ in the degree by which they reach consciousness. The action-relevant parietal system, which is closely connected with the more archaic subcortical structures and has evolved earlier than the temporal one, does not always need full access to consciousness; e.g. during a saccadic eye movement we are not aware of a target changing its position, and yet we adjust and point to the target with a near-perfect precision. However, ventral occipitotemporal and dorsal occipitoparietal systems do cross-communicate and both in turn project to areas in the superior temporal sulcus, adding to a network of polymodal sensory neurons.

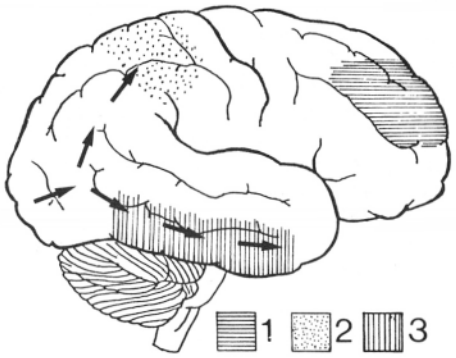


Fig. 1. *Areas, important in post-striate visual processing and attention (1 = dorsolateral prefrontal cortex, 2 = posterior parietal cortex, 3 = inferotemporal cortex).*

Sl. 1. *Področja, pomembna v poststriatni obdelavi vidnih informacij (1 = dorzolateralna, 2 = posteriorna parietalna, 3 = inferotemporalna možganska skorja).*

Visual processing along the two post-striatal pathways can be impaired in some disorders. Patients with a lesion of the posterior parietal lobe can present a picture of ataxia (arguably called "optic ataxia"): they have no problems recognizing objects, but have difficulties positioning their fingers and adjusting grasp for accurately handling objects. Some patients with lesions of the occipitotemporal area suffer from visual agnosia. They are unable to describe common objects, their predicament being in some cases remarkably selective (e.g. an inability for colour discrimination with damage to the lingual and the fusiform gyri).

Attention and visual processing

The responsiveness of different neurons to space, colour, speed or shape, would serve no useful purpose, unless there was a way to select only the relevant features. When you try to spot a friend in a crowd, you do not actively process all colours, all faces and every street sign. You concentrate on a red pullover, search for the familiar facial features and ignore street signs. This filtering is made possible by the mechanism of attention. Attentional modulation occurs in many parts of the extrastriate visual system, but seems to be spatially biased: whatever we attend to, be it colour or location, we attend to it in a certain space. Spatial attention can therefore be associated with the ventral temporal, as well as with the dorsal parietal system and in their interplay the parietal-collicular system may indeed be the "source" of a spatial signal responsible for filtering out irrelevant information in the occipitotemporal stream.

These posterior attentional mechanisms can therefore efficiently select the required visual features. But for the purposeful, goal-oriented behaviour of a human being there is a need for an even higher module of attentional control, which is more effortful (attending to more features as opposed to a single one), more sustained (vigilance), modality independent and socially sensitive. This attentional module is located in the anterior, more recently developed regions of the brain (5) - the dorsolateral prefrontal cortex (DLPF) having a particularly important role. Again, clinical observation of patients with lobar lesions can give us a clue about the anterior attentional mechanisms: a patient with a parietal lesion may well have a unilateral neglect, but if validly cued targets are presented to the damaged hemisphere, his attention is normal and sustained. On the other hand, patients with frontal lesions have great difficulty maintaining goal-oriented motor and cognitive programs. They are easily distracted by the ongoing sensory events and have problems with social interactions. There is also an anatomical reason as to why the DLPF cortex could have a role in the highest-level attentional mechanisms: because it is strategically placed in important loops connecting cortical and subcortical structures (prefrontal cortex - caudate nucleus - thalamus - prefrontal areas) (6). In this circuitry the thalamus provides ongoing sensory information, so that mnemonic traces can be generated, and current sensation is matched with previous emotional (limbic system, ventral striatum) and social (prefrontal lobe) experiences, so that appropriate saccadic and cognitive/attentional behaviour can be planned.

Electrophysiology of visual attention

The neurophysiological basis of visual selective attention can be studied with ERPs (7). Visual ERPs are voltage fluctuations recorded over posterior scalp, generated by the time-locked postsynaptic discharges of large populations of neurons processing the visual information. Modulation of these waves by attention can be observed by asking the patient to attend to particular features of the signal (shape, location, colour etc.). ERPs are simultaneously recorded for attended and non-attended stimuli, but are averaged separately. Analysis of the averaged responses can be simplified by using difference waveforms, where ERPs of an attended stimulus are subtracted from the ERPs of the identical stimulus when it is not attended (8). It is not entirely clear how soon after stimulus presentation ERPs are modulated by attention: there are reports of attention-related changes in the b-wave and after-potential of the electroretinogram (9), but these have been disputed (10). Clear modulation of the ERPs starts at about 100 ms after stimulus presentation. In Mangun's studies (7) the main attention-sensitive components include the P1 (100-140 ms), N1 (160-200 ms), P2 (220-250 ms) and N2 (260-300 ms). The P1 wave seems to be of cortical origin, but its attention-related changes can reflect activity of the earlier cortical or even thalamic structures. Spatial attention increases the amplitude of P1, N1, P2 and N2 without any change in latencies or waveforms, which is consistent with a mechanism of sensory gating. In contrast, attending to colour generates new slow negative ERPs components ("selection negativity"), beginning at about 150 ms and probably originating in different brain regions than the components elicited by attention to spatial location. The selection negativity is much larger in response to attended colour stimuli when they appear on the attended compared to unattended side, which may indicate location to be an early gating mechanism for further visual processing of colour.

A study of attention in Steele-Richardson-Olszewski syndrome

Introduction

We used ERPs to study attention in disorders affecting the dopaminergic system. Results in patients with the Steele-Richardson-Olszewski syndrome will be discussed here. This disease of the elderly is characterized by impairment of balance, axial rigidity, bradykinesia, pseudobulbar palsy with dysarthria and dysphagia, progressive dementia with prominent frontal signs and a characteristic supranuclear gaze palsy, usually predominant in the vertical direction. Typical pathological features of neuronal loss, distinctive neurofibrillary tangles and gliosis occur in the basal ganglia, tectum and periaqueductal grey matter. Conventional neuropathological techniques suggest that cortex is much less affected (11). PET (positron emmission tomography) studies have confirmed a decrease of glucose metabolism in subcortical areas, and also revealed a profound hypometabolism in frontal lobes (12). Although impairment of vertical gaze in Steele-Richardson-Olszewski was well established, Rafal et al. (3) drew attention to abnormalities of orienting of visual attention as a salient component of the clinical picture; even when patients are still able to move their eyes, they are reluctant to do so, and behave as though blind. In a series of elegant reaction time experiments, they studied covert orienting of attention in SRO patients, and compared them to patients with Parkinson's disease. They found that Steele-Richardson-Olszewski patients were slower moving attention in the vertical, but not in the horizontal plane. In view of prominent pre-tectal lesions in this disease, they stressed the importance of midbrain retinotectal pathways, not only for controlling eye movements, but also for orienting attention.

Subjects and methods

We have studied a group of SRO patients electrophysiologically, using methods for covert visual and auditory selective attention. Nine patients, five men and four women, whose mean age was 68.7 years, performed the visual task, and eight of them, five men and three women (mean age 67.8 years) performed the auditory task. They were compared to equal groups of age-matched healthy controls (mean age 68.8 and 68.0 years, respectively). Because of the clinical and PET evidence of frontal cortical involvement, which is not supported by the conventional neuropathology, we used paradigms of reasonably "effortful" attention (attending to two features) that are more likely to reflect the activity of the frontal attentional mechanisms; these mechanisms should also regulate attention in different modalities. For the visual selective attention task, the subjects were presented with either a red or green square to either the left or right of a central fixation cross. The four possible colour/field combinations had probabilities of 0.25. Stimulus duration was 1 s and the interstimulus interval was 1.5 s. There were 4 runs of 150 stimuli. The target varied between runs in the following order: red square on the left, red square on the right, green square on the right, green square on the left. Subjects were instructed to fixate the central cross, and focus their attention to the chosen colour and side, and to ignore non-targets. They were asked to press a button each time they detected a target stimulus. The total analysis time was 960 ms, which included a pre-stimulus interval of 120 ms, and the electrical activity was sampled at 3.75 ms per ordinate. In the auditory selective attention task tone pips of 1.5 kHz and 1.2 kHz were delivered randomly to either right or left ear through headphones. Each of the four possible pitch/ear combinations was presented with equal probabilities of 0.25. There were 150 stimuli per run, and in each of the four runs the target tone was varied in the following order: low pitch tone in the left ear, low pitch tone in the right ear, high pitch tone in the right ear, or high pitch tone in the left ear. Tone duration was 50 ms and rise/fall time was 10 ms. If subjects could not distinguish between the 2 stimuli, the frequency of the 1.2 kHz stimulus was reduced in 0.1 kHz steps until a reliable distinction could be made in both ears. On occasion it was also necessary to increase stimulus intensity to achieve this aim. The interstimulus interval was 1 s. The total analysis time was 640 ms, which included a pre-stimulus interval of 80 ms, and the electrical activity was sampled at 2.5 ms per ordinate. Subjects were instructed to focus their attention on the chosen pitch and ear combination, and to ignore non-targets. They were asked to press a button each time they detected a target stimulus. Speed and accuracy were emphasized equally in the instructions for both attentional tasks.

Electrophysiological signals were recorded by means of Ag/AgCl electrodes fixed by collodion to the scalp. Electrode resistance was kept constant below 5 kOhms. EEG activity was recorded at F3, Fz, F4, C3, Cz, C4, P3, Pz and P4 referred to linked earlobes. An electrode placed between Fz and Cz served as ground. Eye movements were recorded with electrodes above and lateral to the right eye. Activity in the scalp electrodes was later corrected for EOG (electrooculogram) artefact, using the technique described by Gratton et al. (13). Stimulus presentation, data acquisition and response recording were controlled by a PDP 11/34 computer interacting with an Acorn BBC model B computer. Stimulus duration was controlled by a Digitimer D 4030 signal generator.

Subjects were presented with a number of practice trials at the start of the recording, so as to make sure that they understood the task and were responding correctly.

Results

Age-matched controls showed a prominent modulation of brainwaves by attention in both visual and auditory modalities. This effect is seen clearly in the difference waveforms (Fig. 2, 3). In the patient group there is practically no difference in waveforms when auditory and visual stimuli are either attended or ignored, even though their behavioural performance was accurate for the trials contributing to the average waveforms (Fig. 4, 5).

Conclusion

Results showed that these patients have a global, widespread impairment of orienting of attention. They were severely impaired on switching their visual attention in the horizontal plane,

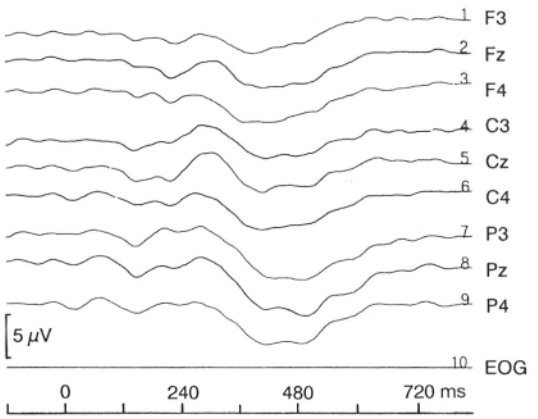


Fig. 2. *Difference waveforms for visual attention task in controls (group averages): ERPs associated with stimulation of the unattended visual field are subtracted fromt hose for stimulation of the attended field.*

Sl. 2. *Krivulja razlik za test vidne pozornosti pri kontrolni skupini (skupinska povprečja): ERP na dražljaje v vidnem polju, na katere naj bi preiskovanci ne bili pozorni, so odšteti od odzivov na dražljaje, na katere so bili preiskovanci usmerjeno pozorni.*

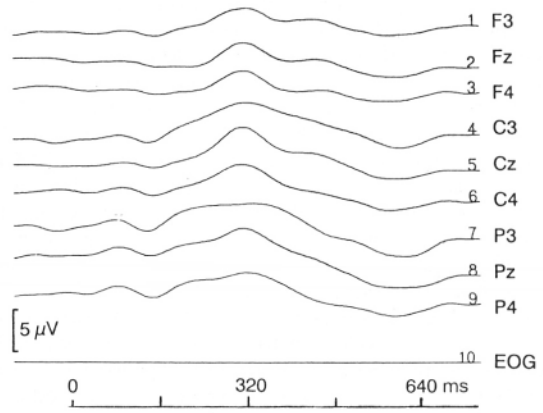


Fig. 3. *Difference waveforms for auditory attention task in controls (group averages): ERPs associated with stimulation of the unattended ear are subtracted from those for stimulation of the attended ear.*

Sl. 3. *Krivulja razlik za test slušne pozornosti pri kontrolni skupini (skupinska povprečja): odzivi ERP na dražljaje v uho, ki naj bi ne bilo pozorno, so odšteti od odzivov na dražljaje v uho, kjer so bili dražljaji pričakovani.*

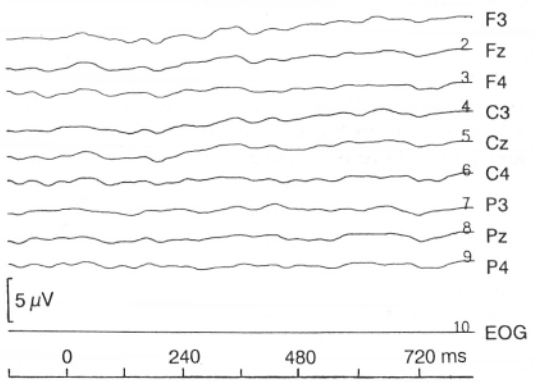


Fig. 4. *Difference waveforms for visual attention task in the SRO patients (group averages): ERPs associated with stimulation of the unattended visual field are subtracted from those for stimulation of the attended field.*

Sl. 4. *Krivulja razlik za test vidne pozornosti pri bolnikih s sindromom SRO (skupinska povprečja): odzivi ERP na dražljaje v vidnem polju, na katere naj bi preiskovanci ne bili pozorni, so odšteti od odzivov na dražljaje, na katere naj bi preiskovanci bili pozorni.*

and this impairment occurred in both visual and auditory modalities. Although lesions in the pretectal area can impair vertical gaze and vertical orienting of attention by denervating efferent structures, our data provide evidence that the disorder of attention is global, and it should be put high in the hierarchy of "anterior" attentional modules. In view of the neuropathological findings (severe changes in the basal ganglia, but relatively mild in frontal cortex) and the PET studies (profound hypometabolism of cortical as well as of subcortical regions), we would be inclined to locate the impairment of orienting of attention in the circuitry of cortico-subcortical loops which connect prefrontal areas with the caudate nucleus.

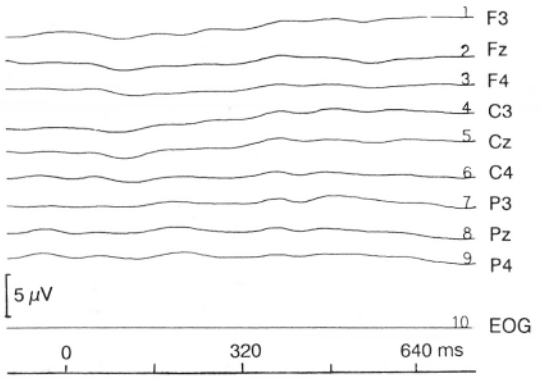


Fig. 5. *Difference waveforms for auditory attention task in the SRO patients (group averages): ERPs associated with stimulation of the unattended ear are subtracted from those for stimulation of the attended ear.*

Sl. 5. *Krivulja razlik za test vidne pozornosti pri bolnikih s sindromom SRO (skupinska povprečja): odzivi ERP na dražljaje v uho, ki naj bi ne bilo pozorno, so odšteti od odzivov na dražljaje v uho, kjer so bili dražljaji pričakovani.*

References

1. Dean P, Redgrave P, Westby GWM. Event or emergency? Two response systems in the mammalian superior colliculus. TINS 1989; 12 (4): 137-47.
2. Goodin DS, Shefrin SL, Aminoff MJ. Electrophysiologic correlates of "blindsight". In: Barber C, Blum T eds. Evoked Potentials III. Butterworths, 1987: 351-4.
3. Rafal RD, Posner MI, Friedman JH, Inhoff AW, Bernstein E. Orienting of visual attention in progressive supranuclear palsy. Brain 1988; 111: 267-80.
4. Goodale MA, Milner AD. Separate visual patways for perception and action. TINS 1992; 15 (1): 20-5.
5. Pardo JV, Fox PT, Raichle ME. Localization of a human system for sustained attention by positron emission tomography. Nature 1991; 349: 61-4.
6. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Ann Rev Neurosci 1986; 9: 357-81.
7. Mangun GR, Hillyard SA. Electrophysiological studies of visual selective attention in humans. In: Scheibel A, Wechsler A eds. The neurobiological foundations of higher cognitive function. New York: Guilford Press, 1990: 271-95.
8. Barrett G. Clinical applications of event-related potentials. In: Halliday AM ed. Evoked potentials in clinical testing. 2nd ed. Edinburgh: Churchill-Livingstone, 1993: 589-633.
9. Eason RG, Flowers L, Oakley M. Central neural influences on the human retina during selective attention. Physiological Psychology 1983; 11: 18-28.
10. Mangun GR, Hansen JC, Hillyard SA. Electroretinograms reveal no evidence for centrifugal modulation of retinal inputs during selective attention in man. Psychophysiology 1986; 23; 156-65.
11. Jellinger K. Progressive supranuclear palsy (subcortical argyrophilic dystrophy). Acta Neuropathol 1971; 19: 347-52.
12. Blin J, Baron JC, Dubois B, at al. Positron emission tomography study in progressive supranuclear palsy. Arch Neurol 1990; 47: 747-52.
13. Gratton G, Coles MGH, Donchin E. A new method for off-line removal of ocular artifacts. Electroenceph Clin Neurophysiol 1983; 55: 468-84.

VIDETI, NE LE GLEDATI: KOGNITIVNO PROCESIRANJE VIDNIH SIGNALOV

Zvezdan Pirtošek, Geoff Barrett, Andrew J. Lees

Izvleček - Izhodišča. *Za smiselno dojemanje in obvladovanje okolja je pomembno, da možgani vidne signale interpretirajo razumno in selektivno. Strukture v zadajšnjih možganskih delih (kolikularna jedra, zadajšnji del temenskega in spodnji del senčnega režnja) igrajo ključno vlogo pri kognitivni obdelavi vidnih signalov. Selektivnost vidne informacije omogočajo mehanizmi pozornosti, od katerih preprostejši potekajo v navedenih strukturah ("zadajšnji mehanizmi pozornosti"). Ko se na okolje odzivamo z bolj zapleteno, multimodalno in dolgotrajnejšo pozornostjo, pa postaja pomembnejša vloga desnega prefrontalnega režnja ("sprednji mehanizmi pozornosti"). Pri sindromu Steele-Richardson-Olszewski so motnje vidne pozornosti pomemben del klinične slike in jih je mogoče opaziti, še preden nastopi za bolezen značilna supranuklearna pareza pogleda v navpični smeri. Tudi motnje pozornosti so bile opisane zgolj pri gledanju v tej smeri, zato so jih razlagali z okvarami v mezencefalonu.*
Klinično izkušnjo, da so motnje pozornosti pri teh bolnikih globalne, smo želeli potrditi z elektrofiziološko metodo od dogodka odvisnih potencialov ("event-related potenciali"); rezultati so pomembni tudi za razumevanje mesta okvare, ki povzroča motnje pozornosti.

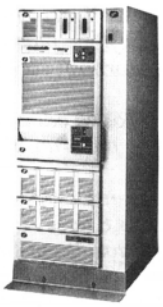
Bolniki in metode. *V študijo smo vključili devet bolnikov s sindromom Steele- Richardson-Olszewski, pet moških in štiri ženske. Njihova povprečna starost je bila 68,7 let. Primerjali smo jih s skupino zdravih prostovoljcev, katerih povprečna starost je bila 68,8 let.*
Preučevali smo slušno in vidno selektivno pozornost, slednjo v vodoravni dimenziji prostora. Bolnikom in zdravim prostovoljcem smo po slušalkah predvajali visoke ali nizke tone v desno ali levo ubo, nato pa na televizijskem zaslonu kazali rdeče ali zelene kvadrate v desnem ali levem vidnem polju. Zaprosili smo jih, naj se osredotočijo na določen signal (npr. na visoke tone levo ali pa rdeče kvadrate desno) in pritisnejo na gumb, ko se ta signal pojavi. Od dogodka odvisne potenciale smo odjemali s površinskimi elektrodami na F3, F2, F4, C3, Cz, C4, P3, Pz in P4. "Surove" rezultate smo nato priredili tako, da smo potenciale, dobljene ob nepozornosti, odšteli od potencialov, dobljenih v popolni pozornosti ("differential waveforms").

Rezultati. *Ko so zdravi prostovoljci usmerili pozornost na izbrani dražljaj, so se njihovi, od dogodka odvisni potenciali očitno spremenili, potenciali bolnikov pa so ostali nespremejeni. To velja za slušno in za vidno selektivno pozornost v vodoravni smeri.*

Zaključek. *Pri bolnikih s sindromom Steele-Richardson-Olszewski ne gre zgolj za relativno žariščno motnjo vidne pozornosti v navpični smeri, ki je seveda zlahka razložljiva s hudimi spremembami v predelu mezencefalona in posledično prizadetostjo "zadajšnjih mehanizmov pozornosti", saj motnja sega tudi v vodoravno razsežnost prostora in celo v slub. Tako motnjo še najlaže razložimo z okvaro (predvsem desnega) prefrontalnega predela, najverjetneje zaradi prekinjenih povezav z bazalnimi gangliji in talamusom.*

Ključne besede: *od dogodka odvisni potenciali; pozornost; procesiranje vidnih signalov; sindrom Steele-Richardson-Olszewski*

UNIX, kakršnega še ni bilo!



AIX je njegovo ime. V sestavi s hardverom **RISC/6000,** je ta operacijski sistem eden izmed vodilnih odprtih sistemov na svetu, prava vrhunska računalniška arhitektura. Za raziskave smo namenili milijarde dolarjev in zdaj vam lahko ponudimo največ, kar je dobiti v svetu odprtih sistemov. S tem operacijskim sistemom in strojno opremo, ki smo jo sami razvili, je vaš obstoječi hardver moč povezati z novimi računalniškimi sistemi IBM.

Hitreje in zanesljiveje kot kdajkoli boste poganjali svoje najbolj zapletene aplikacije. Tudi cenovno je naša vrhunska tehnologija dostopna. Predvsem pa pomeni varno naložbo, kajti poskrbeli smo, da boste lahko svoje sisteme iz leta v leto nadgrajevali z našimi vedno bolj izpopolnjenimi izdelki.

Vabimo vas, da nas pokličete, in razložili vam bomo, kakšno podporo vam lahko nudimo s svojimi svetovnimi izkušnjami na področju odprtih sistemov in z vsem potrebnim vzdrževanjem. IBM Slovenija, telefon: 061/ 163-645 in 152-154.

Electrophysiological evaluation of the visual system

Elektrofiziološko ocenjevanje vidnega sistema

Poskrbite za varnejšo finančno prihodnost. Svojo in svojih najbližjih.

Adriaticovo rentno zavarovanje Vam ponuja novo možnost koristne naložbe. Sklenete ga lahko **za krajše obdobje** ali **za vse življenje. Je prenosljivo.** Podarite ga lahko tudi svojemu otroku.

Adriaticovo rentno zavarovanje je hkrati tudi **varčevanje** in **dobičkonosna naložba.** Toliko bolj, ker Vam bo ob strani stala zanesljiva, zaupanja vredna zavarovalnica.

Zahtevajte podrobne podatke. Pokličite na telefon 066 43 111 ali se oglasite v najbližji Adriaticovi poslovni enoti ali pooblaščeni agenciji.

Adriaticovo rentno
Zdaj čas dela za Vas

Adriatic
Vem, da mi bo ob strani stala dobra zavarovalnica

SOME ANATOMICAL AND PHYSIOLOGICAL ASPECTS OF CLINICAL ELECTROPHYSIOLOGY OF VISION

NEKATERI ANATOMSKI IN FIZIOLOŠKI VIDIKI KLINIČNE ELEKTROFIZIOLOGIJE VIDA

Jelka Brecelj,[1] Martin Štrucl[2]

[1] University Institute of Clinical Neurophysiology, Medical Centre, Zaloška 7, 61105 Ljubljana, Slovenia
[2] Institute of Physiology, University of Ljubljana School of Medicine, Zaloška 4, 61105 Ljubljana, Slovenia

Key words: *clinical electrophysiology; electroretinography; visual evoked potentials; visual pathway*

Abstract - *Selectivity and sensitivity of a visual electrophysiological test is closely associated with the possibility of proper physiological interpretation of the recorded potentials. The present paper discusses the importance of choosing anatomically and physiologically relevant stimulus characteristics in ERG and VEP recordings. The examples are limited to the recommended standard ERG and pattern-reversal VEP tests used in our laboratory.*

Introduction

A battery of noninvasive electrophysiological methods, including electrooculogram (EOG) and electroretinogram (ERG) at the retinal level, and visual evoked potential (VEP) at the cortical level, has been developed for the assessment of the visual system functional status (Fig. 1). The choice of these electrophysiological visual tests is intricately associated with sensitivity and selectivity of these methods. To answer appropriately to the question of the choice of the visual test, we have to appreciate several variables, which are summarised in Fig. 2 and encompass the characteristics of the visual stimulus, the detection methods properties, and current knowledge of physiological factors operating in health and disease.

Surface potentials recorded from the cornea (ERG) or scalp (VEP) are sum potentials (macropotentials) originating from the electrical activities of cell populations, more or less remote from the recording electrodes, and thus inevitably subjected to the laws of volume conduction in the surrounding tissues. The limitation of the methods can readily be apprehended, considering that the spatial distribution of the potentials provides only approximate localisation of their generators (2). Aside from these theoretical and technical considerations, some other factors are important for obtaining as much information as possible from the recorded potentials. In the present paper we focus our interest on the role of stimulus selection as a variable which determines the selectivity and sensitivity of the electrophysiological visual tests.

One of the crucial events in the visual sensory physiology was electrophysiological confirmation of the existence of parallel subsystems or channels in the primate visual system (3), which has already become evident in psychophysical studies. Electrophysiological studies of the visual system at the cellular level have revealed that the majority of the visual sensory nerve cells are selectively activated by specific stimulus qualities (colour and luminance contrast, orientation, movement, ocular dominance etc.) and are relatively insensitive to diffuse illumination. To reveal functional organisation of the visual system, one must find characteristic light stimulus features, to which each neuron will give the best response. Ample evidence suggests that this funda-

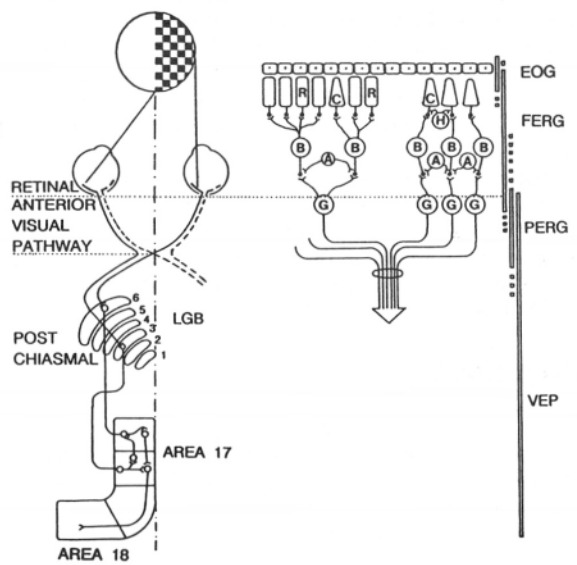


Fig. 1. *Schematic representation of the visual system and the "detecting ranges" of the noninvasive visual electrophysiological tests (with permission from ref. 1).*

Sl. 1. *Shema vidnega sistema in "detekcijska območja" neinvazivnih vidnih elektrofizioloških testov (z dovoljenjem iz ref. 1).*

Abbreviations: *EOG, electrooculogram; ERG, electroretinogram; FERG, flash ERG; PERG, pattern ERG ; VEP, visual evoked potential*

mental physiological principle could also be successfully applied in clinical visual electrophysiology (4).
The introduction of pattern stimulus (i.e. with the presence of contrast elements in the visual scene) has remarkably improved the sensitivity of the electrophysiological visual tests.

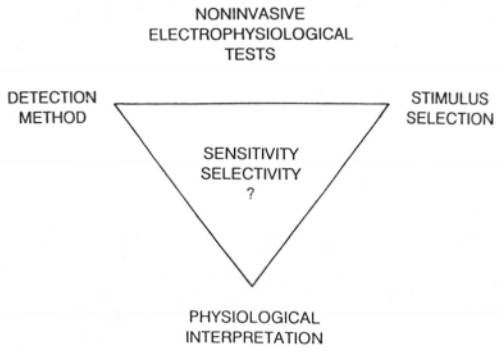


Fig. 2. *Selectivity and sensitivity of the tests as functions of detection methods, stimulus selection and physiological interpretation.*
Sl. 2. *Selektivnost in občutljivost testov kot funkcija metode detekcije, izbora dražljaja in fiziološke razlage.*

However, it is evident from the multidimensional character of this stimulus that it has many variations, which are far from being fully explored. The visual system, for example, can be "kicked" by a sporadic stimulus to obtain the "transient" responses, or brought into the "steady state" periodic response with a high stimulus frequency. The contrast elements in the visual scene can be alternated with homogeneous visual field of equal net luminance (pattern on and off responses) or with opponent contrast (pattern-reversal). A variety of contrast element exists (sinusoidal, bars, squares, hexagonal) in combination with luminance and colour contrast. The electrophysiological exploration, therefore, demands sophisticated methodological approaches. It is mainly for this reason that only a limited number of these methods are used in clinical laboratories, but they represent the most standardised tests at present. At retinal level, these are maximum response ERG, cone and rode response, pattern ERG, oscillatory potentials, and high frequency flicker. At cortical level, pattern-reversal VEP is the most commonly used test in clinical application.
In this paper, the characteristics of stimuli used in clinical electrophysiology are discussed from the anatomical and physiological point of view. On the experience of the ERG tests and pattern-reversal VEP used in our laboratory, we present how the stimulus selection fits the physiological and anatomical properties of the tested level of the visual system.

Retinal level

The retina provides the visual input to the brain, and is its main interface with the outside world. Its anatomy and physiology are relatively well known, and we have also a fairly good idea about some of the information processing operations performed by the retina. Vision begins with the excitation of photosensitive molecules contained in the photoreceptor disc membranes. This excitation triggers a cascade of molecular reactions, which convert packets of electromagnetic energy into neural signals with a remarkable amplification (5). The light-evoked hyperpolarization of the photoreceptor membrane is generated at the outer segment, but it spreads to the synaptic ending, where it is communicated to other retinal cells. The transformation and integration that occur within the retinal network, as well as at the other levels of the visual system, are best analysed in terms of the receptive fields of the neurons, which are typically organised in the central part and an opponent surrounding due to the lateral inhibition.

Origin of EOG

A prerequisite for any retinal excitation is a fairly large standing potential of about 60 mV between the retinal pigment epithelium and the photoreceptor layer, which can be regarded as a battery of the eye. The standing potential depends mainly on normal functioning of the retinal pigment epithelium, on cones and rods, and on their biochemical, metabolic and ionic interactions. It varies with illumination and can be monitored clinically by electrooculography (EOG) (6).

Origin of ERG

All transduction and transformation processes are intricately reflected in macropotentials originating in the retina. However, in the retina most of the ERG components are believed to arise from pigmented epithelial cells (wave a) and from glial cells (wave b) rather than from neurons (7). It is not yet possible to determine precisely all the different components of an electroretinogram, and to decide for every occasion which retinal cells or layers are abnormal on the basis of ERG alone, but a simplified perspective on how the various tests can be used to evaluate cellular layers seems to be justified (Tab. 1).

Tab. 1. *Localization of lesions by visual electrophysiological tests.*
Tab. 1. *Lokalizacija okvar z elektrofiziološkimi testi.*

Location Izvor	Test Test
Retinal pigment epithelum Mrežnični pigmentni epitelij	EOG EOG
	DC ERG c-wave
	DC ERG val c
	ERG c-wave
	ERG val c
Receptor layer Sloj čutnic	ERG a-wave ERG val a
Cone system Sistem čepnic	Photopic ERG Fotopični ERG
	30Hz Flicker ERG
	Bliskovni ERG 30 Hz
Rod system Sistem paličnic	Rod-isolated ERG Izolirani ERG paličnic
Müller cells Müllerjeve celice	ERG b-wave ERG val b
Amacrine-bipolar cells Amakrine bipolarne celice	Oscillatory potentials Oscilacijski potenciali
	PERG
	PERG
Ganglion cell layer Sloj ganglijskih celic	PERG PERG
Macula Makula	PERG PERG
	Focal ERG
	Žariščni ERG
Optic tract Optični trakt	VEP VEP

Clinical aspects of ERG

The surface potentials, evoked by the visual stimulus and recorded on the cornea and skin, are basically analysed in terms of abnormal latency, amplitude and configuration of the responses. It is remarkable how much information can be obtained from macropotentials originating in only half a millimetre thick retinal

layers. The contribution of each cellular component is, in general, dependent on cellular orientation, experimental condition (light adaptation) and stimulus selection. For a specific clinical indication one has to choose proper parameters of ERG recordings: adaptation, electrodes, recording setting and stimulus selection: intensity, duration, frequency, spectral composition, diffuse, local, pattern, check size, contrast, background illumination.

Disadvantage of the variety of stimulus conditions is that it is difficult to compare ERG parameters among different laboratories and research groups. Therefore, the efforts towards the standardisation have become very intense. In our laboratory, we followed the Standard for Clinical Electroretinography, recommended by International Standardisation Committee (8). The clinical application of ERG is comprehensively reviewed elsewhere (9). We shall merely illustrate some typical clinical applications of ERG.

Maximal response ERG evoked by bright flash is initiated by the excitation of the whole population of photoreceptor cells (about 120 millions), only about six millions of which are macular cones, the rest being paracentral and peripheral rods. The sum potential, i.e. the complex of graded electrical responses from each layer of the preganglionic retina, reflects the overall retinal function (7). Since the whole retina is excited, maximal response ERG is an important tool in detection and evaluation of hereditary, as well as acquired disorders, which diffusely affect the distal retinal layers, such as retinitis pigmentosa. Figure 3 represents the five standard ERG responses, obtained in a patient with retinitis pigmentosa, as compared to the responses of a healthy subject. We could differentiate between the rod and cone mediated response by means of spectral filters that suit different spectral sensitivities of the rods (rod response) and cones (cone response), and with frequency modulation (30 Hz flicker ERG) of the stimuli.

In contrast, diseases of the macula, such as Statgardt's disease (Fig. 4), which involve only a small part of the retina, may not be revealed by the flash ERG (FERG). Furthermore, normal FERG may be recorded in a retinal disease, such as glaucoma (Fig. 4), in which the defect mainly involves retinal ganglion cells. In such cases the pattern ERG (PERG) has proven to be helpful (6, 10). Moreover, the choice of optimal luminance, size and temporal frequency seems to increase the sensitivity of the PERG as an objective screening test for early glaucoma (11). Physiological interpretation of the pattern stimulation, usually consisting of black and white elements alternating in phase without overall change in net luminance, lies in antagonistically organised receptive fields of retinal cells in the proximal retinal layers (12). Although it has not been definitely accepted that PERG originates exclusively in the retinal ganglion cells, there seems to be substantial clinical and experimental evidence to conclude that it arises from retinal structures other than those which generate flash ERG (13).

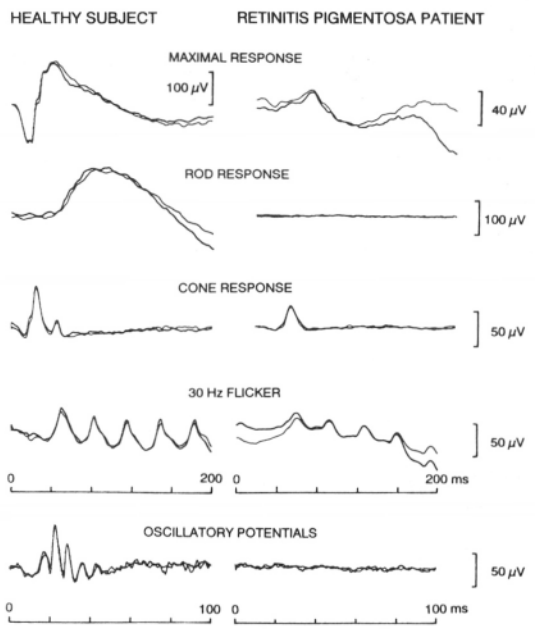


Fig. 3. *Standard ERG tests in a healthy subject and a patient with retinitis pigmentosa.*

Sl. 3. *Standardni ERG testi pri zdravem in pri bolniku s pigmentoznim retinitisom.*

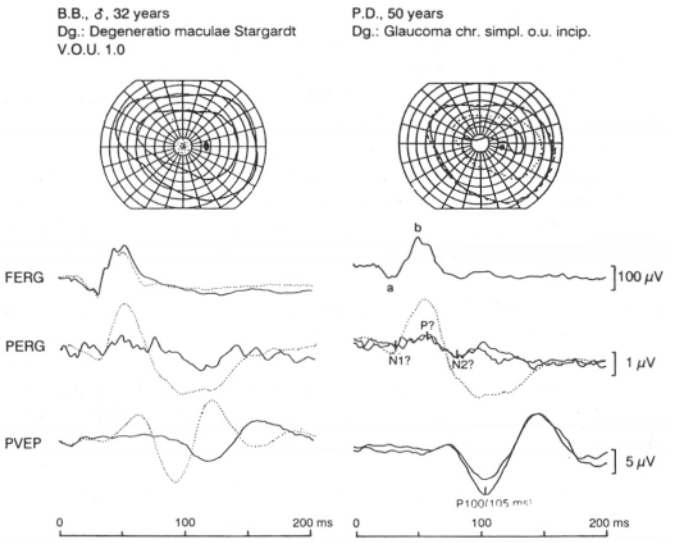


Fig. 4. *Flash ERG (FERG), pattern ERG (PERG) and pattern-reversal VEP in a patient with Statgard's disease of the macula (left) and in a patient with glaucoma (right). Dotted lines exemplify normal responses (with permission from ref. 6).*

Sl. 4. *Bliskovni ERG (FERG), slikovni ERG (PERG) in slikovni VEP pri bolniku s Statgardovo boleznijo makule (levo) in pri bolniku z glavkomom (desno). Pikčaste črte označujejo normalne odgovore (z dovoljenjem iz ref. 6).*

Cortical level

There are several pathways from the eyes to the brain. A detailed discussion of the anatomy of the visual pathways is beyond the scope of this paper, however, some remarks will be helpful in the interpretation of VEPs. The dominant pathway in the vision is the projection from the retina to the lateral geniculate nucleus and to the primary visual cortex (area 17). The fibres from the nasal part of the retina of each eye decussate in the optic chiasm, and reach the primary visual cortex in the contralateral occipital lobe, while the fibres from the temporal part of the retina of each eye do not decussate in the optic chiasm, and reach, therefore, the primary visual cortex in the ipsilateral occipital lobe. The primary visual area is located in the walls of the calcarine sulcus, and extends around the occipital pole onto the lateral surface of the hemisphere. The primary visual area shows a structural retinotopic organisation; the macular fibres terminate in the occipital part of the area 17, whereas the peripheral retinal areas end in more rostral portions, mainly in the calcarine sulcus. Every region of the retina is related in a systematic way to striate cortical regions. The representation of the visual world shows, that a much larger part of the area 17 is devoted to central vision than to peripheral vision. Pyramidal cells from the area 17 project to higher visual areas, such as Brodmann's areas 18 and 19. These areas surround the primary visual area in man.

Pattern-reversal visual stimulus and VEP components

In the clinical VEP work, the pattern-reversal stimulation is still extensively used. One of the reasons for the wide adoption of pattern-reversal stimulation was that with a slide projector no change of the overall mean luminance could be provided easily. Therefore, much of the clinical information has been gathered with the pattern-reversal stimulation (14, 15).

Wide field checkerboard reversal stimulation (16 °r) produces components N70, P100 and N145, which are picked up over the right and left hemisphere. With the half-field stimulation, the waves N70, P100, N145 are picked up over the ipsilateral hemisphere, and the waves P75, N105, P135 over the contralateral hemisphere (Fig. 5). Blumhardt and Halliday (17) have demonstrated that there is no significant transcallosal contribution to the half-field response, therefore, half-field responses may be seen as an activity generated, in each hemisphere, by separately stimulating the crossed or uncrossed retino-geniculo-calcarine pathway.

If compared with pattern VEP, flash VEP is relatively insensitive to the effect of visual impairment in clinical testing. The reasons are a large variability in the waveform and latencies between individuals. This was demonstrated in the study by Halliday et al. (18) in patients with acute unilateral optic neuritis. The amplitude of flash VEP correlates poorly with visual acuity. Flash VEP can be also very often obtained in cases where normal vision is so much impaired that pattern VEP is unobtainable. The reason for this is the physiological properties of the neurons in the visual system; they are relatively insensitive to diffuse illumination, while many are activated by stimulus qualities such as contrast. However, there is no doubt that there are several occasions in the clinical practice where flash VEP is relevant, e.g. albinism.

Visual evoked potential and cortical organisation

VEP is recorded from the scalp over the occipital cortex. In spite of several studies describing the origin of VEP components (19), it may still be said that VEPs are only a scalp representation, and do not have a simple relationship with the activity recorded in the underlying structures. In fact, Barrett et al. (20) showed that components N70, P100, N145 are recorded over the head, ipsilaterally to the half-field stimulated, which is at the opposite site of the activated visual cortex. The so called "paradoxical lateralization" is a result of the posteromedial orientation of the generator neurons.

Half-field stimulation of foveal (2 degrees) areas produces a more symmetrical distribution of the components N70, P100, N145 than wide half-field stimulation, due to the selection of generator areas near the occipital pole (21). The relationship between the anatomical variability of the primary visual cortex (22) and the variability of the foveal responses can be described following the scheme of hypothetical generator sites (20, 23). If the representation of the fovea is located on the convexity of the occipital lobe, VEP response will be well lateralised. When more

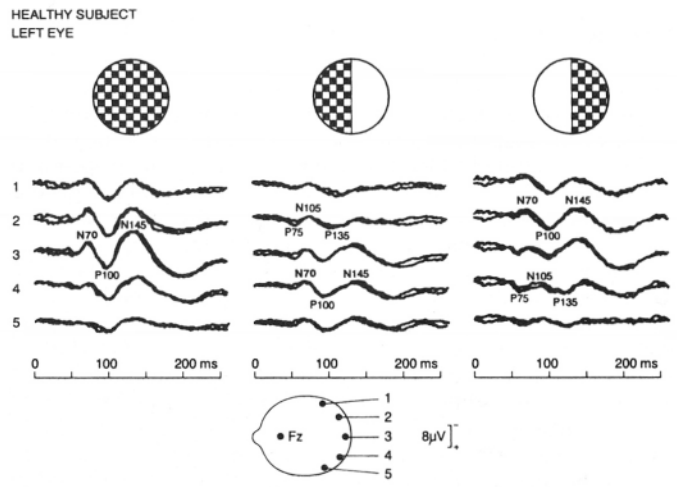


Fig. 5. *Responses to pattern-reversal full-field, nasal and temporal half-field stimulation in a normal subject (with permission from ref. 16).*

Sl. 5. *VEP na draženje s kontrastno izmenjujočim se slikovnim dražljajem v celem vidnem polju in v njegovi nazalni ter temporalni polovici pri zdravem človeku (z dovoljenjem iz ref. 16).*

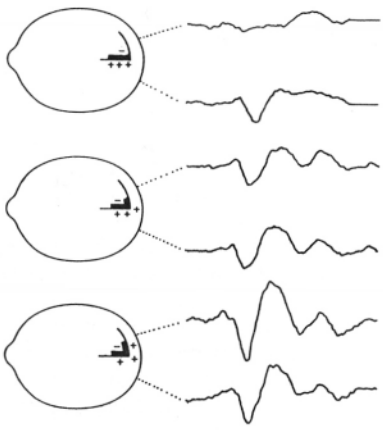


Fig. 6. *Schematic representation of generator areas following the scheme of Barrett et al. (20) and waveform distributions to foveal half-field responses.*

Sl. 6. *Shematski prikaz področja generatorja po shemi Barretta in sod. (20) in razporeditev valov pri fovealnih odgovorih na draženje v polovicah vidnega polja.*

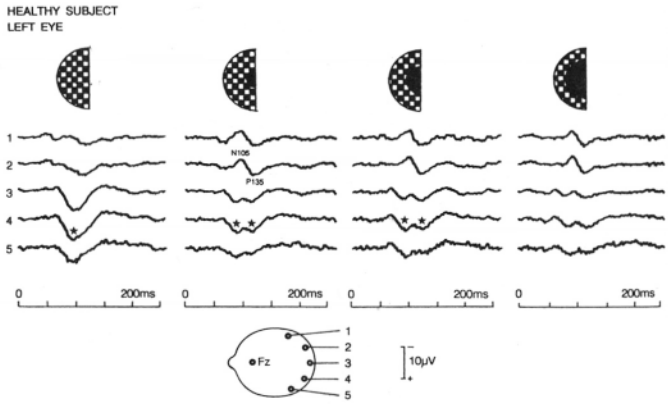


Fig. 7. *The effect on macular and paramacular components after occluding central parts (2°, 4° and 6°) of a 0-16° half-field stimulus presented to a healthy subject. After occluding 2° of a central part, a W-shaped waveform (asterisks) is developed over the ipsilateral hemisphere, and paramacular (N105, P135) components are developed over the contralateral hemisphere (with permission from ref. 26).*

Sl. 7. *Vpliv prekritja centralnih delov (2°, 4° in 6°) polovice dražilnega polja velikosti 0-16° na makularne in paramakularne komponente pri zdravem človeku. Pri zakritju 2° centralnega dela se razvijejo oblika W (zvezdici) nad ipsilateralno hemisfero in paramakularni komponenti (N105, P135) nad kontralateralno hemisfero (z dovoljenjem iz ref. 26).*

of the foveal representation extends around the occipital pole, VEP response becomes symmetrically distributed. If the foveal representation extends far enough around the occipital lobe, the response may even have a contralateral predominance (Fig. 6). This model does not imply that pattern-reversal VEP has a striate origin only, it merely describes the variability of VEP distribution in healthy subjects. According to the studies of Celesia et al. (24), striate and exstrastriate areas are the underlying sources of pattern-reversal VEP. Thus, pattern-reversal VEP components (Fig. 5) have striate and extrastriate origin, while their configuration and distribution may reflect the optic nerve, optic chiasm and retrochiasmal visual pathway function (25).

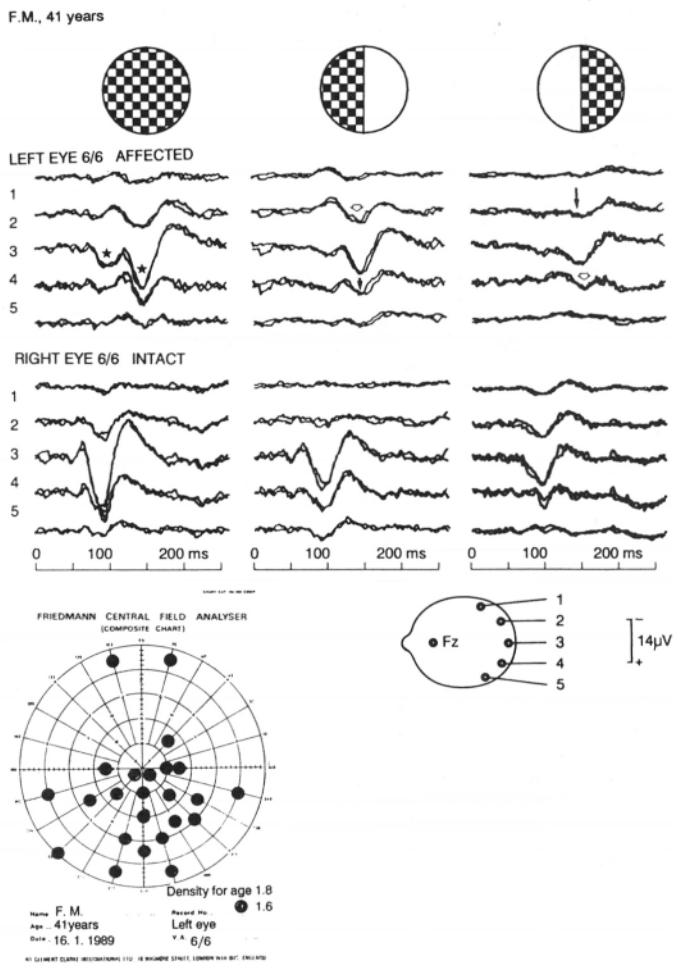


Fig. 8. *The W-shaped waveform (asterisks) in the full-field response of a patient with a history of left eye optic neuritis. Intact right eye shows normal P100 waveform. "Scotomatous" abnormalities are highlighted in the half-field responses from the left eye. The P135 component (open arrow) is well defined, while P100 component is absent or interrupted (P100-P135 interaction, thin arrows). The Friedmann perimetry test revealed relative scotomata (with permission from ref. 25).*

Sl. 8. *VEP z obliko W (zvezdici) na draženje s celim poljem pri bolniku, ki je prebolel optični nevritis na levem očesu. Zdravo desno oko daje normalno obliko vala P100. "Skotomske" abnormnosti so razložljive v odgovorih na draženje levega očesa s polovico polja. Komponenta P135 (široka puščica) je dobro oblikovana, vala P100 pa ni ali je prekinjen (interakcija P100-P135 - ozka puščica). Perimetrija po Friedmannu je pokazala relativne skotome (z dovoljenjem iz ref. 25).*

Macular versus paramacular optic nerve function

In an acute attack of retrobulbar neuritis, pattern-reversal VEP is extinguished. With the restoration of the visual acuity, VEP returns to normal amplitude, whereas the latency of P100 may remain prolonged. Delayed response is the result of the slowed conduction velocity in the optic nerve. On the other hand, the amplitude of pattern VEP, which closely parallells the onset and subsequent recovery of the visual impairment at the time of an attack, appears to be a reflection of the degree of conduction block of the optic nerve fibres.

In healthy subjects, the occlusion of the central part of the visual field can reduce or extinguish N70, P100, N145 components, while P75, N105, P135 components may be recordable. The W-shaped waveform can emerge in some of them when central field contribution is removed (Fig. 7). The macular-paramacular paradigm (27, 23), which predicts that some components are largely macula derived (N70, P100, N145) and others are largely paramacula derived (P75, N105, P135), has been confirmed in patients with the absolute central scotomata (28, 29, 30).

Similar effect on macular components was described in patients with a history of optic neuritis, which resulted in a genesis of the W-shaped waveform (26). Half-field stimulation revealed an absence of macular P100 component, or its interaction with the P135 component, while paramacular N105 and P135 components were enhanced over the contralateral hemisphere (Fig. 8). These VEP changes were accompanied with an attenuated or absent central field response, as well as with a relative central-field defect demonstrated by Friedmann perimetry. Thus, in pa-

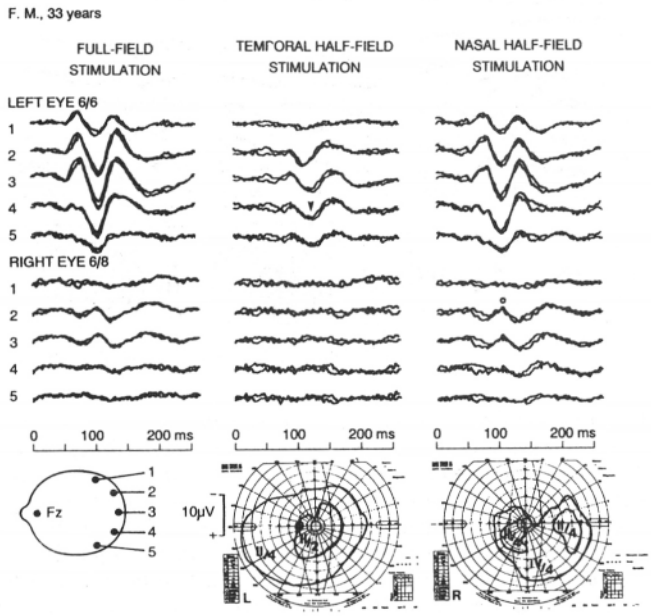


Fig. 9. *Crossed asymmetry pattern is evident in full-field responses from a patient with chiasmal compressive lesion. The P100 component (marked with an arrow) is distributed over the right hemisphere in left eye responses and over the left hemisphere in right eye responses. Waveforms of the temporal half-field responses are not present while of the nasal half-field responses are normal (P100 is marked with an arrow) (with permission from ref. 16).*

Sl. 9. *Navzkrižna asimetrija VEP levega in desnega očesa na draženje s celim poljem pri bolniku s kompresijsko okvaro hiazme: P100 (puščica) je razvidnejši nad desno možgansko poloblo pri draženju levega očesa, nad levo pa pri draženju desnega očesa. Na draženje v temporalnih polovicah vidnega polja odgovorov ni, odgovori na draženje v nosnih polovicah vidnega polja pa so normalni (puščica na P100 - z dovoljenjem iz ref. 16).*

tients with a history of optic neuritis, the W-shaped waveform can be associated with an impaired function of the macular fibres.

Crossed and uncrossed functional fibres in the chiasm

VEP distribution over the scalp can be associated with the crossed visual pathway (31, 32). In chiasmal compressive lesions, the full-field crossed asymmetry distribution (33) is associated with absent or abnormal responses to temporal half- field stimulation, and with normal responses to nasal half-field stimulation. The dysfunction of the crossed fibres, as revealed by temporal half-field stimulation, can be consistent with temporal-field defect (nasal retinal fibers - Fig. 9). On the other hand, a dysfunction of the uncrossed fibres can also be revealed by nasal half-field stimulation (Fig. 10).

In chiasmal lesions, the use of half-field stimulation can enhance the sensitivity, as well as distinguish between dysfunctions of the fibres subserving the temporal and nasal half-fields of vision (35).

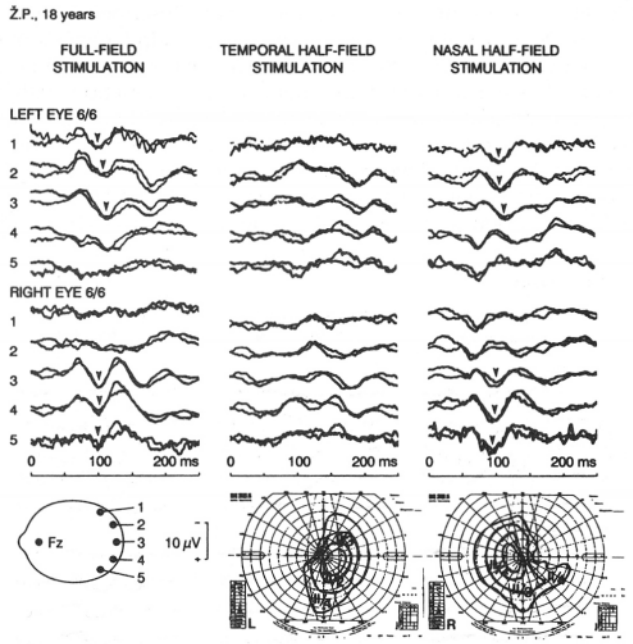


Fig. 10. *VEPs from a patient referred with the right eye visual symptoms indicating dysfunction of the optic nerve fibres subserving the temporal and nasal half-fields of vision. Note absent temporal half-field responses from the symptomatic eye, and delayed responses from the asymptomatic eye (P100 is marked with an arrow at 117 ms). Note also that the major features of the full-field responses arise from the nasal fields. Nasal half-field stimulation from the symptomatic right eye evoked a paramacular wave only (N105 is marked with an open circle). The visual field examination showed a defect in the right eye, as well as an initial defect in the left eye (with permission from ref. 34).*

Sl. 10. *VEP bolnika, napotenega na preiskavo s simptomi, ki so nakazovali motnjo v delovanju tistih vlaken desnega vidnega živca, ki posredujejo temporalno, in tistih, ki posredujejo nazalno polovico vidnega polja. Na draženje opazno prizadetega desnega očesa s temporalno polovico dražilnega polja ni bilo odzivov, na levem očesu (brez simptomov) pa so bili odzivi na tako draženje zapozneli (puščica na P100 pri 117 ms). V odzivih na draženje s celim poljem se vidi, da jih sestavljajo predvsem odzivi na nazalni del polja. Draženje z nazalnim delom polja je pri desnem očesu vzbudilo samo paramakularni val (krožec na valu N105). Preiskava vidnega polja je odkrila okvaro v polju desnega očesa in začetno okvaro v polju levega očesa (z dovoljenjem iz ref. 34).*

Cortical representation of misrouted optic pathway projections

In albinism, the anatomical studies showed that the majority of fibres from one eye cross at the chiasm and project to the contralateral hemisphere (36). This condition of erroneously decussating temporal retinal fibres can be picked up in VEP recordings, already in preverbal children, by means of flash stimulation. The flash VEP associated with albino misrouting is seen as a reversed asymmetry distribution. The asymmetry is seen, at a latency of around 80 ms, as a negativity on the contralateral side of the scalp, and as a positivity on the ipsilateral side of the scalp to the stimulated eye (37). Thus, for the left eye stimulation, a prominent negativity is recorded over the right occipital scalp, and a smaller positive component, at the same latency, is present over the left occipital cortex. For the right eye stimulation the distribution is reversed (Fig. 11). This specific occipital asymmetry is not observed in normally pigmented controls. This albino asymmetry of the flash VEP has been suggested to originate from either end of common dipole generators, which are situated in the medial aspects of the hemisphere, contralaterally to the stimulated eye (37).

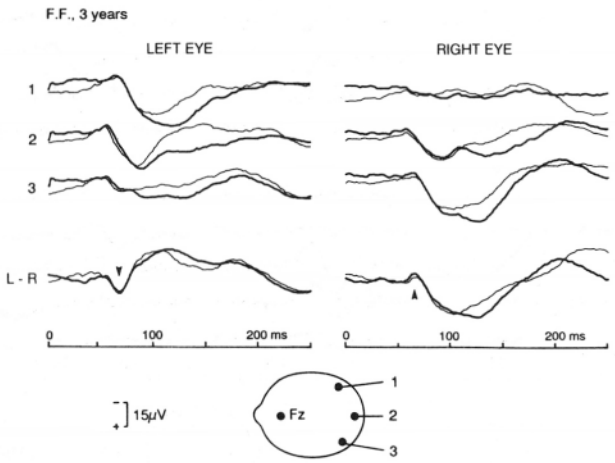


Fig. 11. *Flash VEP from an albino subject: difference in occipital distribution for the two eyes. The reversed left and right eye asymmetry is also seen in a trace where the difference potential is derived by subtracting the left occipital response from the right one (trace 4, reversed asymmetry marked with an arrow).*

Sl. 11. *VEP na bliskavico pri človeku z albinizmom: razporeditev odzivov po zatilju z enega očesa je nasprotna razporeditvi z drugega očesa. Obrnjena asimetrija (polarnost) je še bolje vidna, ko se odziv z leve odšteje od odziva z desne (kanal L-R, puščica).*

VEP to pattern stimulation can be reliable in detecting misrouting in older albino children. However, it seems that pattern onset stimulation suits better than pattern-reversal stimulation. The reason is that P100 to pattern-reversal stimulation is extinguished with nystagmus, which is very common in albinos. The onset stimulus also reveals VEP asymmetry specific for albinism. It is found for the positive CI component (80-110 ms), which is considered to reflect primarily local luminance variation in the response. The negative CII component reflects contrast mechanisms, and it is, therefore, particularly sensitive to pattern size and defocus. Because of the foveal hypoplasia and reduced acuity in albinos, it is common to find an absent or relatively weak CII and identifiable CI component (38).

VEP asymmetries resulting from chiasmal or retrochiasmal pathway lesions can not be confused with the albino asymmetry. The pattern-reversal VEP asymmetry in albinos (39) is opposite to the

crossed asymmetry seen in lesions affecting the crossed optic fibres at the region of the chiasm (33). In albinos, P100 is elicitable for the right eye stimulation over the right hemisphere, and for the left eye stimulation over the left hemisphere. In chiasmal lesions, P100 is found for the right eye stimulation over the left hemisphere, and for the left eye stimulation over the right hemisphere (Fig. 9). Thus, cortical representation of VEP in albinos reflects primarily the activity of the decussating retinal fibres, in chiasmal compressions, on the other hand, a dysfunction of the decussating fibres.

VEP diagnostics of retrochiasmal dysfunctions

The sensitivity of pattern VEP in detecting optic tract, optic radiation and occipital cortex dysfunctions is below that of the perimetry (31, 40). In fact, VEP changes are also not selective enough to reveal the exact site of a lesion along the retrochiasmal pathway. The uncrossed distribution of VEP is associated with homonymous visual field defects, and is characteristic for compressions of the fibres leaving the chiasm posteriorly. It is also associated with the lesions of the occipital cortex. Extensive hemisphere destruction, which spares the primary visual pathways, does not appear to affect VEP (41).

Homonymous field defects cause loss of activity, which results in an asymmetrical distribution of the full-field response. However, the sensitivity of the full-field stimulation for post-chiasmal lesions is rather poor. It can be enhanced by separate stimulation of each geniculo-calcarine pathway and by comparison of the activity generated in each hemisphere. When homonymous field defect is complete (macular splitting), half-field stimulation will detect abnormality, but when the macula is spared, the detection rate of the half-field abnormality is low (25, 40).

In neurological practice homonymous hemianopsias are frequent field defects. If only the periphery of the visual field, or only small parts of the parafoveal visual fields are affected, VEP will be indistinguishable from variants in healthy subjects. Normal VEP does not exclude an organic cause of visual symptoms. It was obtained also in cortically blind patients (42, 43).

Relevance of the size of pattern elements

The question whether the size of a check has any influence on the sensitivity of the VEP, may not be easy to answer. At the beginning of pattern stimulation, different sizes of pattern were used in order to enhance the specificity and sensitivity of detecting visual function abnormality. The use of small, 10 to 30 minutes, checks, has usually been found to increase abnormality detection. However, small checks and fields are optimal stimuli at the fovea, larger checks and fields at the periphery (44).

Physiological mechanisms underlying VEP activity to different pattern sizes still can not be explained. Whether they are related to receptive field organisation at the retinal level (ganglion cells) or at the cortical level is also still the subject of discussion. However, the receptive field size of the foveal ganglion cells is smaller compared to parafoveally located ganglion cells. Similar difference of the receptive field size between the foveal and more peripheral areas is present in the primary visual cortex. Indeed, with the appropriate pattern size, we may activate predominantly different classes of neurons (4).

The size of checks can effect VEP amplitude and latency. A number of studies pointed out that VEP responses were abnormal when optimal pattern size was used. However, this effect is more apparent in the retinal pathology, e.g. in maculopathy and glaucoma (4). In the diagnosis of MS, it is still unclear which pattern size is optimal for detecting VEP abnormalities (45). However, the strategy for identifying amblyopic eyes in children relies on the use of different pattern sizes (46). The figure 12 shows that the change in VEP was evident when the small pattern elements were used.

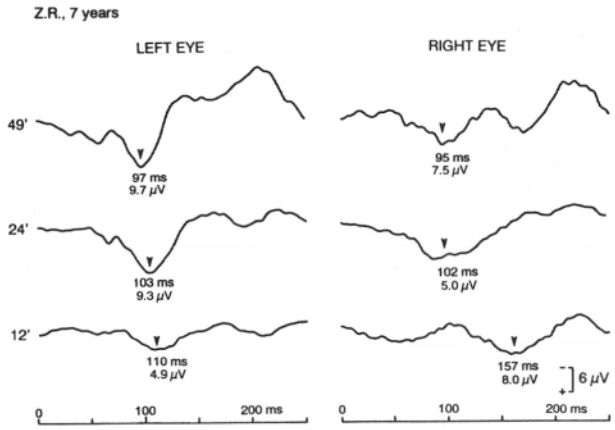


Fig. 12. *VEP amplitude and latency differences between the two eyes are shown only with smaller checks (12').*

Sl. 12. *Razlike v amplitudah in latencah VEP so se pokazale šele pri manjši velikosti dražilnih kvadratkov (12').*

Relevance of N70

The most prominent feature of the transient VEP elicited by pattern-reversal stimulation is the major positive component P100. The preceding negative component N70 is rarely used and described, though there are reports (4, 45) suggesting that it might be a reliable clinical indicator of the visual pathway pathology. There is also some evidence that it might reflect the activity of cortical generators distinct from that of the major P100 (4), which is also in agreement with our experiences. We found that the N70 amplitude versus the check size curve showing the peak values for smaller checks differs from that of the P100 (Fig. 13).

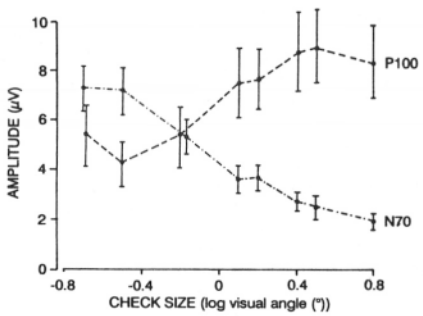


Fig. 13. *Dependence of the wave N70 and wave P100 amplitudes of VEP on the check size of pattern-reversal stimulus (mean amplitudes and 2 SE of the mean; N = 12) (with permission from ref. 1).*

Sl. 13. *Odvisnost amplitud valov N70 in P100 od velikosti kvadratkov v slikovnem dražljaju (srednje vrednosti amplitud in 2 SD; N = 12) (z dovoljenjem iz ref. 1).*

Furthermore, we were able to show that the occlusion of the stimulus from the central part of the visual field affects differently N70 and P100 waves (47). In addition, our study of the pattern-reversal VEP distribution over five electrodes placed in a horizontal row across the occiput, in response to half-field stimulation, showed distinct distribution of the N70 and P100 (48). Thus, we believe that, with selected stimulus characteristics and multichannel recording, the N70 may offer additional insight into clinical VEP diagnostics.

Summary

We can generally conclude that the noninvasive clinical electrophysiological measurements allow an assessment of visual function along the entire length of the visual system. With a cautious consideration of knowledge about basic physiological visual processes, we hope to improve the sensitivity and selectivity of clinical visual electrophysiological tests. The tests assessing the anterior part of the visual pathway, especially the retinal function, could be more easily defined in anatomical and physiological terms, than those assessing the posterior parts (retrochiasmal) of the visual system. From a physiological point of view this is hardly surprising. It is much easier to obtain information from a well defined retinal network with a finite number of cells engaged in the transduction and further processing of the visual stimulus than from complex arrays of millions of cortical cells subserving the higher sensory processes. At present, we may conclude that the stimulus parameters used for pattern-reversal VEPs are more empirically than theoretically justified. Therefore, it is to be expected that the studies concerned with the effect of stimulus characteristics on the anatomical and physiological differentiation of the visual pathway will continue (49). We would like to draw attention to the pattern onset (38) as well as to the sinusoidal gratings pattern (4) stimuli, which promise to improve the electrophysiological differentiation of the visual system.

Acknowledgement. We are grateful to prof. T. S. Prevec for his review of our text.

References

1. Štrucl M. Electrophysiological basis of diagnostics at different levels of the visual system. Neurologija 1990; 39: Suppl 1: 203-10.
2. Van Dijk BW, Spekreijse H. Localization of electric and magnetic sources of brain activity. In: Desmedt JE ed. Visual evoked potentials. Amsterdam, New York, Oxford: Elsevier, 1990: 57-74.
3. Hubel DH, Wiesel TN. Receptive fields and functional architecture of monkey striate cortex. J Physiol 1968; 195: 215-43.
4. Bodis-Wollner I, Brannan JR, Ghillardi MF, Mylin H. The importance of physiology to visual evoked potentials. In: Desmedt JE ed. Visual evoked potentials. Amsterdam, New York, Oxford: Elsevier, 1990: 1-24.
5. Baylor DA, Lamb TD, Yau KW. Responses of retinal rods to single photons. J Physiol 1979; 288: 613-34.
6. Hawlina M. Clinical application of retinal and cortical evoked potentials. Neurologija 1990; 39: Suppl 1: 211-24.
7. Ikeda H. Retinal mechanisms and the clinical electroretinogram. In: Halliday AM, Butler SR, Paul R eds. A Textbook of Clinical Neurophysiology. London: John Wiley & Sons Ltd, 1987: 569-94.
8. Marmor MF, Arden GB, Nilsson SE, Zrenner E: Standard for Clinical Electroretinography. Arch Opthalmol 1989; 107: 816-9.
9. Heckenlively JR, Weleber RG, Arden GB. Testing levels of the visual system. In: Heckenlively JR, Arden GB eds. Principles of practice of clinical Electrophysiology of Vision. St Louis: Mosby Year Book, 1991: 485-93.
10. Hawlina M, Štrucl M, Stirn-Krajnc B, Finderle Ž, Brecelj J. Pattern electoretinogram recorded by skin electrodes in early ocular hypertension and glaucoma. Doc Ophtalmol 1990; 73: 183-91.
11. Bach M, Hiss P, Rover J. Check-size specific changes of pattern electroretinogram in patients with early open-angle glaucoma. Doc Ophtalmol 1988; 69: 315-22.
12. Kuffler SW. The single cell approach in the visual system and the study of receptive fields. Invest Ophtalmol 1973; 12: 794-813.
13. Maffei L, Fiorentini A. Electroretinographic response to alternanting gratings before and after section of the optic nerve. Science 1981: 211; 593-5.
14. Chiappa KH. Evoked potentials in clinical medicine. New York: Raven Press, 2nd ed. 1990: 111-72.
15. Halliday AM. Evoked potentials in clinical testing. 2nd ed. Edinburgh: Churchill-Livingstone, 1993: 1-357.
16. Brecelj J. VEPs in the assessment of visual pathway lesions. Neurologija 1990; 39: Suppl 1: 225-36.
17. Blumhardt LD, Halliday AM. Hemisphere contributions to the composition of the pattern-evoked potential waveform. Exp Brain Res 1979; 36: 53-69.
18. Halliday AM, Barrett G, Halliday E, Mushin J. A comparison of the flash and pattern evoked potential in unilateral optic neuritis. Wissenschaftliche Zeitschrift der Ernst-Moritz-Arndt Universität. Greifswald 1979; 28: 89-95.
19. Harding GFA. Origin of visual evoked cortical potentials components. In: Heckenlively JR, Arden GB eds. Principles and practice of clinical electrophysiology. St Louis: Mosby Year Book, 1991: 132-44.
20. Barrett G, Blumhardt L, Halliday AM, Halliday E, Kriss A. A paradox in the lateralization of the visual evoked response. Nature (Lond.) 1976; 261: 253-5.
21. Brecelj J, Cunningham K. Occipital distribution of foveal half-field responses. Doc Opthalmol 1985; 59: 157-65.
22. Brindley GS. The variability of the human striate cortex. J Physiol 1972; 225: 1-3P.
23. Blumhardt LD, Barrett G, Halliday AM, Kriss A. The effect of field size on the pattern-reversal visual evoked response (PRVER). Clin Vision Sci 1989; 4: 27-40.
24. Celesia GG, Polycin RD, Holden JE, Nickles RJ, Gatley JS, Koeppe RA. Visual evoked potentials and positron emission tomographic mapping of regional cerebral blood flow and cerebral metabolism: Can the neuronal potential generators be visualized? Electroenceph Clin Neurophysiol 1982; 54: 243-56.
25. Brecelj J. Visual evoked potentials and the localization of visual pathway lesions. Spektrum Augenheilk 1991; 5: 114-22.
26. Brecelj J, Štrucl M, Hawlina M. Central fiber contribution to W-shaped visual evoked potentials in patients with optic neuritis. Doc Opthalmol 1990; 75: 155-63.
27. Blumhardt LD, Barrett G, Halliday AM, Kriss A. The effect of experimental "scotomata" on the ipsialteral and contralateral responses to pattern-reversal in one half-field. Electroenceph Clin Neurophysiol 1978; 45: 376-92.
28. Halliday AM. Visually evoked responses in optic nerve disease. Trans opthal Soc UK 1976; 96: 372-6.
29. Blumhardt LD. Variable effects of pathologic scotomata on wave form of pattern-reversal visual evoked response. Doc Opthalmol 1985; 59: 107-19.
30. Fukui R, Kato M, Kuroiwa Y. Effect of central scotomata on pattern-reversal visual evoked potentials in patients with maculopathy and healthy subjects. Electroenceph Clin Neurophysiol 1986; 63: 317-26.
31. Holder GE. Chiasmal and retrochiasmal lesions. In: Heckenlively JR, Arden GB eds. Principles and practice of clinical electrophysiology of vision. Mosby Year Book, 1991: 557-64.
32. Brecelj J, Štrucl M, Škrbec M. Visual evoked potentials in compressive lesions of the optic chiasm. Neuro-opthalmology 1992; 12: 207-14.
33. Halliday AM, Halliday E, Kriss A, McDonald W, Mushin J. The pattern-evoked potential in compression of the anterior visual pathways. Brain 1976; 99: 357-74.
34. Brecelj J. A VEP study of the visual pathway function in compressive lesions of the optic chiasm. Full-field versus half-field stimulation. Electroenceph Clin Neurophysiol 1992; 84: 209-18.
35. Brecelj J. Electrodiagnostics of chiasmal compressive lesions. J Psychophysiol, in press.
36. Guillery RW, Okoro AN, Witkop CJ. Abnormal visual pathways in the brain of a human albino. Brain Res 1975; 96: 373-7.
37. Russell-Eggitt I, Kriss A, Taylor DSI. Albinism in childhood: a flash VEP and ERG study. Br J Ophthalmol 1990; 74: 136-40.
38. Apkarian P. Methodology of testing for albinism with visual evoked cortical potentials. In: Heckenlively JR, Arden GB eds. Principles and paractice of clinical electrophysiology of vision. St Louis: Mosby Year Book, 1991: 425-34.
39. Carroll WM, Jay BS, McDonald WI, Halliday AM. Pattern evoked potentials in human albinism. Evidence of two different topographical asymmetries reflecting abnormal retino-cortical projections. J Neurol Sci 1980; 48: 265-87.
40. Blumhardt L. The abnormal pattern visual evoked response in neurology. In: Halliday AM, Butler SR, Paul R eds. A textbook of clinical neurophysiology. Chichester: John Wiley & Sons, 1987: 307-42.
41. Onofry M. Generators of pattern visual evoked potentials in normals and in patients with retrochiasmatic lesions. In: Desmedt JE ed. Visual evoked potentials. Amsterdam: Elsevier, 1990: 87-113.
42. Bodis-Wollner I, Atkin A, Raab E, Wokstein M. Visual association cortex and vision in man: Pattern evoked occipital potentials in a blind boy. Science 1977; 198: 629-31.
43. Celesia GG, Archer CR, Kuroiwa Y, Goldfader PR. Visual function of the extrageniculo-calcarine system in man. Relationship to cortical blindness. Arch Neurol 1980; 37: 704-6.
44. Meredith JT, Celesia GG. Pattern-reversal visual evoked potentials and retinal eccentricity. Electroenceph Clin Neurophysiol 1982; 53: 243-53.
45. Ghilardi MF, Brannan JR, Bodis-Wollner I. Clinical applications of pattern visual evoked potentials. In: Desmedt JE ed. Visual evoked potentials. Amsterdam: Elsevier, 1990: 121-46.
46. Barnard WM, Arden GB. Changes in the visual evoked response during and after occlusion therapy for amblyopia. Child: care, health and development 1979; 5: 421-30.
47. Brecelj J, Prevec TS. Study of foveal and peripheral visual responses evoked by pattern-reversal stimulation. In: Barber C ed. Evoked potentials II. Stoneham (USA): Butterworths, 1984: 280-6.
48. Štrucl M, Prevec TS, Zidar I. Effect of stimulus variation on early negative wave (N70) of pattern shift visual evoked potential. Electroenceph clin Neurophysiol 1985; 61: S120.
49. Ossenblok P. The sources of the pattern VEP in man. Academisch proefschrift. University of Amsterdam, The Netherlands, 1992: 1-141.

NEKATERI ANATOMSKI IN FIZIOLOŠKI VIDIKI KLINIČNE ELEKTROFIZIOLOGIJE VIDA

Jelka Brecelj, Martin Štrucl

Izvleček - Izhodišča. *Avtorja obravnavata neinvazivne elektrofiziološke metode za klinično ocenjevanje vidnega sistema (elektroretinogram ERG, vidni evocirani potenciali VEP) z vidika nekaterih anatomskih in fizioloških spoznanj. Ob upoštevanju fizioloških in anatomskih značilnosti pri izboru parametrov vidnega dražljaja si obetamo izboljšati občutljivost in selektivnost teh metod. Ena izmed ključnih fizioloških ugotovitev je elektrofiziološki dokaz obstoja vzporednih podsistemov vida. Velika večina nevronov vidnega sistema se maksimalno ne vzdraži z difuzno osvetlitvijo, temveč samo z izbranimi lasnostmi vidnega dražljaja. V retinografiji lahko z ustrezno modulacijo dražljaja prikažemo funkcijo različnih slojev mrežnice. V članku so predstavljeni osnovni retinografski testi ter slikovni VEP na lastnih primerih in izkušnjah laboratorija. Bliskovni ERG prikazuje globalno funkcijo mrežnice in je zlasti pomemben za ugotavljanje prirojenih in pridobjenih okvar mrežnice, ki prizadenejo predvsem njene distalne sloje. Posebej je moč prikazati funkcijo čepnic in paličnic. V nasprotju s tem je za prikaz proksimalnih slojev mrežnice, predvsem njenega makularnega predela, ustreznejši ERG, izzvan s kontrastno strukturiranim dražljajem. Takšen dražljaj, kjer se izmenjujejo temni in svetli kvadratki, je tudi največkrat uporabljan za izzivanje kortikalnih potencialov VEP z dobro opisano obliko potencialov in njihovo razporeditvijo na skalpu, saj je občutljivost slikovnega VEP dokazano večja od občutljivosti bliskovnega VEP. Slikovni VEP kompleksno zrcali anatomske značilnosti vidne možganske skorje, predvsem tistega predela, kamor se projicirajo makularni predeli mrežnice. S selektivnim draženjem nazalne ali temporalne polovice vidnega polja je mogoče ločeno prikazati funkcije križanega in nekrižanega nitja in prirojene anatomske nepravilnosti projekcijskega nitja, kot na primer pri albinizmu. Občutljivost VEP pri odkrivanju retrohiazmalnih disfunkcij je manjša kot pri perimetriji. Velikost kvadratkov je zelo pomeben parameter pri VEP, saj je izbor optimalne velikosti pri določeni indikaciji VEP osnovna strategija za povečanje občutljivosti testa. Čeprav analiza VEP temelji predvsem na ugotavljanju latence in amplitude največjega pozitivnega vala P100, pa lahko ima predhodni val N70 drugačen fiziološki pomen in klinično pomembnost.*

Zaključek. *Splošno velja, da lahko z elektrofiziološkimi testi ocenjujemo delovanje vzdolž celotne vidne poti. S skrbnim upoštevanjem fizioloških lastnosti vidnega sistema si obetamo izboljšati občutljivost in selektivnost teh metod. Ugotovimo pa lahko, da lahko izvide elektrofizioloških testov takrat, ko ocenjujemo sprednji pregenikulatni del vidne poti, anatomsko in fiziološko razložimo veliko lažje kot takrat, ko ocenjujemo retrohiazmalni del vidne poti.*

Ključne besede: *elektroretinografija; klinična elektrofiziologija; vidni evocirani potenciali; vidna pot*

Canon
MAN VERSTEHT SICH BESSER

BIRING

Biring d.o.o.
Ind. cona Trzin, 61234 Mengeš, Slovenija
Tel.: 061/712-427, 712-429, 712-430
Fax: 061/714-793

Canon BN-22

Prenosni računalnik z vgrajenim tiskalnikom

Računalnik: Sistem 486/25, 4-12 MB RAM, disk do 180 MB, 2 x PCMCIA 2.0
Tiskalnik: Tiskalnik bubble-jet, 116 znakov/s, 360 pik/palec
31,1 x 25,4 x 5,5 cm, 3,5 kg z akumulatorjem

ELECTRODIAGNOSIS OF THE PRIMARY AFFERENT VISUAL SYSTEM

PAST, PRESENT AND FUTURE

ELEKTRODIAGNOSTIKA PRIMARNEGA AFERENTNEGA VIDNEGA SISTEMA

PRETEKLOST, SEDANJOST IN PRIHODNOST

Hisako Ikeda

Vision Research Unit of Sherrington School, UMDS, The Rayne Institute, St. Thomas' Hospital, London SE1 7EH, Great Britain

Key words: *compressive optic neuropathy; electrooculogram; electroretinogram; ischaemic optic neuropathy; macular degeneration; optic atrophy; optic neuritis; retinitis pigmentosa; rod/cone functions*

Abstract - *The experience of recording clinical electrooculogram (EOG), electroretinogram (ERG) and visual evoked potentials (VEP) since the late 1960s is described. As the number of patients referred to the electrodiagnostic service escalated to reach 4,826, an attempt has been made to overview the paramount data. In this paper, the following three topics have been chosen from the data obtained with a simultaneous recording of averaged ERGs and VEPs and the light induced change in the EOG. Firstly, the use of ERG/VEP ratio for visual prognosis of babies who showed no visual following. Secondly, the use of ERGs and VEPs evoked by a 60° dim blue flash delivered at 1 Hz, and those evoked by a 5° red spot flickered at 30 Hz for the assessment of rod and cone retinal function respectively. Thirdly, the use of the ERG/VEP ratios and ERG or VEP delays together with EOG light rise to differentiate different categories of optic nerve diseases. It is concluded that simultaneous recordings of ERG and VEP using non-invasive electrodes, provided that many different stimulating conditions are used, may play a unique role in elucidating the functional (physiological) state of the intact human visual system in health and disease.*

Introduction

In 1968, I began to build a single cell recording system for the visual system of the cat at the Department of Ophthalmology of the Royal College of Surgeons in London. At the same time, I was also asked if I could record the electrooculogram (EOG) and electroretinogram (ERG) of patients at the Royal Eye Hospital, which was an affiliated hospital of the Royal College of Surgeons. The only equipment available was an old two-channel EEG pen recorder in the store of an operating theatre. Since the hospital was headed by Professor Arnold Sorsby, a pioneer of genetic ophthalmology (1), the Royal Eye Hospital gathered a large number of patients and their families with hereditary retinal degenerations dating back to the Victorian era. It was, therefore, felt that an early screening of affected members of the family by the electrophysiological technique would be useful.

Although the task was a little formidable, the air of optimism and confidence in the future was boundless. I somehow managed to begin a weekly clinical electrophysiological service with the primitive equipment. I still have a vivid memory of inserting a big copper plate as a common earth into the back garden of the hospital, where hollyhocks were flowering. The service first included measurements of light-induced change in the corneo-fundal potential, using the method of the EOG and ERG with a contact lens electrode (2). Soon the very first model of an averaging computer was purchased with a grant from the Prevention of Blindness Fund (now called the Iris Fund) to record the visual evoked potential (VEP). The averager did not have an artefact rejection facility and I had to change the frequency band by using mini-jumper leads, which involved opening the amplifier drawer each time.

An unforeseen problem, however, was that the number of patients referred to the electrodiagnostic service escalated, particularly following the amalgamation of the Royal Eye Hospital and St Thomas' Hospital in 1974. It reached 5,135 at the end of June 1993, when I terminated the service. About one third of these patients have also been seen more than once. Whilst I was able to write reports on individual patients to the referring consultants, I never had time to overview the mounting set of data, as my time was occupied by our research programme, grant applications and teaching. But in the January 1992, as my time of retirement approached, I began the analysis of 4,826 patients' data. The data in hand are vast and complicated. I therefore proposed for this lecture, to limit the data of discussion to those which are obtained from the simultaneous recording of the ERGs and VEPs and to the EOG, and to address the following three questions: i.e. 1. assessment of visual prognosis of babies with no visual following, 2. differential measurement of rod and cone mediated retinal function in chorioretinal diseases, and 3. electrodiagnosis of different categories of optic nerve diseases.

Abbreviations: *BLOA, bilateral optic atrophy; comp., compressive; EOG, electrooculogram; ERG, electroretinogram; FERG, flash-evoked ERG; FVEP, flash-evoked VEP; isch., ischaemic; MD, macular degeneration; ON, optic neuritis; Onp. optic neuropathy; PERG, pattern-evoked ERG; PVEP, pattern-reversal visual evoked potential; RP, retinitis pigmentosa; VEP, visual evoked potential*

Electrodiagnostic tests

In Figure 1, the sites of generation of the four electrical potentials discussed in the lecture, i.e. the EOG light rise, the flash and pattern-evoked ERGs and the VEP, are indicated.
Figure 1 shows the hierarchical organisation of three principal cells of the retina. The interneurons, the horizontal and interplexiform and amacrine cells are omitted and the macular and the peripheral retina are shown separately. At the macula, the photoreceptors are mainly cones and one to one, or an even greater increase of connectivity occurs from the photoreceptor to the bipolar, and from the bipolar to the ganglion cells (3). Effectively, therefore, over 60 % of the optic nerve fibres are those arising from the maculae, eventually occupying the major portion of the visual cortex. At the peripheral retina, on the other hand, many photoreceptors converge to a small number of bipolars and again to even fewer ganglion cells.

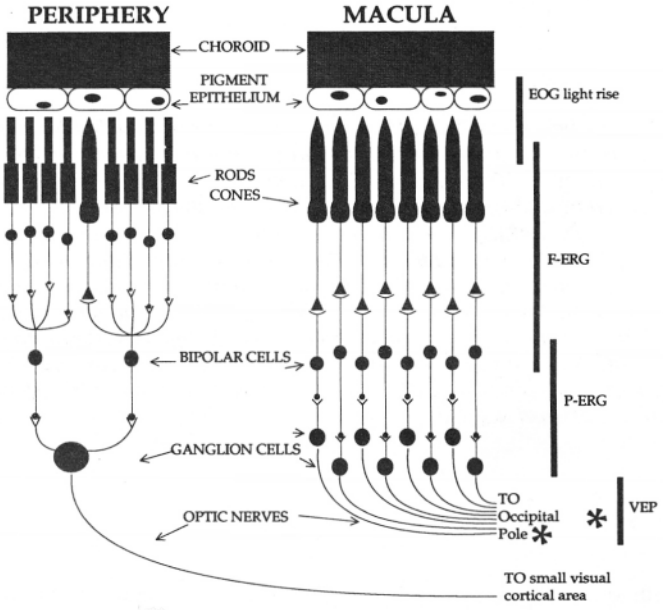


Fig. 1. *Hierarchical neural organisation of the peripheral and the macular region of the retina, and the site of generation of the EOG light rise and the F- and P- ERGs. The VEP is generated at the visual cortex (not shown but indicated by *), which illustrates that the visual cortex receives a disproportionately greater number of optic nerve fibres arising from the maculae.*

Sl. 1. *Hierarbična organizacija obrobnega in makularnega predela mrežnice in mesto izvora svetlobnega porasta EOG ter nastanka FERG in PERG. VEP izvira v vidni možganski skorji (ni prikazana, vendar označeno z zvezdico), ki sprejema nesorazmerno večje število vlaken vidnega živca iz makule.*

EOG light rise originates at the junction of the pigment epithelium and at the photoreceptor outer segments, which contain visual pigments (4, 5). The EOG is recorded between electrodes placed on the medial and lateral canthi of each eye. A patient is asked to look rhythmically between the fixation light spots placed 30° apart on a screen. The horizontal eye movement of a constant amplitude is made, first in the dark and then in the light when the screen is brightly lit. In a normal eye, dark adaptation causes a decrease in the potential, and light adaptation, on the other hand, an increase. This light-induced rise in the potential expressed as a percentage (4) is a measure of the integrity of the pigment epithelium and photoreceptors (5, 6).

Flash-evoked ERG (FERG) consists of two major components; a-wave and the b- wave. The a-wave arises from the photoreceptors and reflects extracellular current flow caused by light-evoked hyperpolarization of the photoreceptors. The b-wave originates from the light depolarising ON-bipolar cells (7).

Pattern-evoked ERG (PERG) is generated at the inner retina which involves light depolarising ON- and dark depolarising OFF-cell pathways, (8, 9).

Visual evoked potential (VEP) is the field potential of the electroencephalogram (EEG) recorded at the scalp over the visual cortex at the occipital pole. Since many optic nerve fibres are the axons of the ganglion cells carrying information from the retinal maculae, the visual cortex receives a disproportionately large projection from the maculae (Fig. 1). VEP, therefore, mainly reflects responses of the cortical cells to the retinal macular inputs. A small number of peripheral ganglion cell fibres eventually go to the small peripheral areas of the visual cortex. However, using a wide scalp electrode distribution and different visual field stimulation techniques, elegant demonstrations of VEPs associated with a variety of field defects due to intra-cranial lesions are indeed possible (10).

Simultaneous recording of flash or pattern ERGs and VEPs. Both F- and P-ERGs are recorded with adhesive skin electrodes under the lower lid of each eye, as shown in Figure 2 left. As monocular stimulation is always used, the electrode on the stimulated eye is the positive electrode and that on the covered eye is the negative. VEPs were recorded between an electrode placed on the scalp over the visual cortex and another over the frontal lobe (Fig. 2 right). The other electrode over the frontal lobe is used as a common ground. The method is non-invasive and exactly the same recording conditions may be used for patients of all ages. Figure 2 also shows examples of FERG and flash evoked VEP (FVEP) averaged 100 responses evoked with a bright flash at a stimulation rate of 4Hz, and PERG and PVEP obtained after averaging 150 responses to a high contrast (0.9) checkerboard pattern of 44' of arc squares, phased reversed at 2 Hz (i.e. 4 reversals/s). The responses were obtained from a normal subject.

Test procedure. The following *sequence of stimuli* was used on each patient. Firstly, PERG and PVEPs were evoked with monocular stimulation of contrast (0.9) reversal (4 Hz) of checkerboard patterns with square sizes of 60', 44', 28' and 15'. The total stimulation area was 30° for the 60' and 44' square patterns, whilst it was 15° for the 28' and 15' square patterns. Following the completion of the recordings of PERG and PVEPs, the pupils of patients were dilated with cyclopentolate hydrochloride BP (1 % W/V) eye drops, and one eye was occluded. The FERG and FVEP were then evoked by 4, 10, 20 and 30 Hz flash from the open eye. The intensity of the flash was approximately 5.5 log units above the human scotopic threshold and subtended the visual angle of 60°. Following the 30Hz stimulation of the bright flash, a deep narrow red filter (Kodak No. 29) was interposed together with a diaphragm of 5° to the flash, to stimulate macular cones at 30 Hz.
After the red flicker stimulation, all lights in the room were switched off and the eye patch was transferred in the dark to the previously opened eye from the other eye which had been dark adapted by the eye patch. The ERGs and VEPs were then recorded from the second eye with a 1 Hz *blue flash* using a tricolour blue filter with the transmission band of 340-530 nm (peak, 475 nm). The intensity of the blue flash was 2.5 log units above the human scotopic threshold. Following this, exactly the same sequence of flash stimulations that had been used for the first eye was followed, starting from bright 4 Hz flash to 30 Hz red spot flicker.

The eye patch was then transferred in the dark to the other eye, re-exposing the first eye to obtain an ERG and VEP with the dim blue flash. The whole recording procedure took approximately 30 min. Only the recordings of flash evoked responses were possible, however, from babies and from some adult patients with severe cataracts or haemorrhages.

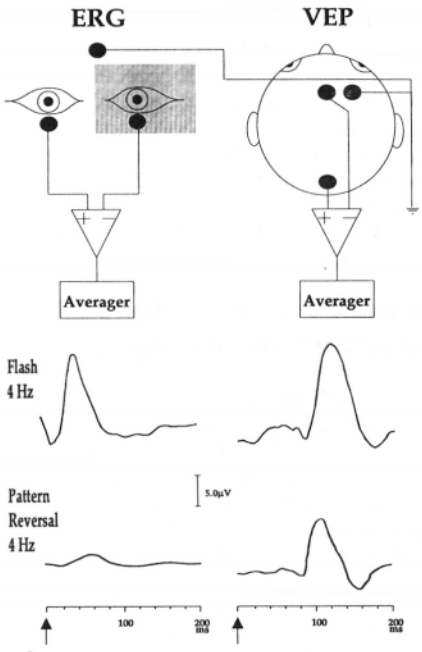


Fig. 2. *A diagram showing the electrode arrangements for the simultaneous recordings of the ERGs and VEPs using averaging technique, and examples of simultaneously recorded FERG and FVEP evoked by a bright flash (4 Hz) and PERG and PVEP evoked by contrast reversal (4 reversal/s) of a checkerboard pattern consisting of 44' squares obtained from a normal subject. For both ERGs and VEPs, positive potentialis shown as an upward and negative potential as a downward deflection.*

Sl. 2. *Razporeditev elektrod pri hkratnem snemanju ERG in VEP s tehniko povprečevanja. Primeri hkrati posnetih FERG in FVEP, pobujenih z bliskom (4 Hz), ter PERG in PVEP, pobujenih s slikovnim dražljajem (4 izmenjave/s) v obliki šahovnice z velikostjo kvadratkov 44 minut vidnega kota pri normalnih osebah. Tako za ERG kot za VEP je pozitivnost prikazana navzgor.*

Analysis of ERGs and VEPs. For both FERG and FVEP, the response amplitudes were measured from the preceding negative trough to the major positive peak. The FERG peak, i.e. "the b-wave implicit time" occurs at about 35-45 ms, and the major positive peak of FVEP, at about 120 ms, when evoked by the bright flash of 4 Hz in normal subjects. From the amplitude measurements, the ratio of ERG and VEP amplitudes, i.e. ERG/VEP, was obtained. The ratio is used as an index of retinal component, relative to a post-retinal component.

Inclusion and exclusion of data. The first stage of the data analysis was to read available clinical notes, examine electrophysiological results on each of 4,826 patients, and classify each into different diagnostic categories. During this process, sadly, the data from a staggering number of patients (1,890) had to be eliminated. The reason for the elimination was due to either (a) lack of clinical information, (b) "mixed condition" or (c) "uncertain diagnosis". The "mixed condition" meant that the patient had a number of conditions which could affect the retinal or optic nerve functions, e.g. diabetes, heavy smoking, and the possibility of compressive lesions. The "uncertain diagnosis" included cases in which the diagnosis was not established or clinical and electrophysiological diagnosis disagreed. The final analysis was thus made for 2,936 patients. Of these, 88 were babies under 3 years of age; 271 were children aged 4-14, and 2,577 were over the age of 15.

As a control for the adults aged over 15 in this study, the data obtained from 502 "normal" eyes were used. These consisted of unaffected eyes of patients with contusion injury or metal siderosis (n = 53), or with optic neuritis (n = 121), and eyes of patients complaining of some neurological or visual disturbances, but all investigations, including the ERGs and VEPs, were normal (n = 328). The mean visual acuity was 6/5.4 (excluding visual acuities recorded from patients with clearly hysterical blindness), and the mean age (± SEM) of patients whose eyes were included 35.1 (± 0.7). Similarly, the control data for the children aged 4-14 were obtained from 39 "normal" eyes of children with monocular injury or hysterical blindness (mean age 8.3 ± 0.7; visual acuity 6/5.2, excluding the acuity of "hysterical" blindness). Only three "normal" babies under the age of 3 were examined.

The FERG/FVEP ratio may be used as a prognostic index for babies with no visual following

The first topic of this lecture chosen from the results of the analysis, concerns electrodiagnosis of babies. Up to the early 1970's, the EOG and ERGs of babies were investigated under general anaesthesia using an EOG machine built in Holland (11). The baby's eyes were held by contact lens and were displaced along the horizontal axis at a constant angle by an electromechanical device to record the EOG. The same apparatus was also used for recording the ERG by replacing the EOG contact lens to an ERG type. We recorded many babies' EOG and ERGs in the early 70's in this way (12). However, the visual-evoked cortical responses were not very successful under anaesthesia, due to the slow high amplitude EEG α-wave, contaminating the light-evoked responses. There was also the ethical question of whether or not one should anaesthetise babies for diagnostic investigation. The development of simultaneous recordings of ERG and VER, using averaging techniques, simplified these problems with the recordings from babies.

All the babies under the age of 3 referred to us showed little or no signs of visual following. Birth asphyxia was the highest referral condition (32 %) followed by cerebral lesion (29 %) which included cerebral palsy, hydrocephalus, microcephalus, cephalitic cysts and meningitis. Severe ocular abnormalities (17 %), including strabismus and nystagmus, were also fairly common referral conditions, and so were prematurities with some stormy postnatal events (12 %). Some babies were thought to have pale discs (7 %) and one had retrolental fibroplasia. We have, in addition, seen 3 normal babies as controls.

To obtain ERGs and VEPs from the babies, we followed the baby's eye with a bright flash and used intermittent averaging, so that only those responses when the baby's eye and the flash were more or less coincidental were averaged. The analysis of the simultaneously recorded FERGs and FVEPs obtained from 85 babies with no visual attention revealed no clear cut difference in the ERG/VEP ratio between different referral conditions. However, all such babies produced significantly subnormal ERG and VEPs: with the amplitudes of the VEPs being proportionately smaller than that of the ERGs. The mean and SEM of ERG/VEP ratios of the babies with no visual following was thus *3.8* (± 1.2), which is very high compared to the ERG/VEP ratios obtained from three normal babies (*0.2, 0.3* and *0.5*).

An encouraging result emerged however from the analysis of 12 babies on whom follow-up studies have been made: babies who

initially showed the ratio between *0.2-1.0*, even if the amplitudes of the responses were very low, later developed good vision, whilst those babies who showed high ERG/VEP ratio (over *4.0*) had poor visual prognosis, regardless of the response amplitudes. Figure 3 illustrates this. ERGs and VEPs obtained from a baby with good visual prognosis (Baby A) are shown in Figure 3A, whilst those from a baby with poor visual prognosis (Baby B) in 3B. For each baby, the initial recording results were shown on the left, and the responses recorded on follow-up studies on the right of Figure 3.

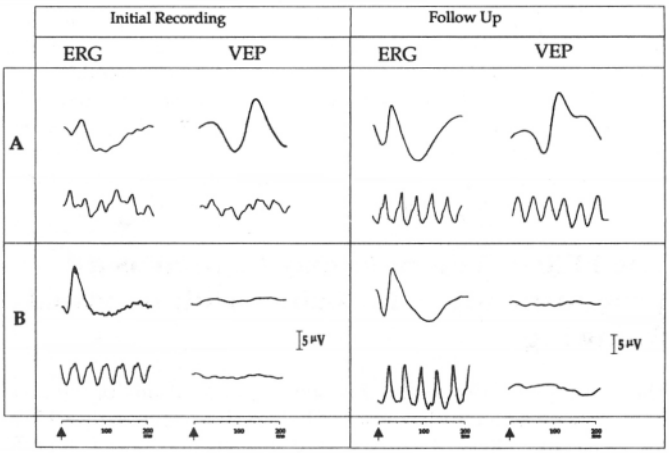


Fig. 3. *Simultaneously recorded ERGs and VEPs evoked by bright flash of 4 Hz (top traces in each case) and 30 Hz (bottom traces in each case) obtained from A) a baby who showed good visual prognosis and B) a baby who showed poor visual prognosis. Note that the ERG/VEP ratio of the baby A is low at the initial recording (3 months), and that all responses show an increase at follow-up study (2 years), whilst the ERG/VEP of the baby B is initially (9 months) very high, since the VEP is very small, and that it shows little change in the follow-up study.*

Sl. 3. *Hkrati posneti ERG in VEP, pobujeni z bliskom 4 Hz (v vseh primerih zgoraj) in 30 Hz (v vseh primerih spodaj) A) pri otroku z dobro in B) pri otroku s slabo prognozo vida. Razmerje ERG/VEP pri otroku A je pri začetnem posnetku (3 mesece) nizko in vsi odgovori se povečajo pri ponovnem snemanju (2 leti), medtem ko je razmerje ERG/VEP pri otroku B v začetku (9 mesecev) zelo visoko, saj je VEP zelo majhen in se le malo spremeni pri ponovnem snemanju.*

The baby A was 3 months old at the initial recording. He was born prematurely by emergency caesarian section, cord around him and scalp/face laceration. He developed convulsions and hypomagnesaemia. His eyes were diverged and had floppy movements and he showed no visual attention or following signs. His ERG/VEP ratio was *0.3* and both ERGs and VEPs followed 30 Hz flicker (Fig. 3A left). When we saw this baby again at age 2, he was visually retarded and general development was delayed. His epilepsy had been controlled by phenytoin. The amplitudes of both ERG and VEP had increased since the initial recording, and ERG/VEP ratio was *0.6* (Fig. 3A left).

The baby B with poor visual prognosis was 9 months old at the initial recording. He was prematurely born, and was showing no visual following responses, although a CT scan was normal. He also showed some pyramidal signs and was thought to have pale discs. His development was generally delayed. In keeping with the optic atrophy, he had good ERGs, but VEPs were minute (Fig. 3B, left). The ERG/VEP ratio was *7.0*. We followed him up every 2 years, since the parents could not come to terms with the prospect of their baby being blind. When last seen at age 7, he was still grossly handicapped, had limited speech and learning difficulties, although the parents thought that he could see the light and his mother. The ERGs had improved, but there were still no signs of measurable VEPs (Fig. 3B right). The reason for the baby's bilateral optic atrophy was never established.

Our analysis of another 10 babies on whom we made follow up studies confirmed the observations made on the two babies shown in Figure 3. These results suggest that the ERG/VEP ratio in simultaneously recorded FERGs and FVEPs, regardless of the amplitudes of the potentials, may have some prognostic value for babies with no visual following. Of course, for electrophysiologists who use the evoked potentials as a research tool to elucidate development of the visual system and diagnosis of paediatric diseases, there are many excellent reviews available (e.g. 13).

Assessment of rod and cone mediated retinal functions by averaging technique

The second topic of this lecture is concerned with the problem of how to overcome the difficulty in assessing the rod retinal function with the averaging method which, by the nature of the technique, leads to light adaptation of the eye. The PERG, PVEP and bright FERGs and FVEPs reflect mainly cone-mediated retinal functions. An assessment of rod functions, however, is requested quite frequently for early diagnosis of retinitis pigmentosa, night blindness, diabetes, sickle cell anaemia, zinc deficiency, and more recently, melanoma associated retinopathy. The determination of the ERG dark adaptation curve and scotopic ERG thresholds in the dark adapted eye, using a corneal ERG electrode, is the most accurate method for meeting this request (9, 14).

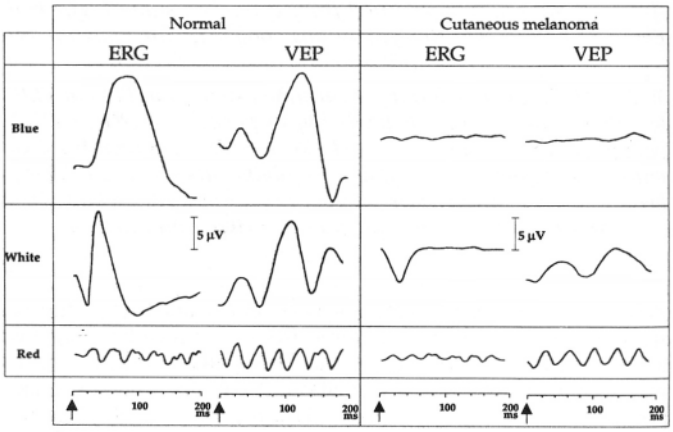


Fig. 4. *Simultaneously recorded ERGs and VEPs evoked by dim blue flash (1 Hz), bright white flash (4 Hz) and 5° red spot flicker (30 Hz) obtained from A) a normal subject and B) a patient with cutaneous melanoma. Note that the blue flash ERG and VEP are abolished, and that the positive b-wave is absent in the bright flash ERG in B, which suggests that rod ON-bipolar function is selectively lost in the case of cutaneous melanoma.*

Sl. 4. *Hkrati posneti ERG in VEP, izzvani z zasenčenim modrim bliskom (1 Hz), belim bliskom (4 Hz) in rdečo bliskavico 5° (30 Hz) pri A zdravem in B pri človeku s kožnim melanomom. Pri B ERG in VEP na modro svetlobo nista izzivna, pa tudi pozitivnega vala b v bliskovnem ERG ni, kar nakazuje, da je pri kožnem melanomu selektivno prizadeta funkcija ON-bipolark.*

As the simultaneous recording of averaged ERG and VEPs becomes a popular technique, I have made an attempt to measure rod retinal functions using the averaging method and lower lid ERG electrodes. It appears that the use of the 1 Hz dim blue flash, as described in "Test procedure", meets the requirement. The blue flash evoked rod type ERGs with b-waves with an implicit time of 80 - 100 ms, and VEPs with a peak time at about 135-140 ms in normal eyes as shown in Figure 4A.

To illustrate that the blue flash may evoke a rod mediated ERG, the ERGs and VEPs obtained from a patient with metastatic cutaneous melanoma are shown in Figure 4B. Patients with metastatic cutaneous melanoma have been found to contain antibodies that react with rod bipolar cells in their sera and present with sudden onset of night blindness (15, 16). Our patient was a 60-year-old male who had had a lump on the left groin for a year, and complained of visual disturbance particularly at night. In this patient with cutaneous melanoma, the blue flash failed to evoke any ERGs, and the white flash produced an ERG with no b-wave, which is generated by the rod driven ON-bipolar cells (7), whereas the cone driven flicker ERGs were intact (Fig. 4B).

Can the blue flash and the red flicker differentiate diseases of rod and cone mediated retinal function? To answer this, the amplitudes of ERGs and VEPs evoked with the blue flash, and those evoked with the red spot flicker, and their ERG/VEP ratios of patients with macular degeneration, *MD*, and those with retinitis pigmentosa, *RP*, were determined. Sub-classification of the patients with *MD* and those with *RP* included or excluded from the analysis, is shown in Table 1. Table 1 also gives information on the number of eyes, mean age and visual acuity of the patients, together with mean EOG light rise (SEMs are not given in the table for clarity). The mean age with its SEM ranging from 0.8 to 4.2 is comparable across groups, suggesting that comparison of mean values of the data is justifiable. SEMs for the mean EOG light rises of all the different diagnostic categories listed in Tables 1, 2 and 3 ranged from 3.8 to 8.6. The control eyes (described under "Inclusion and exclusion of data", mean age 35.1 ± 0.7) showed the mean EOG light rise of 286 (± 4.1 %).

Tab. 1. *Subclassification of macular degeneration (MD) and retinitis pigmentosa (RP) in adult patients.*

Tab. 1. *Nadaljnja razvrstitev makularne degeneracije in (MD) in pigmentne retinopatije (RP) pri odraslih bolnikih.*

MD		n (eyes) n (oči)	age starost	va visus	EOG %	
a.	Best's dystrophy Bestova distrofija	42	39.6	6/25	174.8	included vključeni
b.	Stargardt degeneration Stargardtova degeneracija	22	34.6	6/24	177.8	included vključeni
c.	"Hereditary" degeneration "Dedna" degeneracija	58	32.1	6/24	182.6	included vključeni
d.	Isolated MD Izolirana MD	60	36.2	6/18	197.4	included vključeni
e.	MD with EOG ↑ MD z EOG ↑	42	39.6	6/25	174.8	included vključeni
f.	Cone dystrophy Distrofija čepnic	28	37.5	6/38	190.8	excluded izključeni
g.	Fundus flavimaculatus Fundus flavimaculatus	36	30.5	6/20	193.2	excluded izključeni
h.	Senile MD Senilna MD	42	39.6	6/25	174.8	excluded izključeni
	Total included Skupaj vključeni	236	36.4	6/21	205.7	

RP						
a.	Typical RP Tipična RP	147	36.0	6/16	133.0	included vključeni
b.	Unilateral affected eye Prizadeto oko	11	40.0	6/27	96.0	included vključeni
c.	Unilateral unaffected eye Zdravo oko	11	40.0	6/6	273.8	excluded izključeni
d.	Segmental RP Segmentna RP	13	47.1	6/7	158.0	excluded izključeni
e.	Sine pigmento Sine pigmento	14	37.2	6/22	125.0	excluded izključeni
f.	Usher's syndrome Usherjev sindrom	4	33.0	6/10	121.1	excluded izključeni
	Total included Skupaj vključeni	158	38.0	6/20	114.5	

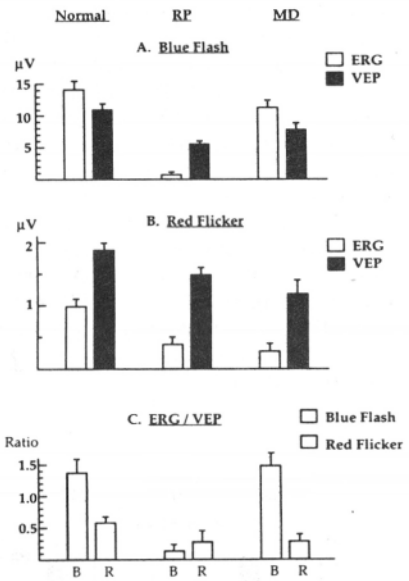


Fig. 5. *Mean (± SEM) amplitudes of simultaneously recorded ERGs and VEPs evoked by A) dim blue flash and B) red spot flicker and C) their ERG/VEP ratios obtained from normal adults, patients with retinitis pigmentosa (RP) and those with macular degeneration (MD). Note that the blue flash ERG is markedly reduced in RP and that the ERG/VEP ratio is higher for the blue than for the red in MD, whilst it is lower for the blue than for the red in RP.*

Sl. 5. *Srednje amplitude in standardne napake srednjih vrednosti (± SEM) hkrati posnetih ERG in VEP, izzvanih z A zasenčeno modro svetlobo, B rdečo bliskavico in C razmerja ERG/VEP pri normalnih odraslih osebah in pri bolnikih s pigmentno retinopatijo (RP) ter makularno degeneracijo (MD). ERG, izzvan z zasenčeno modro svetlobo, je opazno zmanjšan pri RP, razmerje ERG/VEP je večje za modro kot za rdeče pri MD, medtem ko je pri RP to razmerje nižje za modro kot za rdeče.*

Figure 5 shows the mean amplitude (± SEM) of ERGs and VEPs evoked by A) dim blue flash and B) red spot flicker and C) ERG/VEP ratios obtained from normal adults and patients with *RP* and those with *MD*. In Figure 5A, a marked reduction of blue flash response is seen in the *RP*, but not in the *MD* group. Thus the blue flash ERG/VEP ratio of *RP* is *0.16* (± 0.1), whilst that of normal and *MD* are *1.4* (± 0.2) and *1.5* (± 0.2) respectively. Figure 5B shows that the macular cone ERG evoked by 5 ° red spot flicker is reduced in both *RP* and *MD* group, reflecting that the mean visual acuity of the *RP* group is as poor (6/20) as that of the *MD* group (6/21). Consequently, the red flicker ERG/VEP (Fig. 5C) ratio for both *RP* and *MD* groups was *0.3* (± 0.11), whilst the

mean normal value was *0.6* (± 0.08). Consistent with this, both *RP* and *MD* groups showed amplitude reduction, as well as slight delays in PVEPs. But these delays are already apparent at the ERG stage, which indicates that the primary lesion is in the retina.

The above results in adult patients suggest that the blue flash and the red spot flicker distinguish abnormalities of rod and cone mediated retinal function. Measurement of rod ERG and macular cone ERG is, however, particularly important for an early diagnosis of hereditary retinal degeneration. Figure 6 thus plots the data obtained from children aged between 4 and 14 in the same way as those of adults shown in Figure 5. Table 2 lists the sub-classification of the children with *MD* and with *RP*, as well as their mean age, visual acuity and EOG light rise.

Children normally produce proportionately larger VEPs than adults. Figure 6 shows that the ERG/VEP ratios for the normal eyes (n = 39) of children (aged 4 - 14) is *0.7* (± 0.1) for blue and *0.5* (± 0.2) for red flicker stimuli. A striking difference emerged for children with *RP* and *MD*. The children with signs of *MD* showed an ERG/VEP ratio of *0.9* (± 0.1) for blue, but only *0.1* (± 0.05) for red (Fig. 6C), suggesting a selective loss of macular cone function as shown by the loss of red flicker ERG (Fig. 6B). The ERG/VEP ratio of the children with *RP* is, on the other hand, *0.1* (±0.05) for blue flash and *0.6* (± 0.1) for red flicker (Fig. 6C), indicating a selective loss of retinal rod function, as apparent by the marked loss of blue flash ERG (Fig. 6A). Thus the simultaneous recording of averaged ERG and VEP, evoked by a fairly broad band blue flash at the intensity of 2.5 log units above the human scotopic threshold, seems to allow us to detect early abnormalities of rod function.

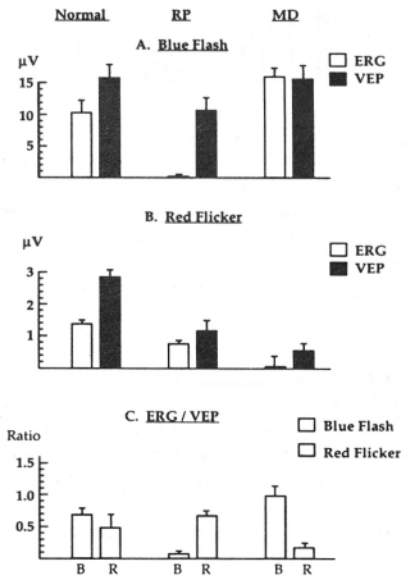


Fig. 6. *Mean (± SEM) amplitudes of simultaneously recorded ERGs and VEPs evoked by A) dim blue flash and B) red spot flicker and C) the ERG/VEP ratios of the normal children (ages 4-14 years), the children with retinitis pigmentosa (RP) and macular degeneration (MD). Note the marked loss of the blue flash in RP and of the red flicker ERG in MD.*

Sl. 6. *Srednje amplitude in standardne napake srednjih vrednosti (± SEM) hkrati posnetih ERG in VEP, izzvanih z A zasenčeno modro svetlobo, B rdečo bliskavico, in C razmerja ERG/VEP pri normalnih otrocih (4-14 let), pri otrocih s pigmentno retinopatijo (RP) in makularno degeneracijo (MD). Pri RP je izgubljen ERG odgovor na modre, pri MD pa na rdeče bliske.*

An additional comment may be made upon the electrodiagnosis of *RP* and *MD*. Both adults and children with *RP* or hereditary *MD* have subnormal EOG light rise: the subnormality is significantly greater for *RP* than for hereditary *MD*, and greater for adults than for children, as expected for the progressive hereditary diseases. The observation also suggests that both *MD* and *RP* involve an abnormality of the pigment epithelium and photoreceptor integrity at an early stage. However, there was a group of patients, (54 eyes, 27 patients) who showed clinically similar *MD* to others but had normal EOG light rise (*296* ± 7.3 %, e of *MD* in Table 1). Their visual acuities were better (6/16) than the low EOG group (6/33 with mean EOG light rise, *183.7* ± 5.1 %, a,b,c & d of *MD* in Table 1). In addition, the mean EOG light rise of children with isolated *MD* was within normal limits (*263* ± 8.6 %, c of *MD* in Table 2). These observations raise the question as to whether macular degenerations with high EOG and those with low EOG represent two etiologically different groups, or the same disease at different stages of development.

Tab. 2. *Subclassification of macular degeneration (MD) and retinitis pigmentosa (RP) in children.*

Tab. 2. *Nadaljnja razvrstitev makularne degeneracije in (MD) in pigmentne retinopatije (RP) pri otrocih.*

MD		n (eyes) n (oči)	age starost	va visus	EOG %	
a.	Stargardt degeneration Stargardtova degeneracija	18	11.9	6/17	180.1	included vključeni
b.	"Hereditary" degeneration "Dedna" degeneracija	14	10.7	6/36	178.6	included vključeni
c.	Isolated MD Izolirana MD	36	9.0	6/12	236.1	included vključeni
d.	Cone dystrophy Distrofija čepnic	8	10.0	6/24	186.7	excluded izključeni
	Total included Skupaj vključeni	68	10.1	6/18	223.7	
RP						
a.	Typical RP Tipična RP	26	11.8	6/11	153.0	included vključeni
b.	Segmental RP Segmentna RP	2	12	6/7	170	excluded izključeni
c.	Usher's syndrome Usherjev sindrom	2	9	6/12	120	excluded izključeni

Electrodiagnosis of different categories of primary optic nerve diseases

The last of the three topics of this lecture concerns electrodiagnosis of the primary optic nerve disease. The primary optic nerve disease was the largest referral diagnostic category of adult patients (29.1 %), followed by primary chorioretinal cases (23.0 %) of adult patients (n = 2,936) who had been included in the analysis. This category included optic neuritis, ischaemic and compressive optic neuropathies and bilateral optic atrophies. Table 3 lists the subclassification of these different categories of primary optic nerve diseases, indicating which group had been included in the present analysis. The most common referral category was optic neuritis, whereas ischaemic or compressive optic neuropathies and bilateral optic atrophies were smaller in numbers.

Tab. 3. *Subclassification of optic neuritis (ON), compressive (Comp. Onp.) and ischaemic (Isch. Onp.) optic neuropathy and bilateral optic atrophies (BLOA).*

Tab. 3. *Nadaljnja razvrstitev optičnih nevritisov (ON), kompresivnih (Comp. Onp.) in ishemičnih (Isch. Onp.) optičnih nevropatij in obojestranskih atrofij vidnega živca (BLOA)*

ON		n (eyes) n (oči)	age starost	va visus	EOG %	
a.	ON with MS ON in MS	460	39.8	6/8	255.0	included vključeni
b.	ON only Samo ON	84	32.2	6/15	276.6	included vključeni
e.	ON with retinal vasculitis ON in retinalni vaskulitis	45	34.0	6/26	240.9	excluded izključeni
	Total included Skupno vključeni	544	38.6	6/9	265.2	
Comp. Onp.						
a.	Comp. Onp. Comp. Onp.	50	37.7	6/27	277.3	included vključeni
b.	Optic Nerve Meningioma Meningiom vidnega živca	11	40.0	6/27	302.1	included vključeni
c.	Exophthalmus Eksoftalmus	48	45.6	6/21	229.9	excluded izključeni
d.	Glaucoma Glavkom	40	58.3	6/12	254.5	excluded izključeni
	Total included Skupaj vključeni	61	38.1	6/27	281.8	
Isch. Onp.						
a.	Isch. Onp.	46	44.0	6/38	239.0	included
b.	Carotid artery disease Bolezen karotidne arterije	19	59.0	6/14	185.2	excluded izključeni
BLOA						
a.	Leber's atrophy Leberjeva atrofija	34	29.7	6/54	245.9	included vključeni
b.	"Familial" atrophy "Familiarna" atrofija	24	31.7	6/30	249.0	included vključeni
c.	Isolated atrophy Izolirana atrofija	16	31.3	6/20	290.0	included vključeni
d.	West Indian Zahodno indijska	26	46.6	6/37	227.8	excluded izključeni
	Total included Skupaj vključeni	74	30.7	6/39	256.4	

The question was whether we could differentiate different categories of optic nerve diseases, using the simultaneous recording of ERGs and VEPs. This was the question which, in 1978, we had attempted to answer (17). But at that time, the ERGs and VEPs were separately recorded: FERGs were recorded using the corneal contact lens electrode (6), and PVEPs were recorded using the method described by Halliday et al. (18).

Figure 7A compares mean amplitudes and SEM of FERGs and FVEPs evoked by (A) bright flashes of 4 Hz, B) those of 30 Hz, and C) PERGs and PVEPs evoked by a 44' arc square checkerboard pattern, obtained from the control eyes and from the affected eyes of patients with the optic neuritis (*ON*), compressive optic neuropathy (*Comp.Onp.*), ischaemic optic neuropathy (*Isch.Onp.*) and bilateral optic atrophy (*BLOA*). The control data were obtained from the same normal subjects, from whom the data shown in Figure 5 had been obtained. The control ERG/VEP ratios for the bright flash of 4 Hz and 30 Hz were *1.1* (± 0.1) and *2.4* (± 0.01) respectively, and that for the pattern-reversal *0.3* (± 0.01). Only the data for the three stimulating conditions are shown for simplicity, and since these three conditions revealed the effects of the optic nerve diseases most clearly. Because 60 % of optic nerve fibres arise from the retinal macular, usually cone mediated visual functions are predominantly affected in optic nerve diseases. Thus, highly reproducible FERGs and FVEPs of large amplitude, evoked by bright flashes of 4-30 Hz, as well as the PERGs and PVEPs, were found to be suitable for assessing the optic nerve diseases.

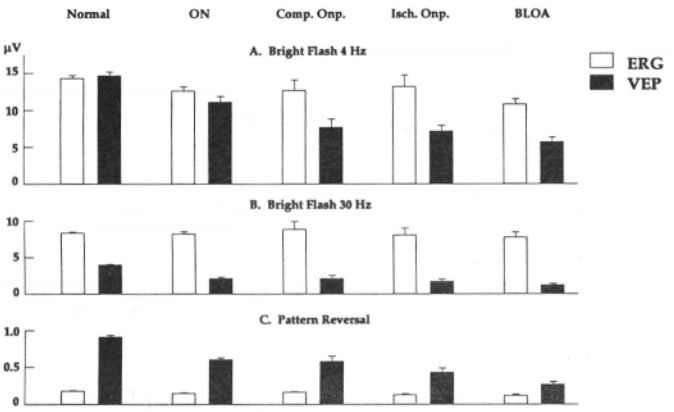


Fig. 7. *Mean (± SEM) amplitudes of simultaneously recorded ERGs and VEPs evoked by A) bright flash of 4 Hz and B) bright flash of 30 Hz and C) a checkerboard pattern-reversal obtained from normal subjects and patients with different categories of optic nerve diseases. Note that all categories of optic nerve diseases show a loss of VEP. The loss is smallest in the optic neuritis (ON) and greatest in bilateral optic atrophy (BLOA).*

Sl. 7. *Srednje amplitude in standardne napake srednjih vrednosti (± SEM) bkrati posnetih ERG in VEP, izzvanih z A) bliskom 4 Hz, B) bliskom 30 Hz in C) s šahovnico pri normalnih osebah in bolnikih z različnimi kategorijami živčnih bolezni. Pri vseh kategorijah živčnih bolezni je prizadet VEP. Prizadetost VEP je najmanjša pri optičnem nevritisu (ON) in največja pri bilateralni optični atrofiji (BLOA). Comp.Onp. - kompresivna optična atrofija, Isch.Onp. - ishemična optična atrofija.*

Figure 7A shows that there is a slight reduction in the F- and PERGs of the four categories of optic nerve diseases, but striking reductions in the amplitudes are found for VEPs, particularly for the 30 Hz flicker VEPs. This suggests that the temporal resolution of the visual system is greatly reduced in the optic nerve diseases. The greater loss of the VEP amplitudes compared with ERGs is furthermore, demonstrated by the elevation of the ERG/VEP ratios as shown in Figure 8A. The effect is greatest in the category of *BLOA* and least in *ON*. This may be due to the axonal damage being probably less in *ON* than in other categories. A similar finding was made in our early study (17).

It might be thought that compressive lesion of the optic nerve could cause a more severe loss of optic nerve function than that caused by ischaemia alone, since it would also lead to ischaemia. *Isch.Onp.*, however, seems to cause a similar if not slightly greater increase in the ERG/VEP ratio and visual deficit than *Comp.Onp.* (Fig. 8A, Table 3).

Whilst there is no doubt that PERG and PVEPs have significant diagnostic values, it is interesting and encouraging that the global flash stimulation can also distinguish the optic nerve disease from the primary retinal disorders. The FERG/FVEP ratio for the

bright 4 Hz flash for *MD* and *RP* was *0.8* (± 0.2) and *0.3* (± 0.1) respectively, whilst that for the normal eye, *1.1*. The ratio of optic nerve diseases ranged from *1.5* (± 0.1) in *ON* to *2.6* (± 0.4) in *BLOA*. Similarly, the bright 30 Hz flash ERG/VEP ratio for *MD* and *RP* was *2.4* (±0.4) and *0.6* (± 0.07) respectively, whereas that for optic nerve disease from *4.0* (± 1.0) to *6.5* (± 1.2).

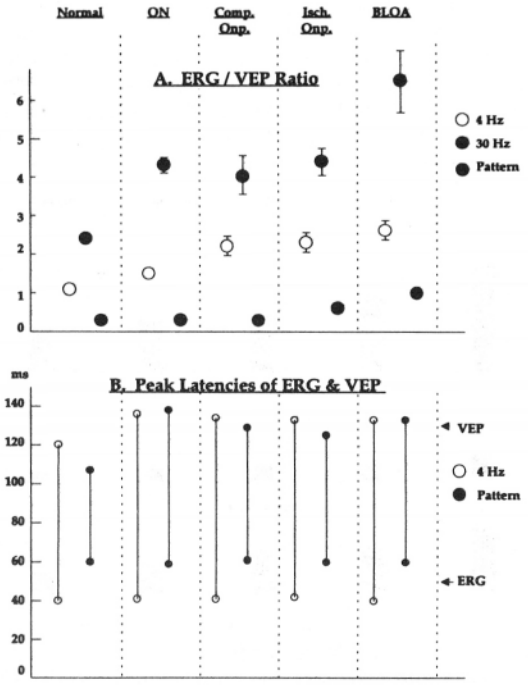


Fig. 8. *A) the ERG/VEP ratios for the responses evoked by bright flash of 4 and 30 Hz and by pattern-reversal of normal subjects and patients with optic neuritis (ON), compressive optic neuropathy (Comp.Onp.), ischaemic optic neuropathy (Isch.Onp.) and bilateral optic atrophy (BLOA). Note that a higher ERG/VEP ratio implies a lower VEP amplitude relative to ERG amplitude, and that the deviation is greatest for BLOA. B) the ERG and VEP peak latencies of the responses evoked by a bright flash (4 Hz) and by a high contrast pattern (4 reversal/s) of normal subjects and patients with different categories of optic nerve disease. Note that the ERG and corresponding VEP are joined by a line so that the length of the line may represent a retino-cortical time. The lines for both F- and P-evoked responses of all categories of optic nerve disease are longer than those of the normal subjects, those of ON being the longest.*

Sl. 8. *A) razmerja ERG/VEP za odgovore, izzvane z bliskom 4 in 30 Hz in šahovnico pri normalnih osebah in pri bolnikih z optičnim nevritisom (ON), kompresivno optično nevropatijo (Comp.Onp), ishemično optično nevropatijo (Isch.Onp.) in pri bilateralni optični atrofiji (BLOA). Višje razmerje ERG/VEP pomeni relativno nižjo amplitudo VEP glede na ERG. Variabilnost odgovorov je največja pri BLOA. B) Latence vrhov ERG in VEP, izzvanih z bliskom (4 Hz) in visoko kontrastnim slikovnim dražljajem (4 izmenjave/s) pri normalnih osebah in bolnikih z raznovrstnimi živčnimi boleznimi. Latence ERG in VEP so povezane s črtami, ki lahko tako prikazujejo retino-kortikalni čas. Črte tako za bliskovno kot slikovno izzvane odgovore pri različnih boleznih so daljše kot pri zdravih osebah. Najdaljše so pri ON.*

Figure 8B, compares the peak latencies of the F- and P-ERGs and VEPs of different categories of optic nerve diseases. It appears that the ERG timing is not affected in optic nerve diseases, whereas all categories of optic nerve disease show delay in VEPs. FVEP delay does not seem to distinguish between the different diagnostic conditions, but the PVEP seems to show that the delay is greatest in *ON*, followed by the *BLOA* group. *Isch.Onp.*, which showed slightly greater VEP amplitude loss than *Comp.Onp.* now shows slightly less delay than *Comp.Onp.* VEPs do not distinguish between *Isch.Onp.* and *Comp.Onp.* It is interesting, that EOG light rise is slightly subnormal in *Isch.Onp.*, whilst normal in all other categories of optic nerve diseases (Table 3). This may suggest that *Isch.Onp.*, at least in some cases, also involves chorioretinal ischaemia.

To conclude this section, although the results are not so clear as in the first two topics, the following may be said: *1.* All categories of the primary optic nerve diseases show an increase in F- and P-ERG/VEP ratios. The increase is greatest in *BLOA 2.* All categories of primary optic nerve disease show a delay in both F- and P-VEPs, but the delay in PVEPs is greater than that in the FVEPs, and greatest in *ON. 3. Isch.Onp.* and *Comp.Onp.* reveal similar ERG and VEP profiles, whilst EOG light rise is normal in *Comp.Onp.*, but subnormal is *Isch.Onp.*

Epilogue

I have described some early days of electrodiagnosis and also conveyed my faith in the currently used non-invasive method of simultaneous recording of F- and P-ERGs and VEPs, emphasising the importance of using different stimulating conditions. My chosen three messages from the analysis are: 1) The ERG/VEP ratio may be useful for making visual prognosis of babies with no visual following, 2) A 1 Hz dim blue flash and 30 Hz red spot flicker may be used to differentiate rod and cone-mediated retinal functions 3) The simultaneous recording of ERG/VEP together with the EOG light rise data may differentiate different categories of optic nerve diseases.

Over many years I have studied the electrical responses of neurones at different stations of the visual and also pupillary pathways in different animals and in different animal models of diseases. I have also recorded ERGs from animals ranging from the snake to the monkey. In all this basic research, we were able to control the variables scrupulously. The recordings from patients in which no such controls were possible gave me food for thought for my basic research.

My final message for the future is a belief that electrophysiological assessment of the visual pathway, regarded as a "window of the central nervous system", is important, since it may reveal biochemical and physiological abnormalities which precede pathological changes. Studies of the nervous system *in situ* will continue to be necessary, even if great advances are made in the molecular biological field and in our knowledge of membrane properties of isolated or cultured cells.

Acknowledgements. My affectionate thanks go to Janet Turner, Jonathan Robbins, Susan Surguy, Christine Kay, Elizabeth Dawes and Gail Turner for assisting with the recordings, John Muckelroy and Peter de Villiers for construction and trouble shooting of some of the equipment and Gill Blake, Angela Dalton and Janet Gladwell for secretarial assistance, at different periods of the last 25 years. I have been extremely lucky to have such dedicated crews in my unit. I also gratefully acknowledge financial support of The Special Trustees of St Thomas' Hospital, and grants from the Godfrey Robbinson Fund, Royal National Institute for the Blind, and the Iris Fund. Finally my special thanks go to Gail Turner for assisting most ably in the formidable task of analysing the vast amount of patients' data and preparation of the figures.

References

1. Sorsby A. Genetics in ophthalmology. London: Butterworth, 1959.
2. Ikeda H, Friedmann, AI. Electrooculography, electroretinography and the visually evoked occipital response. In: Sorsby A, ed. Modern ophthalmology. London: Butterworth, 1972: 499-504.
3. Wässle H, Boycott BB. Functional architecture of the mammalian retina. Physiol Rev 1991; 71: 447-80.

4. Arden GB, Kelsey JH. Some observations on the relationship between the standing potential of the human eye and the bleaching and regeneration of Visual purple. J Physiol 1962; 161: 205-26.
5. Steinberg RH, Linsenmeier RA, Griff ER. Retinal pigment epithelial cell contributions to the electroretinogram and electrooculogram. In: Osborne NN, Chader GJ eds. Progress in retinal research. Oxford: Pergamon Press, 1985; 4: 33-66.
6. Ikeda H. Electrophysiology of the retina and visual pathway. In: Rose FC ed. Modern ophthalmology. London: Chapman and Hall, 1976: 38-55.
7. Stockton R, Slaughter M. B-wave of the electroretinogram. A reflection of ON-bipolar cell activity. J Gen Physiol 1989; 93: 101-22.
8. Berninger TA, Arden GB. The pattern electroretinogram. Eye (suppl) 1988; 2: 257-83.
9. Ikeda H. Clinical electroretinography. In: Halliday AM ed. Evoked potentials in clinical testing. 2nd ed. London: Churchill Livingstone, 1993: 115-39.
10. Halliday AM. The visual evoked potential in the investigation of chiasmal and retrochiasmal lesions field defects and systemic diseases. In: Halliday AM ed. Evoked potentials in clinical testing. London: Churchill Livingstone, 1993: 279-57.
11. Ikeda H, Friedmann AI. The applications and value of the EOG and ERG in clinical practice especially in young children. Trans Ophthal Soc UK 1974; 94: 226-32.
12. Henkes HE, Lith F, van Legein C. Electrodiagnosis of the visual system of the young child with defective vision. Trans Ophthal Soc UK 1973; 93: 17-20.
13. Taylor MJ. Evoked potentials in paediatrics. In: Halliday AM ed. Evoked potentials in clinical testing. London: Churchill Livingstone, 1993: 489-522.
14. Ikeda H. Retinal mechanisms and the clinical electroretinogram. In: Halliday AM, Butler SR, Paul R eds. A textbook of clinical neurophysiology. Chichester: John Wiley, 1985: 569-5.
15. Alexander KR, Fishman GA, Peachey NS, Marchese AL, Tso MOM. "On" response defect in paraneoplastic night blindness with cutaneous malignant melanoma. Invest Ophthalmol Vis Sci 1992; 33: 477-83.
16. Milam AH, Saan JC, Jacobson SG, Lubinski WP, Fenn LG, Alexander KR. Autoantibodies against retinal bipolar cells in cutaneous melanoma-associated retinopathy. Invest Ophthalmol Vis Sci 1993; 34: 91-100.
17. Ikeda H, Tremain KE, Sanders MD. Neurophysiological investigation in optic nerve disease: combined assessment of the visual evoked responses and electroretinogram. Br J Ophthalmol 1978; 62: 227-39.
19. Halliday AM, McDonald WI, Mushin J. Delayed visual evoked response in optic neuritis. Lancet 1972; 1: 982-5.

ELEKTRODIAGNOSTIKA PRIMARNEGA AFERENTNEGA VIDNEGA SISTEMA. PRETEKLOST, SEDANJOST IN PRIHODNOST

Hisako Ikeda

Izvleček - *Predstavljene so izkušnje kliničnega snemanja elektrookulograma (EOG) elektroretinograma (ERG) in vidnih evociranih potencialov (VEP) od leta 1968. S številom pacientov, napotenih na elektrodiagnostično testiranje, ki se je povzpelo na 4826, predstavlja to delo poskus ovrednotenja najpomembnejših podatkov. Iz meritev na osnovi sočasnega snemanja ERG in VEP in s svetlobo izzvanih sprememb v EOG so bile izbrane tri teme: prva je prikaz uporabe razmerja ERG/VEP za prognoziranje vida pri dojenčkih brez znakov vidnega zaznavanja; druga je uporaba ERG in VEP, izzvanih z modrimi (60°, 1 Hz) in rdečimi bliski (5°, 30 Hz), za ocenjevanje delovanja paličnic in čepnic; tretja tema je uporaba razmerij ERG/VEP in zakasnitev ERG ali VEP, kot tudi sprememb EOG za razlikovanje raznih kategorij bolezni vidnega živca.*
Sočasno snemanje ERG in VEP z neinvazivnimi elektrodami in v različnih pogojih draženja lahko da dragocene podatke o funkcionalnem stanju vidnega sistema zdravega in bolnega človeka.

Ključne besede: *elektrookulogram; elektroretinogram; funkcija paličnic/čepnic; ishemična optična nevropatija; kompresijska optična nevropatija; makularna degeneracija; optična atrofija; optični nevritis; retinitis pigmentosa*

OSEBNA IZKAZNICA

MOBO INTERNATIONAL d.o.o.

Sodobno oblikovani izdelki, ki so uporabni in estetski, lepšajo in izboljšujejo naše delovno in bivalno okolje! To je samo eno vodilo, ki mu sledi strokovna ekipa **MOBO International**.

MOBO je predvsem grafično podjetje, katerega dejavnost je celotna obdelava papirja, najkakovostnejši tisk, izdelava koledarjev, prospektov, brošur, reklamnih katalogov in ostale drobne papirne galanterije.

Podjetje je staro skoraj tri desetletja. Danes v njem ustvarja 30 ljudi visoke strokovnosti, ki znajo izkoristiti najsodobnejšo tehnologijo, ki jo ima **MOBO**.

Z leti se je **MOBO** poleg grafični obdelavi papirja posvetil tudi oblikovanju in izdelavi predmetov, primernih za poslovna darila. S tem smo na svoje področje vpeljali novost: na tržišču so se pojavili domiselni in sveži artikli, kot na primer: usnjeni bloki, rokovniki, usnjene poslovne mape, adresarji, poslovni kovčki in aktovke. Velik del tega programa ostaja paradni konj firme **MOBO**, vendar se pahljača izdelkov nenehno dopolnjuje in bogati z novimi idejami in pristopi, ki sledijo novim potrebam in sprejemajo nove izzive.

Naši izdelki so odlični, njihov spisek pa je predolg, da bi jih lahko tu našteli. Zato nam dovolite, da vas povabimo na obisk v eno izmed naših treh Galerij, kjer vam bomo svoje izdelke z veseljem pokazali:

- **Galerija MOBO**, Ljubljana, Stari trg 11
- **Galerija MOBO International**, Ljubljana, Slovenska cesta 5
- **Galerija MOBO Cadeau**, Letališče Ljubljana - Brnik

K nam rade prihajajo prav vse generacije, ko si zaželijo popestritve, ko iščejo darilo za določeno priložnost. Prijetno vzdušje, strokoven nasvet, široka paleta kakovostnih izdelkov, oblikovanih in izdelanih z ljubeznijo, jih vedno znova privabljajo k nam. Pridite še vi, veseli bomo vašega obiska.

S spoštovanjem,

MOBO International d.o.o.
Bogdan Margon

MOBO INTERNATIONAL d. o. o., 61000 Ljubljana, Groharjeva 18
tel. 061/213-493, 315-440, fax. 061/131-144
Žiro račun št. 50101-601-173397

VISUAL EVOKED POTENTIALS IN NEUROLOGY: CLINICAL APPLICATIONS IN PRE- AND POST-CHIASMAL LESIONS

VIDNI EVOCIRANI POTENCIALI V NEVROLOGIJI: KLINIČNA UPORABNOST PRI PRE- IN POSTHIAZMALNIH OKVARAH

Klaus Lowitzsch

Department of Neurology, Acad. Hospital Ludwigshafen of University Mainz, D-6700 Ludwigshafen/Rhein, Germany

Key words: *central nervous diseases; chiasmal lesions; eye disorders; multiple sclerosis; optic nerve lesion*

Abstract - *Pattern-reversal visual evoked potentials (VEP) are often superior to ophthalmological examination, since they detect clinical as well as subclinical lesions of the visual pathways. VEP is affected by a great variety of neuroophthalmological lesions.*

While retinal and optic disc involvements usually don't delay VEP, optical nerve and chiasmal lesions change latency and shape of VEP.

Several central nervous system (CNS) disease processes lead to segmental demyelination, which causes delays in conduction, increases temporal dispersion, as well as conduction blocks, which is visualized by VEP alterations. On the other hand, neuronal or axonal degenerations are mostly demonstrated by a decrease of VEP amplitude.

The main indication for VEP is the suspicion of a demyelinating process somewhere along the visual pathway, particularly in the pregenicular segment. Additional important indications are optic disc changes, possible pressure on the optic nerve or chiasma, as well as toxic or traumatic optic nerve lesions.

Retrogenicular processes along the visual pathway, however, are much more difficult to capture, therefore multichannel recordings and half-field stimulation have to be additionally applied.

In some systematic disorders and hereditary diseases the pregenicular parts of the visual system may be affected, therefore VEP is very important to clarify differential diagnosis.

Introduction

Visual evoked potentials (VEP) have been introduced into clinical medicine in the 1960s by Cigánek (1) using flash-stimulation, and in the 1970s by Halliday (2) using contrast stimulation by pattern-reversal. This method is often superior to ophthalmological investigation, since it detects clinical as well as subclinical lesions of the visual pathways. Therefore, during the past 20 years, several syndromes have been investigated in clinical neurology including retinal and ophthalmological diseases (Tab. 1, 2).

The fovea and the periphery of the retina differ in their neuroanatomic structure: centrally we find the greatest concentration of cones, the greatest resolution and color recognition ability, and the greatest sensitivity to contrast, but little sensitivity to movement; the number of related ganglion cells diminishes toward the periphery and so does the resolution ability. Vision is 100 % in the fovea and drops to 50 % at 2.5 degrees, 33 % at 5 degrees, and 20 % at 10 degrees from the center.

Accordingly, VEP is triggered centrally (in the fovea) primarily by small pattern checkerboard shift. The most amplitude-effective pattern increases in size paracentrally and eccentrically. Peripherally, VEP is triggered primarily by luminance. As in peripheral nerves, there are CNS disease processes that lead to a segmental demyelination, cause delays in conduction and increase temporal dispersion and conduction blocks. Disease processes that involve neuronal or axonal degeneration affect the conduction sys-

Tab. 1. *Indications for VEP in pregenicular visual pathway lesions.*
Tab. 1. *Indikacije za VEP pri pregenikulatnih okvarah vidne proge.*

Eye	Optic disk changes (prominence inflammation, papilledema, STP, glandular disc, atrophy) Amblyopia, refraction abnormality Retinal disease (+ ERG)
Oko	Spremembe papile (vnetje, edem, STP, grozdasta papila, atrofija) Slepota, motnje refrakcije Bolezni mrežnice (+ ERG)
Optic nerve	Optic neuritis/neuropathy Compression injury Ischemic injury Toxic optic neuropathy
Optični živec	Optični nevritis/nevropatija Kompresijska poškodba Ishemična poškodba Toksična optična nevropatija
Chiasma, tract	Demyelination (e.g. by MS) Compression (neoplasms) Opticochiasmatic arachnitis
Hiazma, proga	Demielinizacija (npr. zaradi MS) Kompresija (neoplazme) Optično-hiazmatični arahnitis

Abbreviations: *CNS, central nervous system; ERG, electroretinogram; MS, multiple sclerosis; ON, optic neuritis; VEP, visual evoked potential*

tem to a lesser degree. The latency of VEP may still be within normal range, although the amplitude is clearly reduced.
Retinal diseases primarily affect the amplitude and may even a complete disappeareance of VEP, whereas optical nerve and chiasma involvements change the shape and latency of VEP. The principal indication is the suspicion that there may be a demyelinating process somewhere along the visual pathway, particularly in the pregenicular segment. Even in optic disk changes, however, differential diagnostic information may be obtained. Additional important indications are possible pressure on the optic nerve, chiasma, and optic pathway (Tab. 1).
Retrogenicular processes along the course of the Gratiolet optic radiation and in the occipital cortical fields are much more difficult to capture, so that multichannel recordings and half or quadrantic visual field stimulation must be used. In some systemic disorders the pregenicular parts of the visual system may be affected, which is very important in the differential diagnosis of several diseases (Tab. 2).

Tab. 2. *Indications for VEP in special groups of diseases.*
Tab. 2. *Indikacije za VEP pri posebnih skupinah bolezni.*

Cerebral systemic diseases
Sistemske bolezni možganov
Demyelinating diseases (MS, leukodystrophies)
Demielinizacijske bolezni (MS, levkodistrofija)
Storage diseases
Bolezni kopičenja
Neuro-lues, sarcoidosis, neuro-borreliosis
Nevrolues, sarkoidoza, nevroborelioza
Metabolic diseases
Presnovne bolezni
Inflammatory and vascular diseases
Vnetne in žilne bolezni
Chorea, Parkinsonism
Horea, parkinsonizem
Spinal systemic diseases
Sistemske bolezni hrbtenjače
Congenital ataxias
Kongenitalne ataksije
Funicular myelosis
Funikularna mieloza
Spastic spinal paralysis
Spastična spinalna paraliza
(Chronic) myelopathy
(Kronična) mielopatija
Spinal muscular atrophy
Spinalna mišična atrofija
Neuropathies
Nevropatije
Genetic optic neuropathy
Dedne nevropatije vidnega živca
Genetic polyneuropathy
Dedne polinevropatije
Reduced levels of consciousness
Zožena zavest
Coma
Koma
(Epilepsy)
(Epilepsija)
Psychiatric illness
Psihiatrične bolezni
Cortical blindness (psychogenic)
Kortikalna slepota (psihogena)
Dementia
Demenca

Diseases of the eye

Optic disc changes. From a differential diagnostic point of view, prominence of the optic disc may be due to inflammatory, vascular-degenerative, obstructive, or tumescent causes. We studied 62 patients with papilledema of varying severity and found normal amplitude, latency, and shape in the contrast VEP in all cases. In spite of considerable bulging (4 to 5 diopters), VEP remained normal (3). Minor clinical changes occur only after an extended period of time, or with chronic edema, when chronic increase in pressure causes minor damage in the optic nerve fibers in the area of the optic disc. VEP is, therefore, useful in distinguishing between papillitis and choked disc in cases of papilledema of unknown origin.

In *glandular optic disc*, VEP showed widening and reduction in amplitude, but normal latencies representing an involvement of neuronal elements in the parafoveal region, with consecutive axonal degeneration (3).

Papillitis corresponds to an anterior optic nerve neuritis, and it is less frequent than the retrobulbar neuritis. The VEP changes are the same as those described in ON.

Pseudopapillitis is a vascular-ischemic degenerative change of the optic disc. Morphologically, it resembles a papillitis, and it is linked to vision loss amounting to amaurosis. In contrast to inflammatory papillitis, VEP changes occur only when there is considerable vision loss.

Amblyopia is a loss of vision without identifiable anatomic changes, and usually occurs in one eye as a consequence of visual deprivation during the critical period, e.g. refractive error or strabismus during infancy. If this problem is recognized early, it is treatable (i.e. with vision training).
The patient usually has one normal and one amblyopic eye, which allows comparison via VEP. As a rule, the amplitude in the amblyopic eye is reduced. The extent of the visual disturbance can be determined by varying the size of the stimulus pattern and by evaluating the amplitudes in VEP (4). The VEP in the amblyopic eye is primarily generated in the area between 3 and 6 degrees.

Glaucoma. Cappin and Nissim (1975) were the first to study 21 patients with visual field defects and glaucoma. VEP was abnormal if the disturbed visual field quadrants were stimulated selectively. In 38 eyes suffering from different glaucomatous stages (0-2 after Aulhorn) we could demonstrate, in a combined ERG-VEP study, a differential affection of retinal and neuronal elements (5).

Diseases of the optic nerve

Optic neuritis. The clinical manifestations of optic neuritis (ON) include vision and color perception loss, and primarily central visual defects. Parallel to loss of vision, the pattern-reversal VEP shows a reduction in amplitude, as well as a delay due to the conduction defect. This delay in latency remains as a permanent, demonstrable defect even after recovery of normal vision, and can be observed in about 95 % of isolated ON, while the shape is maintained. Occasionally, the contour specific P1-N2- P2 complex is spread out that a P3 is mistaken for a P2, or a paramacular P135 is considered to be a delayed P100 ("Pseudodelay" - Halliday (6)) by comparison, the fall-out rate in strobe VEP is definitely lower, at the 40 to 80 % level (7).
In a small percentage of about 5 to 10 %, the contrast VEP is normal in spite of obvious ON in history and clinical examination. It seems that in these cases probably 50 % of the fibers serving the macula are not affected. In some of these cases, however, a pathologic interocular difference (> 7.5 ms) can be seen.

Multiple sclerosis. The frequency of *pathologic VEP findings* in large groups depends on diagnostic classification and duration of

the disease. In our group of more than 500 patients, as well as in a cumulative sample of 30 groups with almost 3,000 patients, VEP was pathologic in 84 % of definite multiple sclerosis (MS), 62 % of probable MS, and 36 % of questionable MS (8). Demonstration of optic nerve or chiasma involvement, therefore, is important for diagnosis and follow-up. The discovery of *clinically asymptomatic (silent) foci* is particularly important, since proof of such spread allows a positive diagnosis in about 30 % of suspected MS cases (7, 8, 9, 10, 11, 12). However, peripheral visual field defects due to periphlebitis, uveitis or rather optic neuritis, demonstrated by the computerized static perimetry ("Octopus"), can not be shown by VEP, since VEP measures primarily macular function (13).

Neurosyphilis. In secondary and tertiary lues, the optic nerve and the chiasma are frequently involved in a type of perineuritis with the development of papilledema. More than 50 % of the eyes show VEP changes, even though there are no changes in the seropositive latent lues (14, 8, 12).

Inflammatory diseases. In chronic meningitis with basal prominence, the optic nerve and chiasma can be directly or indirectly involved, and show VEP changes (15). In temporal arteritis, the optic nerve can become ischemic to the point of amaurosis, so that VEP can provide an important monitoring function (15, 16).

Compression of the optic nerve by an intraorbital mass or by an optic glioma can lead to unilateral reduction in amplitude, mild delays in latency, and in most cases, a definite dissociation of the shape of VEP. These can frequently occur before any visual field defects can be demonstrated (17, 18).

Direct or indirect trauma to the optic nerve frequently produces a transient or permanent loss of vision, depending on the severity of the contusion. In such cases, particularly in sleeping or unconscious patients, the flash VEP represents a good function test of the visual system.

Endocrine orbitopathies can also produce indirect optic nerve compression and corresponding VEP changes (18).

The *anterior ischemic optic nerve neuropathy* of the elderly includes axonal damage with central and paracentral visual field loss, but not focal demyelination. This leads to a significant reduction in amplitude and a broadening of VEP, without any delay in latency (19). Loss of macular P100 response frequently unconvers normal paramacular subcomponents (P135), and simulates a delay in latency (20).

Toxic optic nerve neuropathy caused by chronic tobacco and alcohol abuse (tobacco- alcohol amblyopia), with bilateral vision, color perception disturbances, as well as central and paracentral scotoma (21, 22), produces a low-amplitude VEP (23). The *Myambutol amblyopia* is a typical example of toxic optic neuropathy. VEP can be used as a screening technique for identification of subclinical optic nerve lesions (11, 24).

Lesions of the chiasma

Compression of the chiasma (or optic tract) by a neoplasm of the sella, or by a craniopharygioma, usually produces bilateral VEP changes, such as wave dissociations, decreases in amplitude, and a delayed-onset increase in latency (25, 26, 27). By separate stimulation of the nasal and temporal hemiretina, the losses of symmetry can be frequently demonstrated even without additional horizontal leads. The *craniopharyngioma* is the most common neoplasm at the base of the skull in childhood, and produces a compression of the anterior visual pathway. This neoplasm can produce changes in VEP, even before visual disturbances or visual field losses can be detected subjectively. 15' VEP ist the most sensitive parameter, since the maculopapular bundle is apparently the first one to respond to pressure. Postoperatively, both the vision and VEP recover, as we were able to show in children who had craniopharyngiomata surgically removed (28).

Central visual pathway disturbances

Localized hemispheral processes

Vascular processes. Unilateral vascular processes produce VEP asymmetry only when there are also perimetrically detectable visual field defects. At that time, decreases in amplitude, mild changes in shape, and later, slight delays in latency appear (29).

Neoplasms and multiple sclerosis. Neoplasms and hemispheral foci in MS affect VEP, which depends on the localisation and extent of the perifocal edema. Most of the literature references are anecdotal in nature (16).

"Cortical blindness". In older persons, extensive geniculocalcarine lesions, primarily of vascular origin, or more rarely, neoplasms, inflammatory processes or central demyelination result in acute blindness. A partial basilar thrombosis, a saddle embolus at the division of the basilar artery, or softening or bleeding in the (left) parieto-occiptal region can also lead to cortical blindness. In contrast to acute retinal or optic nerve ischemia the pupillary light reflex is maintained. The VEP findings are not consistent (11) and range from isolated loss of early components to complete disappearance of all VEPs.

Diffuse cerebral processes

Vascular dementias. Diffuse vascular processes do not affect VEP significantly, and amplitude variations remain within normal range. In presenile dementias, Wright et al (30) found prolonged P3 components only after strobe stimulation, but normal P2 latency after pattern shift stimulation. Similar findings were reported in patients with senile dementia (31). In these patients, the P100 latencies were within normal range, whereas the later components, N130, P165, and P220, showed mild delays.

Alzheimer dementia. In most studies, the flash VEP shows abnormalities first, especially with prolongation of the later components N130, P165, N220, while the pattern-VEP remains normal for a long time. (16).

Parkinson's disease. The latency delays observed in patients with Parkinson's disease regress under L-dopa therapy (32). It is assumed that the dopaminergic cells in the inner plexiform layers of the retina are affected by the disease process, but respond to L-dopa therapy (33). It seems, therefore, that at least a part of the visual evoked potentials delays and interocular differences have a retinal origin (34).

Huntington's chorea. Ellenberger et al (35) found decreased amplitudes without latency delay in 17 of 18 patients (strobe stimulation), other groups found the same responses following television pattern shift stimulation (36, 37). Our studies also showed the predominance of amplitude reduction. It is possible that VEP may be useful in identification of family members at risk (38).

Migraine. The findings following strobe stimulation on patients with migraine are not consistent. Gastaut and Regis (39) found no appreciable changes, whereas others found some variations in individual components, or amplitude changes in classic migraine patients, even in migraine-free periods (40, 41).

Epilepsy. Particularly in the light-sensitive forms of epilepsy, increased amplitude of one or more components were found (39, 42, 11). Kooi and Marshall (43) identified a surface-positive wave of 80 to 100 ms, and a negative wave of 100 to 120 ms, which demonstrated increases in amplitude.

Systemic illness. Neurologic and medical systemic illness can affect the optic nerve, so that VEP can be used as a screening technique. Some examples shall be presented.

Sarcoidosis. Sarcoidosis is a generalized granulomatous disease that involves multiple systems and leads to visual and neurologic symptoms in 50 % of all cases. (44). The optic nerve can be involved as papilledema, papillitis, retrobulbar neuritis, or as optic nerve atrophy. Primary ocular manifestations (e.g. uveitis, glaucoma, keratoconjunctivitis) are seen in more that 75 % of the cases (45). In a group of 50 sarcoid patients, Streletz et al. (46) found latency and amplitude changes in 30 %. More recently, other researchers found the changes in 40 % of the patients they examnied (47, 48). Using the STIR-technique (MRI), one can visualize papilledema and uveitis (49).

Vitamin B_{12} deficiency and pernicious anemia. A funicular myelosis and a B_{12} deficiency syndrome can produce not only polyneuritis, but also subclincal involvement of the visual system. In recent publications there are many reports on delays in latency in VEP, which largely dissappear after therapy (50, 51, 52, 53).
We were also able to show VEP delays in patients with pernicious anemia. The almost common finding was a symmetrical P2 delay of 2 to 4 SDs in the presence of normal ophthalmologic findings (11).

Alcobol damage. Chronic alcoholism leads not only to a polyneuropathy, cerebellar ataxia, and cirrhosis of the liver, but to optic nerve damage as well, which can be demonstrated by delayed VEPs (54, 55).

Hereditary diseases. Optic nerve atrophy is of great differential diagnostic importance in hereditary degenerative diseases of the CNS. The differentiation between MS and other inflammatory-demyelinating diseases is frequently difficult, particularly if the symptoms in the chronic progressive stages of the disease are asymmetrical.

Friedreich's ataxia. About 60 % of the patients show reduced amplitudes and moderate delays in latency in VEP, presumably because of axonal damage (56, 57, 16).

Hereditary spastic paraplegias. Although after an appropriately long observation period, the diagnosis of MS can be made in about 20 % of the cases (31 % at autopsy) (58), VEP changes occur more frequently (i.e. in 25 to 90 % (11)). A symmetrical impairment with only moderate delay in latency suggests a systemic disease, whereas an asymmetrical, obvious delay in latency favors MS.

Charcot-Marie-Tooth disease. Optic nerve atrophy is a rare accompaniment of neural muscle atrophy, and VEP delays are rarely seen. More common are reductions in amplitude and broadenings of VEP (57, 59, 60).

References

1. Cigánek L. The EEG response (evoked potential) to light stimulus in man. Electroenceph Clin Neurophysiol 1961; 13: 165.
2. Halliday AM, McDonald WI, Mushin J. The value of pattern-evoked response in the diagnosis of multiple sclerosis. Electroenceph Clin Neurophysiol 1974; 36: 551.
3. Lowitzsch K, Neuhann Th. Musterumkehr-VEP in der Diagnostik von Drusen und Stauungspapille. Fortschr Ophthalmol 1983; 79: 509-11.
4. Sokol S. Visual evoked potentials to checkerboard pattern stimuli in strabismic amblyopia. In: Desmedt JE ed. Visual evoked potentials in man: new developments. Oxford: Clarendon, 1977: 410-7.
5. Lowitzsch K, Welt R. VEP und Elektroretinographie durch Musterumkehrreizung in der Frühdiagnostik des Glaukoma chronicum simplex. EEG-EMG 1991; 22: 217-23.
6. Halliday AM. Visual evoked potentials in demyelinating disease. In: Waxman SG, Ritchie JM eds. Demyelinating disease: basic and clinical electrophysiology. New York: Raven Press, 1981: 201-15.
7. Lowitzsch K, Kuhnt U, Sakmann C, Maurer K, Hopf HC, Schott D, Thäter K. Visual pattern evoked responses and blink reflexes in assessment of MS diagnosis. A clinical study of 135 MS-patients. J Neurol 1976; 213: 17-32.
8. Lowitzsch K. Visuell evozierte Potentiale (VEP) bei der Multiplen Sklerose. Akt Neurol 1982; 9: 170-4.
9. Lowitzsch K. Pattern evoked visual potentials in 251 MS patients in relation to ophthalmological findings and diagnostic classification. In: Bauer HJ, Poser S, Ritter G eds. Progress in multiple sclerosis. Heidelberg: Springer, 1980: 571.
10. Lowitzsch K, Maurer K. Pattern-reversal visual evoked potentials in reclassification of 472 MS patients. In: Courjon J, Mauguière F, Révol M eds. Advances in neurology. Vol. 32. Clinical application of evoked potentials in neurology. New York: Raven Press, 1982: 487-91.
11. Lowitzsch K. Visuell evozierte Potentiale: In: Lowitzsch K, Maurer K, Hopf HC eds. Evozierte Potentiale in der klinischen Diagnostik. Stuttgart: Thieme, 1983: 2-154.
12. Lowitzsch K. Pathophysiologie des VEP bei der Multiplen Sklerose. Akt Neurol 1985; 2: 62.
13. Lowitzsch K, Welkoborsky HJ. Musterumkehr-VEP und Computer-Perimetrie am Partnerauge bei Opticusneuritis. EEG-EMG 1987; 18: 179-84.
14. Lowitzsch K, Westhoff M. Optikusaffektionen bei Neurolues-Diagnose durch das visuell evozierte Potential (VEP). EEG-EMG 1980; 11: 77-80.
15. Lowitzsch K. Visuell evozierte Potentiale (VEP) in der Diagnostik entzündlicher Erkrankungen des ZNS. In: Berlitt P, Gänshirt H eds. II. Internationales Symposium zur Koordinierung der Neurologischen Wissenschaften, Heidelberg, 1981.
16. Lowitzsch K, et al. Evozierte Potentiale bei Erwachsenen und Kindern: VEP, ERG, AEP, P300, SEP, MEP. 2. Auflage. Thieme Verlag: 1993.
17. Halliday AM, Kriss A, McDonald WI, Mushin J. The pattern-evoked potentials in compression of the anterior visual pathways. Brain 1976; 99: 357-74.
18. Wijngaarde R, van Lith GHM. Pattern EPs in endocrine orbitopathy. Doc Ophthalmol 1979; 48: 327-32.
19. Wilson B. Visual-evoked response differentiation of ischemic optic neuritis from the optic neuritis of MS. Am J Ophthalmol 1978; 86: 530.
20. Thompson PD, Mastaglia FL, Carrol WM. Anterior ischaemic optic neuropathy. A correlative clinical and visual evoked potential study of 18 patients. J Neurol Neurosurg Psychiat 1986; 49: 128-35.
21. Potts AM. Tobacco amblyopia. Surv Ophthal 1973; 17: 313.
22. Ikeda H, Tremain KE, Sanders MD. Neurophysiological investigations in optic nerve disease: combined assessment of the visual evoked response and electroretinogram. Br J Ophthal 1978; 62: 227-39.
23. Kriss A, Caroll WM, Blumhardt D, Halliday AM. Pattern- and flash-evoked potential changes in toxic (nutritional) optic neuropathy. In: Courjon J, Mauguière F, Révol M eds. Advances in neurology. Vol. 32. Clinical applications of evoked potentials in neurology. New York: Raven Press, 1982: 11-9.
24. Yiannikas CJ, Walsh JC, McLeod JG. Visual evoked potentials in the detection of subclinical optic toxic effects secondary to ethambutol. Arch Neurol 1983; 40: 645-8.
25. Gott PS, Weiss MH, Apuzzo M, van der Meulen JP. Checkerboard visual evoked response in evaluation and management of pituitary tumors. Neurosurgery 1979; 5: 553.
26. Müller-Jensen A, Zschocke S, Dannheim F. VER analysis of the chiasmal syndrome. J Neurol 1981; 225: 33-40.
27. Camacho LM, Menzel W, Aschoff JC. The pattern-reversal visual evoked potentials in the clinical study of the optic chiasm pathway. In: Courjon J, Mauguière F, Révol M eds. Advances in neurology. Vol. 32. Clinical application of evoked potentials in neurology. New York: Raven Press, 1982: 49-59.
28. Kempkes K, Rochel M, Lowitzsch K. VEP in children with craniopharyngeoma. In: Rothenberger A ed. International Symposium: evoked potentials in children. Essen 1982. Amsterdam: Elsevier, 1982: 195-9.
29. Vaughan HG, Katzmann R, Taylor J. Alterations of visual evoked responses in the presence of homonymous field defects. Electroenceph Clin Neurophysiol 1963; 15: 737.
30. Wright CE, Harding GFA, Orwin A. Presenile dementia - the use of the flash and pattern VEP in diagnosis. Electroenceph Clin Neurophysiol 1984; 57: 405- 15.
31. Visser SL, van Tilburg W, Hooijer C, Jonker W. Visual evoked potentials (VEPs) in senile dementia (Alzheimer type) and in non-organic behavioural disorders in the elderly; comparison with EEG parameters. Electroenceph Clin Neurophysiol 1985; 60: 115-21.
32. Bodis-Wollner I, Yahr MD. Measurement of visual evoked potentials in Parkinson's disease. Brain 1978; 101: 661.
33. Watling KJ, Dowling JE, Iversen LL. Dopamine receptors in the retina may all be linked to adenylate cyclase. Nature 1979; 281: 578-80.
34. Bodis-Wollner I, Ghilardi MF, Mylin LH. The importance of stimulus selection in VEP practices: the clinical relevance of visual physiology. In: Cracco RQ, Bodis-

Wollner I eds. Frontiers of clinical neuroscience, evoked potentials. New York: Liss, 1986.
35. Ellenberger C, Denis JP, Ziegler SB. The visually evoked potential in Huntington disease. Neurology 1978; 28: 95-7.
36. Oepen G, Doerr M, Thoden U. Huntington's disease: alterations of visual cortical evoked potentials in patients and offspring. In: Courjon J, Mauguière F, Révol M eds. Advances in neurology. Vol. 32. Clinical application of evoked potentials in neurology. New York: Raven Press, 1982: 141-7.
37. Jossiassen RC, Shagass C, Mancall EL, Roemer RÄ eds. Auditory and visual evoked potentials in Huntington's disease. EEG Clin 1984; 57: 113-8.
38. Hennerici M, Hömberg V, Lange HW. Evoked potentials in patients with Huntington's disease and their offspring. II. Visual evoked potentials. Electroenceph Clin Neurophysiol 1985; 62: 167-76.
39. Gastaut H, Regis H. The visually evoked potentials recorded transcranially in man. In: Proctor LD, Adey WR eds. NASA symposium on the analysis of central nervous system and cardiovascular data using computer methods. Washington: NASA, SP-72, 1965: 7.
40. Richey ET, Kooi KA, Waggoner RW. Visually evoked responses in migraine. Electroenceph Clin Neurophysiol 1966; 21: 23.
41. Regan D, Heron JR. Simultaneous recording of visual evoked potentials from the left and right hemispheres in migraine. In: Background to migraine. London: Heinemann, 1970: 66-70.
42. Morocutti C, Sommer-Smith JA, Creutzfeldt O. Das visuelle Reaktionspotential bei normalen Versuchspersonen und charakteristische Veränderungen bei Epileptikern. Arch Psychiatr Nervenkr 1966; 208: 234.
43. Kooi KA, Marshall RE. Visual evoked potentials in central disorders of the visual system. Hagerstown: Harper & Row, 1979.
44. Delaney P. Neurology manifestations in sarcoidosis. Ann Intern Med 1977; 8: 336-45.
45. Iwata DG, Nanba K, Sobue K, Abe H. Ocular sarcoidosis. Ann NY Acad Sci 1975; 278: 445.
46. Streletz LJ, Chambers RA, Sung Ho Bae, Israel HL. Visual evoked potentials in sarcoidosis. Neurology 1981; 31: 1545-9.
47. Oksanen V. et al. Visual and auditory evoked potentials in the early diagnosis and follow-up of neurosarcoidosis. Acta Neurol Scand 1986: 74: 38-42.
48. Stern BJ et al. Neurosarcoidosis presentation and management. Ann NY Acad Sci 1986: 465: 722-30.
49. Eidelberg D et al. Chronic unilateral optic neuropathy: a magnetic resonance study. Ann Neurol 1988; 24: 3-11.
50. Troncoso J, Mancall EL, Schatz NJ. Visual evoked responses in pernicious anemia. Arch Neurol 1979; 36: 168-9.
51. Bodis-Wollner I, Korczyn AD. Dissociated sensory loss and visual evoked potentials in a patient with pernicious anemia. Mt Sinai J Med 1980; 47: 579.
52. Krumholz A, Weiss HD, Goldstein PJ, Harris KC. Evoked responses in vitamin B12 deficiency. Ann Neurol 1981; 9: 407-9.
53. Fine EJ et al. The neurophysiological profile of vitamin B12 deficiency. Muscle Nerve 1990; 13: 158-64.
54. Posthuma J, Visser SL. Visual evoked potentials and alcohol-induced brain damage. In: Courjon J, Mauguière F, Révol M eds. Advances in neurology. Vol. 32. Clinical application of evoked potentials in neurology. New York: Raven Press, 1982: 149-55.
55. Chan YW et al. Visual evoked responses in chronic alcoholics. J Neurol Neurosurg Psychiat 1986; 49: 945-50.
56. Wenzel W, Camacho L, Claus D, Aschoff J. Visually evoked potential in Friedreich's ataxia. In: Courjon J, Mauguière F, Révol M eds. Advances in neurology. Vol 32. Clinical Application of evoked potentials in neurology. New York: Raven Press, 1982: 131-9.
57. Carrol WM, Jones SJ, Halliday AM. Visual evoked potentials abnormalities in Charcot-Marie-Tooth disease and comparison with Friedreich's ataxia. J Neurol Sci 1983; 61: 123-33.
58. Marshall J. Spastic paraplegia of middle age. A clinicopathological study. Lancet 1955; I: 643-6.
59. Tackmann W, Radü EW. Pattern shift visual evoked potentials in Charcot-Marie-Tooth disease, HMSN type I. J Neurol 1980; 224: 71.
60. Triantafyllou N et al. Electrophysiological study (EEG, VEPs, BAEPs) in patients with Charcot-Marie-Tooth (type HMSN I) disease. Electromyogr Clin Neurophysiol 1989: 29: 259-63.

VIDNI EVOCIRANI POTENCIALI V NEVROLOGIJI: KLINIČNA UPORABNOST PRI PRE- IN POSTHIAZMALNIH OKVARAH

Klaus Lowitzsch

Izvleček - *Članek podaja pregled klinične uporabnosti slikovnih vidnih evociranih potencialov (VEP) v nevrologiji. VEP je pogosto občutljivejši v odkrivanju kliničnih in subkliničnih okvar vidnega sistema kot oftalmološke preiskave. Nanj vpliva veliko število nevrooftalmoloških okvar. Medtem ko prizadetost mrežnice in optičnega diska običajno ne poveča zakasnitve VEP, pa okvare optičnega živca in hiazme spremenijo njegovo latenco in obliko. Različni procesi v osrednjem živčevju privedejo do demielinizacije, ki upočasni prevajanje, poveča časovno disperzijo in povzroči blok prevajanja, kar se odraža v spremembah VEP. Na drugi strani pa se aksonska degeneracija v glavnem odraža v zmanjšani amplitudi VEP. Glavna indikacija za VEP je sum na demielinizacijski proces vzdolž vidne poti, posebej v pregenikulatnem predelu. Nadaljnje pomembne indikacije so spremembe papil, verjeten pritisk na optični živec in hiazmo, kakor tudi toksične in travmatske okvare optičnega živca. Veliko težje pa je odkriti retrogenikulatne procese vzdolž vidne poti, kjer moramo uporabiti večkanalno zapisovanje in draženje očesa ločeno v polovicah vidnega polja. Pri nekaterih sistemskih in dednih okvarah, kjer je lahko prizadet pregenikulatni del vidnega sistema, je VEP zelo pomemben pri diferencialni diagnozi.*

Ključne besede: *bolezni osrednjega živčevja; hiazmalne okvare; multipla skleroza; očesne bolezni; okvare optičnega živca*

MULTIMODAL EVOKED POTENTIALS AND CENTRAL MOTOR LATENCIES IN EVALUATION OF PATIENTS WITH OPTIC NEURITIS

MULTIMODALNI EVOCIRANI POTENCIALI IN CENTRALNE MOTORIČNE LATENCE PRI BOLNIKIH Z OPTIČNIM NEVRITISOM

Miro Denišlič

University Institute of Clinical Neurophysiology, Medical Centre, Zaloška c. 7, 61105 Ljubljana, Slovenia

Key words: *central motor latencies; evoked potentials; multiple sclerosis; optic neuritis*

Abstract - Background. *Optic neuritis (ON) is a frequent visual disorder in patients with multiple sclerosis (MS). After prolonged follow-up one third of patients with ON may develop demyelinating disease. The aim of our study was to evaluate clinical silent lesions of CNS occurring in patients with ON. The finding of silent lesions supports the possible diagnosis of MS.*

Method. *15 patients with ON and 26 with possible, probable or definite MS were included. In ON patients, evoked potentials and transcranial cortical stimulation were performed. In the second group, visual pathway was assessed using visual evoked potentials.*

Results. *In all patients with ON, delayed latencies of the wave P100 were recorded, while acoustic brain stem evoked potentials were abnormal in 20 %, and somatosensory in 13 % of patients. Delayed central motor latencies were noticed in 40 % of the patients. In 9 patients (56 %) with possible or probable MS, electrophysiological involvement of clinically unaffected eye was evaluated. Delayed visual evoked responses, indicating electrophysiologic dysfunction of unaffected optic nerve, were found in only 3 patients (19 %) with definite MS.*

Conclusions. *Visual evoked potentials are a very sensitive method in detection of optic nerve impairment, while neurophysiological evaluation of corticospinal pathway turned out to be the most sensitive method in discovering clinically silent lesions in CNS.*

Introduction

Optic neuritis (ON) is an acute inflammatory neuropathy, defined as a condition causing a relatively rapid onset of visual failure, without signs of a toxic, vascular or compressive etiology, in cases where the local retinal lesions have been excluded (1).

Clinical features

Eye pain most commonly precedes the onset of visual symptoms, though sometimes may occur simultaneously or subsequently. The pain is localised in the involved eye, or spreads to the supraorbital region, and it is occasionally accompanied by unilateral or generalised headache. The intensity of pain varies and may cause severe disability. It is often manifested, or even aggravated, by eye movements. Although the optic nerve is pain-insensitive, its covering of meninges contains pain fibres of trigeminal origin (1). The pain is produced by stretching of the meninges surrounding the swollen optic nerve. Recently Lepore (2) supported the hypothesis that the pain of the optic nerve inflammation is caused by traction of the origins of the superior and medial recti on the optic nerve sheath at the orbital apex. The eye pain reflects neither severity nor origin of the optic neuropathy. The frequency of pain varies between 20 and 87 % of cases (3). Occasionally, the tenderness of the eyeball is the main symptom of ON. The severity or duration of pain does not influence the prognosis of vision recovery, and it usually decreases before the vision recovery is achieved.

The vision

The most prominent visual symptom of ON is a blurred vision. The onset of visual failure is often demonstrated as being sudden after waking up, and progressive deterioration of vision is noted. The maximum loss of the visual acuity is achieved in 3 to 7 days after the onset, exceptionally, progression for more than two weeks has been reported (3). The degree of visual acuity loss varies from none at all to a complete loss of light perception. Severe impairment of the visual acuity has been noted in 92 % (4). The degree of visual impairment usually depends on the period from the onset to the point when the patient was presented to the doctor. Colour vision failure and abnormal contrast sensitivity are often associated with the visual acuity deficit. Immediately after the optic nerve involvement, the normal optic disc is described in 50 % (3). Occasionally, complete loss of disc margins, sign of papillitis, or, more commonly, subsiding of disc swelling have been described. Rarely, haemorrhages have been reported (5). Vascular abnormalities and/or exudation of cells into the media were reported in about 25 % of patients with ON. Fluorescein leakage, perivenous sheathing, cells in the vitreous

Abbreviations: *ADM, abductor digiti minimi; BAEP, brainstem auditory evoked potential; CML, central motor latency; CNS, central nervous system; CSF, cerebrospinal fluid; MEP, motor evoked potential; MRI, magnetic resonance imaging; MS, multiple sclerosis; ON, optic neuritis; SSEPs, somatosensory evoked potentials; TA, tibialis anterior; VEP, visual evoked potential*

and the anterior chamber were described (6). After attacks of ON, pallor of the disc develops. The ON recurrence rate of 10 % within one year has been reported (1, 7). The probability of recovering normal vision decreases with each recurrence (5, 8).
Shortly after recovery of ON, or preceding the attack, brief flashes of light produced by eye movements, either in a dark room or with the eyes closed, may occur (movement phosphenes). Phosphenes usually persist for approximately six weeks, a period similar to other transient symptoms of multiple sclerosis (9).
The visual field abnormality is a common feature of ON, whereas permanent field deficit persists rarely (10). Central scotomas were observed in 83 %, while bitemporal hemianopia or altitudinal defects occurred rarely - 6.6 % and 9 % (4).
After an initial attack of ON, regularly good visual acuity with a mean interval of two months from the onset has been reported (11). However, slow recovery of vision may continue in some cases for up to 12 months from the onset (12). The improvement of visual acuity has been reported in 24 % (13), 59 % (12, 14) and 80 % (10) of the cases. This discrepancy is most likely due to the retrospective nature of the studies. Similar results are reported in recovery of contrast sensitivity and colour vision (15). However, it is important to remember that any single test can not sufficiently represent the complexities of vision, and that the assessment of visual acuity is an inadequate indicator of recovery in ON (13, 16). Therefore, more than a single test in evaluation of a visual function has been recommended (10).

The pupils

In ON patients, the affected pupils are often moderately enlarged. The involvement of the afferent arc of the pupillary light reflex has been supposed. This observation explains the Marcus Gunn reaction, which consists of pupillary dilatation of the affected eye (3). Namely, when the light torch is rapidly switched to the involved eye, the illuminated pupil is dilating, meanwhile, on the healthy pupil, consensual constriction is observed. It is interesting that this phenomenon may persist even after full recovery of ON. Temporary blurring of vision provoked by exercise has been recognised as Uhthoff's phenomenon (3). This effect is common during the recovery stage. Similar effect has been described during menstruation, increased environmental temperature, eating of hot meals, smoking and after taking a hot bath. The illusion that a pendulum swinging in one plane is describing an ellipse is reported as Pulfrich's effect (17). The three phenomena described may promote the demonstration of the optic nerve involvement.

Optic neuritis and multiple sclerosis

ON is a common presenting feature of multiple sclerosis (MS). Relationship between ON and MS is still obscure. Involvement of the optic nerve may be an initial manifestation of MS, but recurrent episodes of ON may influence the risk of the development of MS (18). The incidence of MS after ON varies from 13 % to 85 % in American and European studies (18-21) and from 10 % to 27 % in Japanese studies (4). After a prolonged follow-up study (11.6 years), 57 % of the patients with ON developed signs of the demyelinating disease. On the life table method of analysis, the probability of developing MS reached 75 %, 15 years after the initial attack of ON (18). MS is most likely to develop within the first 5 years after ON. Several different factors promote and influence the outcome in patients with ON. The role of age, sex, cerebrospinal fluid (CSF) changes (22. 23), and HLA system (1, 22-24) has been discussed. Simultaneous bilateral ON has lower risk of MS than the sequential occurrence, but obviously decreases incidence in childhood (1).
ON causes abnormal responses in visual evoked potentials (VEPs) recording. After ON, almost all patients have a delayed response, which could be one of the first symptoms of MS, but parallel to optic nerve lesion, several lesions may develop in various parts of the central nervous system (CNS). In clinical praxis, several neurophysiological methods have been developed to demonstrate silent lesions in CNS, and to confirm the presence of demyelination. They are non-invasive, not too expensive and provide very important specific information (25).

Patients and methods

Our study examined 15 patients, 12 females and 3 males, mean age 29 years (range 20-37 years), with definite idiopathic ON according to the accepted diagnostic criteria (1, 27), and 26 patients, 18 females and 8 males, mean age 35 years (range 18-52 years), classified as having possible or probable MS according to McAlpine's criteria (27). They were complaining of relatively rapid visual loss, and none of them had either systemic disease or visual pathway compression. Due to the decrease of the visual acuity, the patients were first referred to ophthalmologists. After the diagnosis of ON, neurological assessment was started. No neurological symptoms or signs were found on clinical examination.
Six patients experienced previous visual alteration, and their ophthalmological examination revealed bilateral optic nerve involvement.
Visual evoked potentials (VEPs), brainstem auditory evoked potentials (BAEPs), and somatosensory evoked potentials (SSEPs) were recorded 1 to 9 months after the initial attack of the ON.
Pattern-reversal VEPs with checker-board stimulation at 2 Hz were recorded. Five recording electrodes over the occipital region, 5 cm above the inion, were used. Reference electrode was Fz. Full- and half-field stimulation was performed (28, 29). The P100 wave latency was analysed and compared with the values of a control group of 24 healthy subjects with a mean age of 32 years (range 22-44 years).
BAEPs were recorded using monoaural stimulation at 5 Hz with electrodes on the earlobes and reference on Cz. The latencies of typical waves N1-N5, interpeak latencies and amplitude ratio N1 : N5 were calculated. The control group consisted of 33 healthy subjects with a mean age of 30 years. Recordings were made by Medelec Sensor equipment.
SSEPs were obtained by submaximal electrical median nerve stimulation at wrist, with 2 Hz. Electrodes were placed at the Erb's point, over the C7 process, and on the scalp over the contralateral parietal cortex. The analysis time was 50 ms, filters 10 Hz - 5 kHz. Waves latencies and central conduction time (N13-N20) were recorded by Medelec-Sensor. The control group consisted of 30 subjects, mean age 30 years.
Results of 2.5 SD above the mean normal values were considered abnormal.
The motor cortex was stimulated using a high voltage stimulator (Digitimer 180) with maximal intensity 750 V. Stimuli applied were of 60-70 % of the maximal intensity. Electrodes were placed according to previously described technique (30). Motor evoked potentials (MEPs) during slight voluntary contraction were recorded from the abductor digiti minimi (ADM) on the upper limbs and from tibialis anterior (TA) muscle on the lower limbs (Medelec-Sensor). At least two motor responses were averaged. By subtracting mean latency, obtained to cervical (at the C7 level) and lower thoracic region stimulation (at the Th12 level), from the mean cortical latency, the so called central motor latency (CML) was calculated. It was measured from the stimulus artefact to the onset of the response. Normal values of CMLs were calculated in 21 volunteers (11 males and 10 females), mean age 32 years (range 23-44 years).
Motor cortex response was considered abnormal when no response could be elicited or when the CML exceeded upper limits of the normal range in at least one muscle.

Results

Table 1 shows summarised personal data and results of visual, acoustic and somatosensory evoked potentials.
For 6 patients the history of previous visual acuity disorders was evaluated. In these cases, bilateral abnormal VEPs were recorded. Simultaneous bilateral occurrence of the ON was diagnosed only in one patient.
In two cases (number 2 and 10), VEPs of the unaffected eye showed delayed P100 latencies.
Recorded CMLs are listed in Table 2.

Tab. 1. *Personal data and results of multimodal evoked potentials.*

Tab. 1. *Klinični podatki in vrednosti multimodalnih evociranih potencialov.*

Patient Bolnik		Sex Spol	Age at ON Starost*	VEP	BAEP	SSEP
1	D.A.	m	37	A	N	N
2	P.D.	f	25	A	N	N
3	J.M.	m	26	A	N	N
4	M.D.	f	37	A	N	N
5	J.K.	f	35	A	A	N
6	R.T.	f	26	A	N	N
7	R.Z.	f	35	A	N	N
8	K.A.	f	34	A	N	N
9	S.M.	f	20	A	N	N
10	Z.L.	f	30	A	N	A
11	K.V.	f	35	A	N	N
12	K.J.	m	34	A	N	N
13	K.T.	f	30	A	N	N
14	Z.J.	f	28	A	A	A
15	M.B.	f	30	A	A	N

f, female; m, male; A, abnormal; N, normal; ON, optic neuritis; VEP, visual evoked potential; BAEP, brain stem auditory evoked potential; SSEP, somatosensory evoked potential
*f, ženska; m, moški; A, patološko; N, normalno; *, starost bolnika ob diagnozi optičnega nevritisa; VEP, vidni evocirani potenciali; BAEP, akustični potenciali možganskega debla; SSEP, somatosenzorični evocirani potenciali*

Tab. 2. *Central motor latencies of 15 patients with optic neuritis.*

Tab. 2. *Centralne motorične latence pri 15 bolnikih z optičnim nevritisom.*

Patient number Bolnik številka	ADM right desno	ADM left levo	TA right desno	TA left levo
1	4.6	4.8	15.6*e	15.6*e
2	4.4	5.0	11.2	11.8
3	9.0*	6.4	17.8*	18.6*
4	4.4	3.4	12.0	12.0
5	5.6	6.0	16.4*	16.0*
6	4.8	4.4	14.4	13.6
7	4.6	5.3	12.4	13.4
8	5.6	6.4	18.0*	20.4*
9	4.6	4.4	13.0	11.4
10	6.4	5.4	17.8*	16.4*
11	5.0	5.2	10.9	11.2
12	5.2	8.8*	11.6	11.6
13	5.6	4.4	11.6	11.2
14	6.8*	4.8	9.8	10.6
15	6.4	5.8	12.3	11.9

ADM, abductor digiti minimi; TA, tibialis anterior
**, abnormal recording; *e, equivocal;*
Upper normal limit for ADM is 6.5 ms and for TA 15.4 ms.
**, patološki zapis; *e, mejno patološki zapis*
Zgornja meja normale za ADM je 6,5 ms in za TA 15,4 ms.

Motor evoked responses after cortical, cervical and lower thoracic cord stimulation are presented in Figure 1. In the last traces, M-waves after the ulnar nerve stimulation at wrist and the peroneal nerve stimulation at the capitulum fibulae were recorded. Scattering of CMLs in normal subjects and in patients is presented in Figure 2.
Seeking for clinically silent demyelinating lesions in the CNS, BAEP showed abnormalities in 3 patients (20 %), while SSEP was altered in two cases (13 %).
Among 16 patients with probable and possible MS, 14 patients did not report the history of ON. Despite the neglect of optic

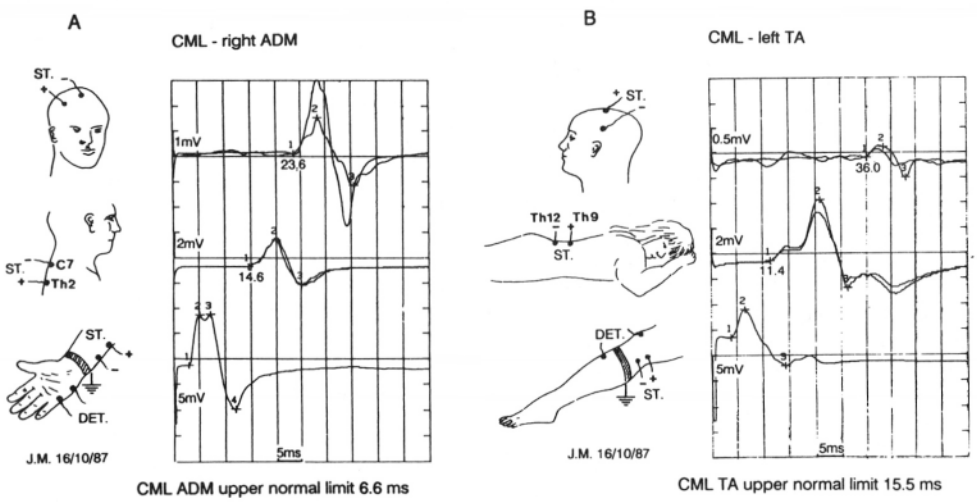


Fig. 1. *Motor evoked responses in J. M. with optic neuritis. Traces were recorded from the abductor digiti minimi (A) and tibialis anterior muscles (B). Calculated central motor latencies are 9.0 ms and 18.6 ms respectively. (upper trace - cortical stimulation; middle trace - cervical (thoracic) stimulation of spinal cord; lower trace - M-wave).*

Sl. 1. *Motorični evocirani odzivi pri bolniku J. M. z optičnim nevritisom. Odzive smo odvajali z mišic abductor digiti minimi (A) in tibialis anterior (B). Izračunana centralna motorična latenca je 9,0 ms oziroma 18,6 ms. (zgornji zapis - draženje skorje; srednji zapis - draženje v vratnem (prsnem) delu hrbtenjače; spodnji zapis - val M).*

nerve involvement in 5 patients (31 %), the delay of P100 wave was detected (Tab. 3). Meanwhile, 10 patients with definite MS (33 %), without history of ON, had abnormal latency of P100 wave. In patients with known history of ON the latencies of P100 wave were significantly delayed.

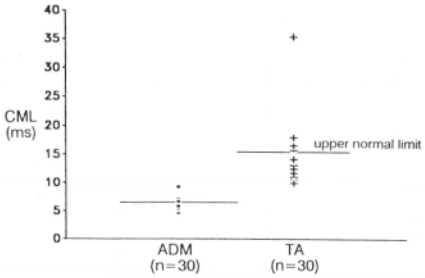


Fig. 2. *Scattering of CMLs in the group of healthy subjects and in patients.*

Sl. 2. *Razsoj centralnih motoričnih latenc pri zdravih preiskovancih in bolnikih.*

Tab. 3. *VEPs in MS patients with and without optic neuritis.*

Tab. 3. VEP pri bolnikih z MS in optičnim nevritisom ali brez njega.

Multiple sclerosis Multipla skleroza	With ON z ON		Without ON brez ON		
	Delayed Zakasnjen P100	Normal Normalen P100	Delayed Zakasnjen P100	Normal Normalen P100	Total Skupaj N
Possible Možna Probable Verjetna	2	0	5	9	16
Definite Zanesljiva	6	0	3	1	10

Discussion

Clinical neurological assessment of our patients revealed no abnormalities.

VEPs were abnormal in all cases. It is interesting that we obtained positive history of a previous alteration of the visual acuity of the other eye in 6 patients (40 %). All these patients showed bilaterally delayed VEPs. In two cases (13 %), clinically silent involvement of the optic nerve was observed. Only in one patient (7 %), simultaneous bilateral affection was noted. It seems that VEPs are the test of choice in detecting the optic nerve dysfunction. Additionally, central and peripheral half-field stimulation is recommended for a more reliable identification of macularly and paramacularly derived components (31).

In the group of possible and probable MS, clinically silent optic nerve lesion was detected in 31 % of patients (32). All patients with positive history of ON showed abnormal values of P100 wave latencies, which indicates that VEPs are highly sensitive in evaluation of optic nerve involvement. However, the previous study revealed normal VEP latency after ON in only 10-15 % (33). The modern technique of magnetic resonance imaging (MRI), including the contrast injection of gadolinium, provides more reliable means for discovering acute optic nerve lesions. Leakage of gadolinium across the blood-optic nerve barrier was described as consistent finding in the acute optic nerve lesion. This abnormal finding was associated with abnormal visual acuity and colour vision, retroocular pain, an afferent pupillary defect (Marcus Gunn phenomenon), and reduced amplitude of the P100 component of VEP. The leakage of gadolinium reflects inflammation which plays important role in the conduction block and clinical deficit (34). It seems that gadolinium enhanced lesions in the patient's CNS represent acute MS plaques, while lesions without enhancement may signify the process which began long ago and will probably lead to development of MS (35).

BAEPs provide very useful information about the brainstem auditory pathway, and are in this respect close to MRI. In some studies, BAEP recordings revealed even greater sensitivity (44 %) than MRI (39 %). BAEPs were abnormal in 21 % of patients without clinical signs of the brainstem lesion (36, 37). Clinically silent lesions were demonstrated in 5 % to 15 % of patients (28, 39). In our study 20 % of patients showed abnormal BAEPs.

Our findings obtained by SSEP recordings after median nerve stimulation (13 %) correspond well to published results which showed detection of clinically silent lesions in 12-13 % of patients (38, 40). Stimulation of the peroneal or tibial nerves, on the other hand, was found to be less successful (41).

However, calculating CMLs after electrical motor cortex stimulation, at least one CML was abnormal in 6 patients (40 %) and in one (7 %) the recording was equivocal. Abnormal were mainly the CMLs from the TA muscles, while those from the ADM were abnormal less frequently, only in 2 cases (number 12 and 14).

Transcranial electrical motor cortex stimulation was well tolerated by all patients. However, they were often complaining because of the long evoked potential procedures. Definite motor responses were recorded and CMLs could be calculated in all cases. Higher sensitivity was obtained in recordings from the leg muscles, presumably due to anatomically longer corticomotor pathway. The increase of CML is most probably due to slowing of the conduction of the largest diameter fibres of the pyramidal tract (42). Prolonged CML was the most prominent feature recorded in MS, while in patients with a motor neuron disease motor responses in limb muscles are often absent (42-44). This finding is in agreement with reports in the literature. Close correlation of CMLs in leg muscles with signs of an upper motor neuron disturbance was described, while, in the upper limb muscles, higher proportion of subclinical silent lesions was detected (44). CMLs were measured particularly in cases of definite and probable MS, providing a useful parameter to assess the fast corticospinal fibres. Therefore, motor cortex stimulation permitted selective and direct assessment of the corticospinal tract (45). Threshold of stimulation tends to increase in degenerative and demyelinating disorders, and for this reason they require higher stimulus intensity. Transcutaneous magnetic stimulation of the motor cortex, which produces depolarisation of pyramidal cells by magnetic field, is more comfortable, painfree and preferred in clinical praxis. Comparison of these two methods is difficult due to stimulation of different neural structures (43, 46).

MRI is a very sensitive technique in detecting demyelinating lesions in CNS. Seeking for demyelinating lesions in CNS, MRI reveals abnormalities in ON in a much higher proportion than MEPs or CML measurements (47, 48). The last studies reflect frequency of silent lesion in CNS, confirmed by MRI, lower than in previous reports, but still high - 44 to 48 % (49, 50). The conversion rate of ON to definite MS varies between 35 % to 38 % after follow-up of more than 12 years (50, 51). However, MEPs and CMLs are very useful neurophysiological parameters in evaluation of the patients with ON. These methods are available in many laboratories, and provide an easy way to demonstrate the disturbance of the long motor and sensory pathways in CNS. It has to be stressed that the diagnosis of MS is still clinical, and that the subject with MRI-confirmed demyelinating lesion in CNS is not destined to develop MS (52). It is quite possible that in the majority of ON patients with positive MRI findings, the brain lesion will always remain clinically silent and never produce symptoms of demyelinating disease (49). Measurement of CML has apparent advantage to MEPs in detecting demyelinating lesions.

Motor cortex stimulation was confirmed to be the most sensitive neurophysiological method in discovering corticomotoneuron dysfunction. Finally, diagnosis of MS is still clinical and depends on the demonstration of multiple demyelinating lesions in CNS. Since not every patient with ON develops MS, it is important to rule out the lesions outside the optic pathway.

CMLs and MEPs provide an early relevant diagnosis of the demyelinating disease, evaluating a silent paraclinical lesion (53). In spite of higher sensitivity of MRI, neurophysiological assessment indicating functional disorder in CNS plays an important role in evaluation of the patients with ON.

References

1. Perkin GD, Rose FC. Optic neuritis and its differential diagnosis. Oxford: The University Press, 1979: 1-92.
2. Lepore FE. The origin of pain in optic neuritis. Arch Neurol 1991; 48: 748-9.
3. Matthews WB, Acheson ED, Batchelor JR, Weller RO. McAlpine's multiple sclerosis. Edinburgh: Churchill Livingstone, 1985: 1-358.
4. Isayama I, Takahashi T, Shimoyoma T, Yamadori A. Acute optic neuritis and multiple sclerosis. Neurology 1982; 32: 73-6.
5. Nikoskelainen E. Symptoms, signs and early course of optic neuritis. Acta Ophthalmol 1975; 53: 254-72.
6. Lightman S, McDonald WI, Bird AC et al. Retinal venous sheathing in optic neuritis. Brain 1987; 110: 405-14.
7. Celesia GG. Steady state and transient visual evoked potentials in clinical practice. Ann NY Acad Sci 1982; 388: 290-305.
8. Hutchinson WM. Acute optic neuritis and the prognosis for multiple sclerosis. J Neurol Neurosurg Psychiatry 1976; 39: 283-9.
9. Davis FA, Bergen D, Schauf C, McDonald WI, Deutsch W. Movement phosphenes in optic neuritis: a new clinical sign. Neurology 1976; 26: 1100-4.
10. Celesia GG, Kaufman DI, Brigell M et al. Optic neuritis: a prospective study. Neurology 1990; 40: 919-23.
11. Earl CJ, Martin B. Prognosis in optic neuritis related to age. Lancet 1967; 1: 74- 6.
12. Bradley WG, Whitty WM. Acute optic neuritis: its clinical features and their relation to prognosis for recovery of vision. J Neurol Neurosurg Psychiatry 1967; 30: 531-7.
13. Nikoskelainen E. Late course and prognosis of optic neuritis. Acta Ophthalmol (Copenh) 1975; 53: 273-90.
14. Jacobson DM, Thompson HS, Corbett JJ. Optic neuritis in the elderly: prognosis for visual recovery and long-term follow-up. Neurology 1988; 38: 1834-7.
15. Sanders EA, Volkers AC, van der Poel JC et al. Spatial contrast sensitivity function in optic neuritis. Neuro-ophthalmology 1984; 4: 255-9.
16. Fleishman JA, Beck RW, Linares OA, Klein JW. Deficits in visual function after resolution of optic neuritis. Ophthalmology 1987; 94: 1029-35.
17. Frisén L, Hoyt WF, Bird AC, Weale RA. Diagnostic uses of the Pulfrich phenomenon. Lancet 1973; 2: 385.
18. Francis DA, Compston DAS, Batchelor JR, McDonald WI. A reassessment of the risk of multiple sclerosis developing in patients with optic neuritis after extended follow-up. J Neurol Neurosurg Psychiat 1987; 50: 758-65.
19. Taub GR, Rucker CV. The relationship of retrobulbar neuritis to multiple sclerosis. Am J Ophthalmol 1954; 37: 494-7.
20. Percy AK, Nobrega FT, Kurland LT. Optic neuritis and multiple sclerosis: an epidemiologic study. Arch Ophthalmol 1972; 87: 135-9.
21. Frick E, Stickl H. Optic neuritis in multiple sclerosis. An immunological study. Eur Neurol 1980; 19: 185-91.
22. Cohen MM, Lessell S, Wolf PA. A prospective study of the risk of developing multiple sclerosis in uncomplicated optic neuritis. Neurology (NY) 1979; 29: 208-13.
23. Sola P, Merelli E, Schoenhuber R, Penne A, Faglioni P. Neurophysiological and CSF immunological study of 19 patients affected by acute idiopathic optic neuritis. Acta Neurol Scand 1987; 75: 140-4.
24. Compston DAS, Batchelor JR, Earl CJ, McDonald WI. Factors influencing the risk of multiple sclerosis developing in patients with optic neuritis. Brain 1978; 101: 495-511.
25. Denišlič M, Pirtošek Z. Multimodal evoked potentials in multiple sclerosis. Neurologija 1990; 39: Suppl 1: 39-48.
26. Ebers GC, Cousin HK, Feasby TE, Paty DW. Optic neuritis in familial MS. Neurology 1981; 31: 1138-42.
27. McAlpine D, Lumsden CE, Acheson ED. Multiple sclerosis - A reappraisal. Edinburgh: Churchill - Livingstone, 1972: 81-307.
28. Halliday AM, Halliday E, Kriss A, McDonald WI, Mushin J. The pattern-evoked potential in compression of the anterior visual pathway. Brain 1976; 99: 357-74.
29. Štrucl M, Prevec TS. Pattern-reversal visual evoked potentials: methods and standardization. Zdrav Vestn 1981; 50: 67-71.
30. Rossini PM, Di Stefano E, Boatta M, Basciani M. Evaluation of sensory-motor "central" conduction in normal subjects and patients with multiple sclerosis. In: Morocutti C, Rizzo PA eds. Evoked potentials, Neurophysiological and Clinical Aspects. Amsterdam: Elsevier, 1985: 115-30.
31. Brecelj J, Kriss A. Pattern-reversal VEPs in optic neuritis. Neuro-ophthalmology 1989; 9: 55-63.
32. Brecelj J, Denišlič M, Prevec TS, Štrucl M. Vizualni evocirani potenciali pri odkrivanju demielinizacijskih lezij vidnega sistema. Zdrav Vestn 1981; 50: 145-9.
33. Hely MA, McManis PG, Walsh JC, McLeod JG. Visual evoked responses and ophthalmological examination in optic neuritis. A follow-up study. J Neurol Sci 1986; 75: 275-83.
34. Youl BD, Turano G, Miller DH et al. The patophysiology of acute optic neuritis. Brain 1991; 114: 2437-50.
35. Christiansen P, Frederiksen JL, Henriksen O, Larsson HBW. Gd-DTPA-enhanced lesions in the brain of patients with acute optic neuritis. Acta Neurol Scand 1992; 85: 141-6.
36. Chiappa KH, Harrison JL, Brooks EB, Young RR. Brainstem auditory evoked responses in 200 patients with multiple sclerosis. Ann Neurol 1980; 7: 135-43.
37. Baum K, Scheuler W, Hegerl V, Girke W, Schoerner W. Detection of brainstem lesions in multiple sclerosis: comparison of brainstem auditory evoked potentials with nuclear magnetic resonance imaging. Acta Scand Neurol 1988; 77: 283-8.
38. Hume AL, Waxman SG. Evoked potentials in suspected multiple sclerosis: diagnostic value and prediction of clinical course. J Neurol Sci 1988; 83: 191-210.
39. Fischer C, Mauguière F, Ibanez V, Courjon J. Potentiels évoques visuels, auditifs précoces et somestesiques dans la sclérose en plaques (917 cas). Rev Neurol 1986; 142: 517-23.
40. Kjaer M. Evoked potentials in the diagnosis of multiple sclerosis. Electroenceph Clin Neurophysiol 1987; 39: 291-6.
41. Rossini PM, Caramia M, Lavaroni F et al. Non-clinical tests for the diagnosis of multiple sclerosis. Riv Neurol 1987; 57: 33-40.
42. Berardelli A, Inghilleri M, Cruccu G, Fornarelli M, Accornero N, Manfredi M. Stimulation of motor tracts in multiple sclerosis. J Neurol Neurosurg Psychiatry 1988; 51: 677-83.
43. Hess CV, Mills KR, Murray NMF. Measurements of central motor conduction in multiple sclerosis by magnetic brain stimulation. Lancet 1986; 2: 355-8.
44. Ingram DA, Thompson AJ, Swash M. Central motor conduction in multiple sclerosis: evaluation of abnormalities revealed by transcutaneous magnetic stimulation of the brain. J Neurol Neurosurg Psychiatry 1988; 51: 487-94.
45. Merton PA, Morton HB. Stimulation of the cerebral cortex in the intact human subject. Nature 1980; 285: 227.
46. Day BL, Thompson PD, Dick JP, Nakashima K, Marsden CD. Different sites of action of electrical and magnetic stimulation of the human brain. Neurosci Lett 1987; 75; 101-6.
47. Ormerod IEC, McDonald WI, du Boulay GH, et al. Disseminated lesions at presentation in patients with optic neuritis. J Neurol Neurosurg Psychiatry 1986; 49: 124-7.
48. Kinnunen E, Larsen A, Ketonen L, Koskimies S, Sandstrom A. Evaluation of central nervous system involvement in uncomplicated optic neuritis after prolonged follow-up. Acta Neurol Scand 1987; 76: 147-51.
49. Jacobs L, Munschauer FE, Kaba SE. Clinical and magnetic resonance imaging in optic neuritis. Neurology 1991; 41: 15-9.
50. Sandberg-Wolheim M, Bynke H, Cronquist S, et al. A long term prospective study of optic neuritis: evaluation of risk factors. Ann Neurol 1990; 27: 386-93.
51. Rizzo JF III, Lessell S. Risk of developing multiple sclerosis after uncomplicated optic neuritis: a long term prospective study. Neurology 1988; 38: 185-90.
52. Gilbert JJ, Salder M. Unsuspected multiple sclerosis. Arch Neurol 1983; 40: 533- 6.
53. Poser CM, Paty DV, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. Ann Neurol 1983; 13: 227-31.

MULTIMODALNI EVOCIRANI POTENCIALI IN CENTRALNE MOTORIČNE LATENCE PRI BOLNIKIH Z OPTIČNIM NEVRITISOM

Miro Denišlič

Izvleček - Izhodišča. *Bolniki z multiplo sklerozo (MS) v poteku bolezni zelo pogosto prebolijo optični nevritis (ON). Raziskave so pokazale, da približno tretjina bolnikov z ON kasneje zboli za multiplo sklerozo. Namen naše študije je bil odkrivanje klinično tihih okvar v osrednjem živčevju pri bolnikih z optičnim nevritisom. Ugotovljene tihe lezije namreč dokaj zanesljivo napovedujejo, da bo bolnik zbolel za MS.*

Metode. *V raziskavo smo vključili 15 bolnikov z ON in 26 z možno, verjetno oz. zanesljivo obliko MS. Pri skupini bolnikov z ON smo opravili preiskavo evociranih potencialov in električno draženje motorične skorje. Pri drugi skupini bolnikov smo z vidnimi evociranimi potenciali ocenili delovanje vidne poti.*

Rezultati. *Pri vseh bolnikih z ON smo ugotovili abnormno podaljšane latence vala P100, akustični evocirani potenciali so bili abnormni pri 20 % bolnikov, somatosenzorični pa pri 13 %. Podaljšanje centralne motorične latence smo izmerili pri 40 % bolnikov z ON. Pri devetih bolnikih (56 %) z možno oz. verjetno obliko MS smo ugotovili elektrofiziološko prizadetost klinično zdravega vidnega živca. Zakasnjene vidne odzive, ki so pokazali elektrofiziološko prizadetost klinično zdravega očesa, smo našli le pri treh bolnikih (19 %) z zanesljivo obliko MS.*

Sklepi. *Vidni evocirani potenciali so izredno občutljiv kazalnik okvare vidnega živca, pri odkrivanju tihih okvar osrednjega živčevja pa se je pokazala kot najobčutljivejša metoda nevrofiziološka preiskava kortikospinalne proge.*

Ključne besede: *centralne motorične latence; evocirani potenciali; multipla skleroza; optični nevritis*

THE ELECTROOCULOGRAM, ELECTRORETINOGRAM AND PATTERN-REVERSAL VISUAL EVOKED POTENTIALS IN JUVENILE X-LINKED RETINOSCHISIS

A MODEL FOR CURRENT DEVELOPMENT IN CLINICAL VISUAL ELECTRODIAGNOSIS

ELEKTROOKULOGRAM, ELEKTRORETINOGRAM IN VIDNI EVOCIRANI POTENCIALI PRI JUVENILNI, NA KROMOSOM X VEZANI RETINOSHIZI

MODEL ZA RAZVOJ KLINIČNE ELEKTRODIAGNOSTIKE BOLEZNI VIDA

Demetrios Papakostopoulos, Robert M. L. Doran, Nicola K. Ragge

Electrodiagnostic Department, Bristol Eye Hospital, Lower Maudlin Street, Bristol BS1 2LX, Great Britain

Key words: *electrooculogram; electroretinogram; visual evoked potentials; X-linked retinoschisis*

Abstract - *The purpose of this investigation was to establish the electrophysiological profile of juvenile X-linked retinoschisis and to investigate the latency of pattern-reversal visual evoked potentials in this condition. Eight patients with juvenile X-linked retinoschisis were examined with a battery of visual electrodiagnostic tests including electrooculogram (EOG), electroretinogram (ERG) to white and blue flashes of light, and pattern-reversal visual evoked potentials (PVEP). Skin electrodes were used for all recordings. The EOG light/dark ratio and the "a" wave of the ERG were within, or close to the normal range, but the "b" wave of the ERG to white and blue flashes of light was absent from all patients. The PVEPs were abnormally delayed in all cases. This should be attributed to intraretinal disturbance of visual information processing, and be considered as another electrophysiological index of the disease.*

Introduction

X-linked retinoschisis is a rare inherited degenerative disease of the neuroretina which presents in boys during the first decade (1, 2, 3). The condition is slowly progressive and may lead to significant visual disability in later life. Occasional complications, such as vitreous haemorrhage, may cause more severe visual loss at an earlier stage.

The predominant clinical features of the condition include large retinal cysts, abnormal retinal pigmentation, vitreous veils, and microcystic degeneration of the retina within the fovea. The diagnosis may be made on ophthalmic examination, if the characteristic foveal changes are seen.

Electrophysiological tests are useful in confirmation of the diagnosis, together with the finding of a consistent X-linked pedigree. The typical electrodiagnostic features are a decrease or absence of the "b" wave of the electroretinogram (ERG), while the "a" wave and the electrooculogram (EOG) remain normal (4, 5). These ERG findings have been obtained by using corneal electrodes, which involves superficial ocular anaesthesia and usually uniocular examination. We have previously reported that standardised ERG recordings are obtainable with skin electrodes in central serous retinopathy, cone dystrophy, multiple sclerosis and retinitis pigmentosa (6, 7, 8). Skin electrodes have the advantage that they allow bilateral simultaneous ERGs and pattern-reversal visual evoked potentials (PVEP) to be obtained at the same session. Using these techniques, abnormal latencies in PVEPs have been demonstrated in the above mentioned conditions.

The pathology of X-linked retinoschisis principally consists of cleavage and cyst formation within the inner plexiform and ganglion cell layers of the retina (9, 10, 11). This generated the hypothesis that increase in PVEP latency might also be observed in this retinal condition. We report our results of combined testing of ERG, EOG and PVEP, obtained using skin electrodes throughout, in eight patients with clinical signs and genealogical evidence of X-linked retinoschisis.

Materials and methods

Case reports

Cases 1 and 2. Brothers M.E. and R.E.

1. M.E. d.o.b. 23.02.1971. This boy presented at the age of 3 years with an intermittent left convergent squint, which his mother had noticed at the age of 9 months. Visual acuities were R. eye 6/12 and L. eye 6/12 (Sheridan-Gardiner) with normal fundoscopy. Three maternal male relatives were reported as having reduced vision due to progressive retinal disease. The diagnosis in this case was made at the age of 10 years, when he presented with a vitreous haemorrhage in the right eye, and it was also noticed that macular stippling and an inferior retinoschisis were present in the left eye. Further vitreous haemorrhage occurred the following year in the right eye and eventually cleared leaving visual acuities of R. eye 6/24, and L. eye 6/18. Electrophysiological tests were performed on 31.03.1981 and 28.10.1987.

2. R.E. d.o.b. 16.03.1974. Case 2 presented at the age of 6 years, having been referred to the optician with decreased visual acuities on the school eye test. On examination, corrected Snellen visual acuity was R. eye 6/12 and L. eye 6/12 with +1.00 D

Abbreviations: *EOG, electrooculogram; ERG, electroretinogram; PVEP, pattern-reversal visual evoked potential; VEP, visual evoked potential*

spheres. The only ocular abnormality observed was pigmentary stippling in each macula. Visual acuities remained constant up to 1985, when, on further examination, microcystic changes at the maculae were noted. Minimal peripheral retinal changes of "white without pressure" were also seen. Electrophysiological tests were carried out on 31.03.1981 and 28.10.1987.

Cases 3 and 4. Brothers S.S. and P.S.

3. S.S. d.o.b. 23.09.1978. Case 3 presented at the age of 7 1/2 years with poor visual acuities noted by the optician, who had prescribed glasses for mild myopia at the age of 5 years. Four maternal male relatives were registered with visual disability, one of whom has been independently diagnosed as having X-linked retinoschisis.

Examination of case 3 showed Snellen visual acuity of 6/18 in each eye. The fundi showed some retinal hypopigmentation and clumps of pigmentation in the midperiphery. By the age of 9 years, his visual acuity had decreased to 6/24 in each eye, and he demonstrated fine foveal schises and extensive bullous schises in the inferior periphery of both eyes. Electrophysiological testing was carried out on 24.02.1988. One month later he developed a left vitreous haemorrhage.

4. P.S. d.o.b. 14.02.1981. Case 4 presented at the age of 3 1/2 years with visual acuity on Sheridan-Gardiner of R. eye 6/36 and L. eye 6/60, but no obvious fundal abnormality was detected. By the age of 6 years, the visual acuities were R. eye 6/24 and L. eye 6/24, wearing R. eye -1.50 D cyl x 90, L. eye -2.50 DS/+1.50 D cyl x 90. Fine foveal cysts and large anterior vitreous floaters were present bilaterally, with a large peripheral cyst present inferiorly in the right retina. Both eyes also showed posterior embryotoxon and situs inversus of the optic discs. Electrophysiological tests were carried out on 24.02.1988.

Cases 5 and 6. Brothers P.T. and S.T.

5. P.T. d.o.b. 13.02.1965. Case 5 presented at the age of 12 years with an extensive inferior and temporal retinal detachment of the right eye, following a trivial injury with a cricket ball 3 months previously. Vision in the left eye had been defective since the age of 5 years, and was thought to be amblyopic. A maternal uncle with a "retinal condition" died in a home for the blind. On examination, visual acuities were R. eye 6/60 and L. eye 6/24. Vitreous condensations were seen in the left fundus at the time. Two years later, the right retina became completely detached, and further surgery was unsuccessful. Electrophysiological testing was carried out on 23.12.1977.

6. S.T. d.o.b. 16.11.1966. Case 6 was referred by his mother at the age of 11 years because of progressive visual loss. He had Snellen visual acuity of R. eye 6/60, and L. eye 6/18 with glasses. Fundal examination showed slightly pale R. optic disc with situs inversus, normal L. optic disc, bilateral vitreous floaters, and extensive peripheral retinal degeneration with early pigmentation and fine cystic change at the maculae. Electrophysiological testing was carried out on 23.12.1977.

7. H.S. d.o.b. 20.06.1951. Case 7 presented at the age of 6 years with a right retinal detachment treated with scleral resection. Snellen visual acuities at presentation were R. eye 6/36 and L. eye 6/36. His maternal grandfather lives in a home for the blind. Further shallow retinal detachment occurred in the R. eye at the age of 19 years. Fine chronic macular oedema, disc pallor, vitreous fibrosis (extensive in the right and minimal in the left eye) were all noted at follow-up a the age of 27 years. Electrophysiological testing was carried out on 05.05.1987.

8. P.B. d.o.b. 09.02.1943. Case 8 presented to the opticians at the age of 7 years with difficulty reading the blackboard at school, and was prescribed glasses. Gradual deterioration in visual acuity occurred, and by the age of 42 years his Snellen visual acuities were R. eye 6/12 and L. eye 6/12. Fundal appearances showed discrete macular changes with some sub-retinal pigment disturbance. A maternal uncle and maternal second cousin (male) both have severe visual problems. Electrophysiological testing was carried out on 12.05.1987.

Electrophysiological methods

The procedure followed and the values obtained from normal control subjects have been previously reported in detail (8).

The electrooculogram. For recording the EOG, the time constant was 5 seconds, and the upper frequency response 100 Hz (-3 dB). The ratio of the maximum EOG value, called the light peak (Lp), after exposure to intense illumination (3000 cds/m^2), and the lowest EOG value after 10 minutes in darkness, called the dark trough (Dt), multiplied by 100 (Lp/Dt x 100), were calculated for each eye separately for eye movements of 30° (12).

The electroretinogram. The ERG was recorded from 5 silver/silver chloride electrodes, attached periorbitally with collodion. Two electrodes, one for each eye, were placed infraorbitally. Another two electrodes were attached to each external canthus, and one electrode to the bridge of the nose. The amplitude was such that a 100 μV signal was recorded as a 1 cm pen deflection. The time constant was 0.3 seconds, and the upper frequency response 2000 Hz (-3 dB). Flashes at 1/second were delivered with an SLE stroboscope lamp, set at intensity 4, and positioned 25 cm in front of the subject.

Averages of the electrical activity following 100 flashes were obtained with a PDP-12 computer. The analysis time (epoch) was 256 ms. The activity preceding each flash for 100 ms was used as a baseline. All channels were equalised with respect to amplitude prior to recording by passing a 20 μV pulse through the whole system.

Subjects were pre-adapted in room illumination for 15 minutes, and a test trial was carried out with the room light on to provide familiarisation with the procedure and to check the performance of the whole system. Averaging started after the sixth flash, when a steady pupil diameter was established.

Trials contaminated by blinking of eye movements, or any other activity generating voltages exceeding ± 160 μV, were automatically rejected.

During the trial run the position of the subject's pupils was marked on the screen of a closed circuit television. The use of an infrared lamp and camera also permitted the monitoring of the pupil during darkness.

After the initial run, two averages were recorded, after the room lights had been switched off. Then followed a period of 5 minutes without any light stimulation, and a further two averages were obtained. The room lights were then switched on again, and the procedure was repeated.

For a more sensitive examination of dark adaptation, the subject was light-adapted for 10 minutes at a luminance of 3,000 cds/m^2. A blue filter (Wratten 47B) was positioned in front of the stroboscopic lamp, reducing the intensity of the flash by 2 log units. Again, 2 averages were recorded immediately after switching off all the lights. A period of 5 minutes rest ensued, and another 2 averages were obtained. Subsequently, 2 minute rest periods alternated with the collection of 2 averages until 10 complete averages were obtained.

Pattern-reversal visual evoked potentials (PVEPs). The PVEPs were recorded from 5 electrodes placed at O_z, and 5 cm and 10 cm laterally according to the 10-20 system (13). The F_z electrode acted a a reference. The checkerboard was reversed every 496 ms, and averages of 200 reversals were obtained. The reversal time was 8 ms. The contrast was 95 %, and the luminance of the

white squares 250 cd/m². Each square subtended 60' of visual arc, and the whole checkerboard 25° of the visual arc. The analysis time (epoch) was 256 ms.

Normal controls

Twenty-four normal subjects, ranging from 16 years to 54 years of age acted as normal control subjects for all electrodiagnostic procedures. In addition, nine children aged between 6 and 13 years were examined with a similar battery of tests (14). The means of the tests performed were comparable in the adults and children, however the variability was slightly greater in the children. In view of this, reference to normal controls will be made to adults only throughout.

Results

The EOG, ERG to white light and PVEP were recorded from both eyes of our 8 patients. The ERG to blue flashes of light during a 30-minute period of dark adaptation was recorded from 6 patients. The cooperation of all patients was good throughout the two hour recording session. The normal control data for all tests in our laboratory are shown in Table 1.

Tab. 1. *Normals.*
Tab. 1. *Zdravi.*

EOG L/D ratio Razmerje EOG svetlo/temno	Mean Sr. vr.	237 %
	Range Območje	186-335 %
	SD	36.50
ERG (white light) "a" wave	Mean amp.	10.00 µV
ERG (bela svetloba) val "a"	Sr. ampl.	
Dark adaptation Prilagoditev na temo	Range Območje	6-20.2 µV
	SD	3.40
ERG (white light) "b" wave	Mean amp.	27.30 µV
ERG (bela svetloba) val "b"	Sr. ampl.	
Dark adaptation Prilagoditev na temo	Range Območje	12 - 40
	SD	11.10
ERG (blue light) "b" wave	Mean amp.	30.30 µV
ERG (modra svetloba) val "b"	Sr. ampl.	
Dark adaptation Prilagoditev na temo	Range Območje	20-50
	SD	9.50
PVEP	Latency Latenca	100.00 ms
	Range Območje	90-108 ms
	SD	4.00

The EOG values of our 8 patients can be seen in Figure 1 and in Table 2. Five of the patients show results within one standard deviation (SD) of the normal mean. The other three lie within two SD of the mean. Of the patients with the lowest EOG ratios, case 7 (142 % for the left eye and 133 % for the right eye) had received surgical treatment to a peripheral retinal detachment in the right eye, as well as photocoagulation to the retina of the left eye, some sixteen years before the recordings were obtained. Case 5 (150 % for the left eye and no EOG increase for the right) had undergone an encirclement procedure for retinal detachment in the right eye three months earlier.

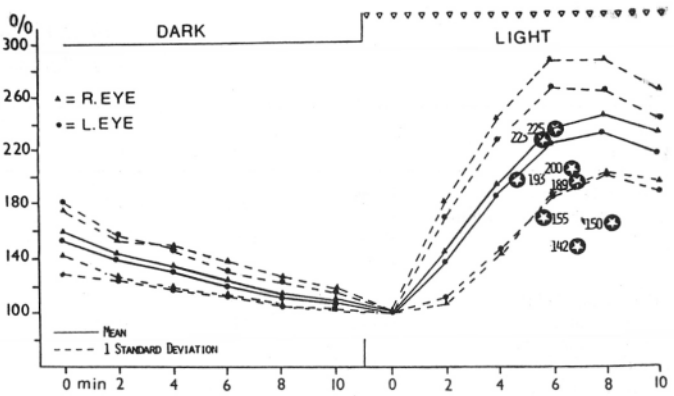


Fig. 1. *Average EOG values (- - -) for left (.) and right (≠) eyes and their SD (- - -) from 14 normal subjects during darkness (DARK) and exposure to light (LIGHT), normalised to lowest value (dark trough). Maximum values during light of 8 patients are shown as *.*

Sl. 1. *Povprečne vrednosti EOG (Mean) za leve (L.EYE) in desne (R.EYE) oči in standardne deviacije (- - -) pri 14 normalnih osebah v temi (DARK) in na svetlem (LIGHT), normalizirane na najnižjo vrednost. Največje vrednosti pri osmih bolnikih na svetlobi so prikazane z zvezdicami.*

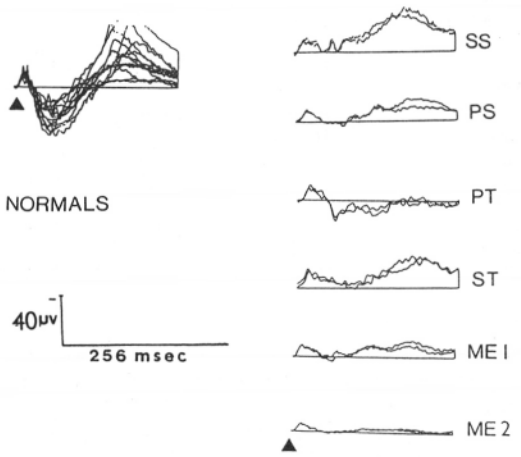


Fig. 2. *Left of figure (NORMALS), superimposed averages of normal ERGs to white light in the dark. Right, superimposed averages of ERG of 6 patients. Note preservation of the "a" wave and extinction of the "b" wave.*

Sl. 2. *Levo (NORMALS) superponirani povprečeni normalni ERG, izzvani z belo svetlobo v temi. Desno, superponirani ERG pri šestih bolnikih. Val a je ohranjen, val b pa izgine.*

Figure 2 shows the recordings of the white light ERG in the dark of normal controls on the left, and of 6 of our patients on the right. Figures 3a and 3b show the recordings of the white light ERG in the dark of one patient (case 1) on two occasions six years apart. Both eyes show a normal "a" wave, while the "b" wave is absent. The individual values for the "a" and "b" wave for each patient are shown in Table 2. It can be seen that only two patients (cases 7 and 8) have amplitude values outside the normal limits, and both of them have had the condition for at least thirty years.

Figure 4 shows the results in the six patients who had blue filter ERG recordings compared with the normal on the left of the figure, where it can be seen that the "b" scotopic wave failed to develop throughout the thirty minute period of dark adaptation.

Tab. 2. Electrodiagnostic data.
Tab. 2. Elektrodiagnostični podatki.

Patient Bolnik		S.T.	P.T.	M.E.	R.E.	P.B.	S.S.	P.S.	H.S.
EOG L/D ratio Razmerje EOG svetlo/temno	L. eye L. oko	225.00	150.00	193.00	255.00	200.00	155.00	223.00	142.00
	R. eye D. oko	190.00	150.00	157.00	244.00	200.00	173.00	214.00	133.00
ERG (white light) "a" wave ampl. (μV) ERG (bela svetloba) Amplit. vala "a" (μV)	L. eye L. oko	11.40	10.50	8.65	8.90	2.90	10.90	8.65	2.15
Dark adaptation Prilagoditev na temo	R. eye D. oko	9.40	8.50	9.50	8.90	1.90	9.90	8.75	1.90
ERG (white light) "b" wave ampl. (μV) ERG (bela svetloba) Amplit. vala "b" (μV)	L. eye L. oko	-	-	-	-	-	-	-	-
Dark adaptation Prilagoditev na temo	R. eye D. oko	-	-	-	-	-	-	-	-
ERG (blue light) "b" wave ampl. (μV) ERG (modra svetloba) Amplit. vala "b" (μV)	L. eye L. oko			-	-	-	-	-	-
Dark adaptation Prilagoditev na temo	R. eye D. oko			-	-	-	-	-	-
PVEP Slikovni VEP	L. eye L. oko	120.00	120.00	120.00	114.00	148.00	158.00	144.00	114.00
(Latency ms) Latenca (ms)	R. eye D. oko	120.00	116.00	118.00	118.00	146.00	156.00	156.00	136.00
PVEP Slikovni VEP	L. eye L. oko	5.00	5.00	12.50	20.50	8.00	9.00	13.50	1.00
Ampl. (μV) Amplituda (μV)	R. eye D. oko	3.00	3.00	12.00	19.00	8.00	8.00	13.00	2.00

The pattern-evoked potentials to full field stimulation of each eye of Case 1, recorded from O_z and four lateral locations, on two occasions 6 years apart, is shown in Figure 5a and 5b. It is well developed in amplitude, and assumes the normal spatial distribution. However, its latency is prolonged by more than three SD from the mean of our normal population. The PVEP following stimulation of one eye of all patients is shown in Figure 6. The P100 is delayed by more than 3 SD in every case as is also shown in Table 2, where the latency and amplitude values for each eye are presented.

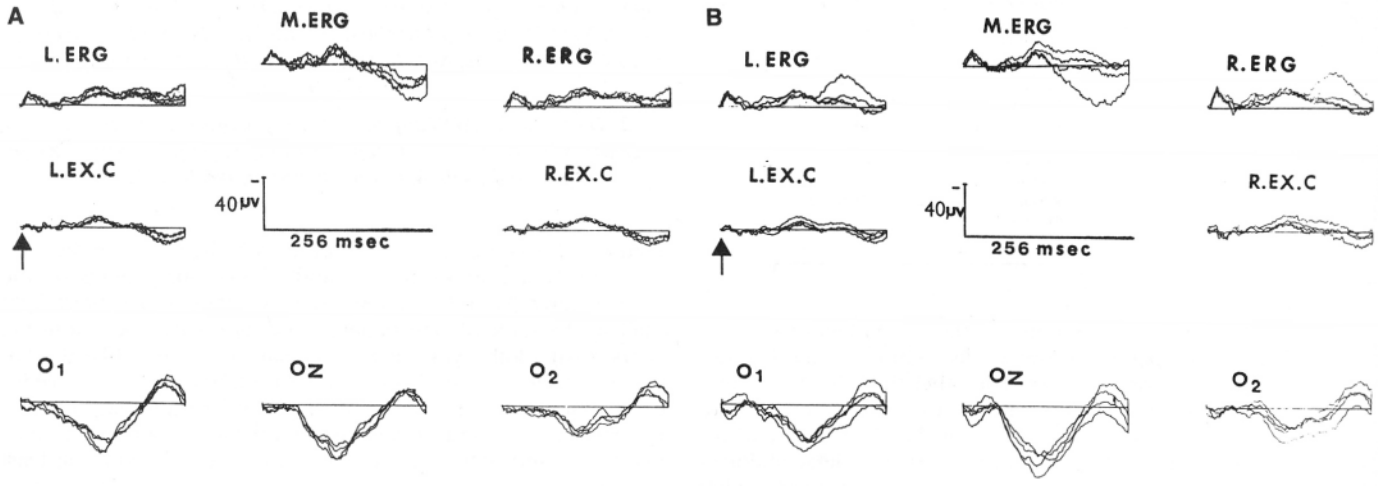


Fig. 3. *Superimposed averages of ERG and flash VEP (bottom 3 traces) recorded from left (L) and right (R) eyes, nasion (N) and external canthi (EX.C.). O_1, O_z and O_2 occipital electrodes (10-20 system). 3a shows results of tests performed in 1981 and 3b in 1987.*

Sl. 3. *Superponirani povprečeni ERG in bliskovni VEP (spodnji zapisi), posneti na levem (L), desnem (R) očesu, glabeli (M) in zunanjih očesnih kotih (EX.C.); zatilne elektrode O_1, O_z in O_2 (sistem 10-20); 3a prikazuje rezultate testiranja v letu 1981, 3b pa leta 1987.*

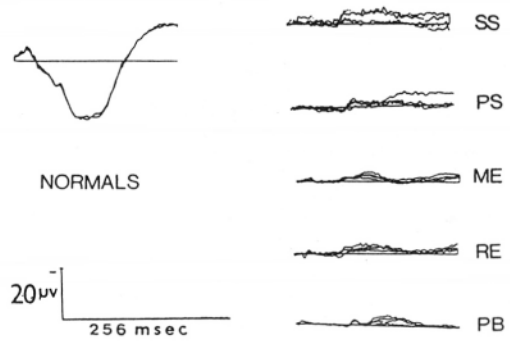


Fig. 4. *Left of figure (NORMALS), across subject average (n = 24) of normal ERGs to blue flashes of light after 15 minutes of dark adaptation. Right, superimposed averages of ERG of 5 patients. Note the extinction of the "b" wave.*

Sl. 4. *Levo (NORMALS), povprečen (n = 24), normalen ERG na modri blisk po 15 minutah adaptacije na temo. Desno, superponirani povprečeni ERG pri petih bolnikih. Vala b ni!*

Discussion

The eight cases which have been presented are clear examples of X-linked retinoschisis according to clinical and genetic criteria. Electrophysiological findings demonstrated the typical extinction of the "b" wave of the ERG to white light stimuli, and the preservation of the EOG reaction to light. The finding of reduced "a" wave ERG amplitude in two patients (Cases 7 and 8) should be expected in view of the long duration of the disease (5). The noticeably reduced EOG ratios found in Cases 5 and 7 are most probably associated with the history of retinal surgery and photocoagulation. Verification of "b" wave changes in the ERG is provided by the technique of using blue flashes of light during a 30-minute period of dark adaptation.

There are no previous reports, to our knowledge, of delayed PVEPs in juvenile retinoschisis. We have found consistent abnormalities in the latency of the P100 component to pattern-reversal stimulation, without changes in its waveform or spatial distribution. We believe that this is another characteristic of the electrophysiological picture in this condition. We found no correlation between the extent of the delay in the P100 and the corrected Snellen visual acuity in our patients. Indeed the patient with the best visual acuity, i.e. case 8, had severe delay in the P100.

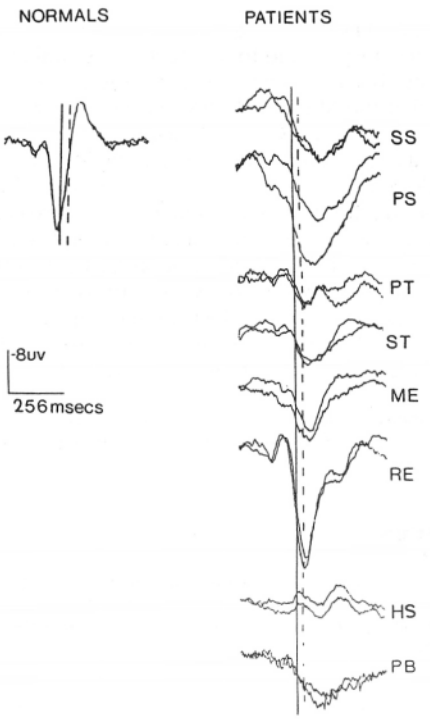


Fig. 6. *Left of figure (NORMALS), across subject average (n = 24) of PVEP from O_z location. Continuous vertical line, mean latency of the P100. Interrupted vertical line, 3 SD from the mean. Right, superimposed averages of PVEP of 8 patients.*

Sl. 6. *Levo (NORMALS), povprečen (n = 24) slikovni VEP, posnet na mestu O_z. Neprekinjena navpična črta pomeni latenco P100, prekinjena pa 3 SD od srednje vrednosti. Desno, superponirani slikovni VEP pri osmih bolnikih.*

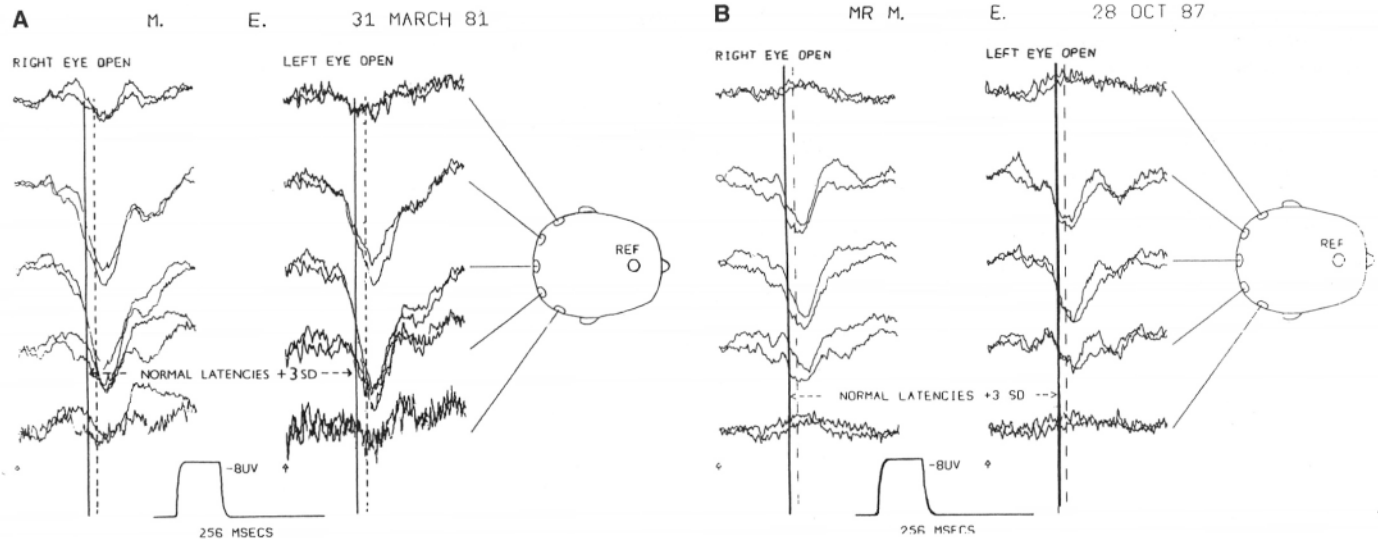


Fig. 5. *Superimposed averages of PVEP from central and lateral occipital locations after stimulation of right eye (left traces) and left eye (right traces) from one patient in 1981 (5a) and 1987 (5b). Vertical line, mean latency of P100 in normals.*

Sl. 5. *Superponirani slikovni VEP, posnet na osrednjih in stranskih predelih zatilja po draženju desnega (levi zapisi) in levega očesa (desni zapisi) pri bolniku leta 1981 (5a) in 1987 (5b). Navpične črte pomenijo srednjo latenco P100 pri normalnih osebah.*

Condon et al. (11) have suggested that the abnormality in the ERG in retinoschisis is due to a defect in the Müller cells, and in particular cite this as an explanation of the reduced "b" wave. It is possible that the Müller cell dysfunction may cause an abnormality in transmission of visual information within the retina, manifested as a delayed PVEP. Alternatively, the splitting and cyst formation within the ganglion cell and axonal layers of the retina, found in pathological examination, may explain the delay. In either case, the cause of the delay is, therefore, intra-retinal, which is supported by the lack of published data suggesting demyelination of the visual pathways in retinoschisis.

Our results suggest that skin electroretinography is a reliable diagnostic tool for X-linked juvenile retinoschisis, and reveal profoundly delayed PVEPs as a typical feature of this condition.

Acknowledgement. The authors wish to thank Mr. J. C. Dean Hart for discussion, and consultant colleagues from the Bristol Eye Hospital for permission to use their patients.

References

1. Jager GM. A hereditary retinal disease. Trans Ophthal Soc U.K. 1953; 73: 617-9.
2. Deutman AF. Vitreoretinal dystrophies. In: Krill A, Archer DB eds. Hereditary retinal and choroidal diseases. New York: Harper & Row Publishers Inc., 1977: 2: 1043-108.
3. McMahon TT, Rosenthal BP. X-linked juvenile retinoschisis. J Am Optom Assoc 1983; 54: 55-61.
4. Carr RE, Siegel IM. Visual electrodiagnostic testing: a practical guide for the clinician. Baltimore, Md.: Williams and Wilkins, 1982.
5. Peachey NS, Fishman GA, Derlacki DJ, et al. Psychophysical and electroretinographic findings in X-linked juvenile retinoschisis. Arch Ophthal 1987; 105: 513-6.
6. Papakostopoulos D, Dean Hart C, Cooper R, Natsikos V. Combined electrophysiological assessment of the visual system in central serous retinopathy. Electroenceph Clin Neurophysiol 1984; 59: 77-80.
7. Papakostopoulos D, Fotiou F, Dean Hart JC, et al. The electroretinogram in multiple sclerosis and demyelinating optic neuritis. Electroenceph Clin Neurophysiol (in press).
8. Papakostopoulos D. Clinical electrophysiology of the human visual system. In: Chiarenza GA, Papakostopoulos D eds. Clinical application of cerebral evoked potentials in pediatric medicine. Amsterdam: Excerpta Medica, 1982: 3-40.
9. Yanoff M, Rahn EK, Zimmerman LE. Histopathology of juvenile retinoschisis. Arch Ophthal 1968; 79: 49-53.
10. Manschot WA. Pathology of hereditary juvenile retinoschisis. Arch Ophthal 1972; 88: 131-8.
11. Condon GP, Brownstein S, Wang N-S, et al. Congenital hereditary (juvenile X-linked) retinoschisis - histopathology and ultrastructural findings in three eyes. Arch Ophthal 1984; 104: 576-83.
12. Arden GB, Kelsey JH. Changes produced by light in the standing potential of the human eye. J Physiol 1962; 161: 189-204.
13. Jasper HH. The ten-twenty system of the International Federation. Electroenceph Clin Neurophysiol 1958; 10: 371-5.
14. Papakostopoulos D, Oriani S, Newton P. Combined electrophysiological assessment of the visual system in children. In: Chiarenza GA, Papakostopoulos D eds. Clinical application of cerebral evoked potentials in pediatric medicine. Amsterdam: Excerpta Medica, 1982: 115-42.

ELEKTROOKULOGRAM, ELEKTRORETINOGRAM IN VIDNI EVOCIRANI POTENCIALI PRI JUVENILNI, NA KROMOSOM X VEZANI RETINOSHIZI. MODEL ZA RAZVOJ KLINIČNE ELEKTRODIAGNOSTIKE BOLEZNI VIDA

Demetrios Papakostopoulos, Robert M. L. Doran, Nicola K. Ragge

Izvleček - *Izhodišča. Avtorji so želeli dognati, katera merila elektrofiziološkega testiranja so pomembna pri bolnikih z juvenilno, na kromosom X vezano retinoshizo. Proučevali so tudi spremembe latence vidnih evociranih potencialov na slikovni dražljaj.*

Metode. *Pri osmih bolnikih (starosti 3 do 12 let) s klinično potrjeno diagnozo juvenilne, na kromosom X vezane oblike retinoshize so napravili naslednje elektrofiziološke teste: elektrookulogram (EOG), elektroretinogram (ERG) in vidne evocirane potenciale (VEP). ERG so izzvali z belim in modrim bliskovnim draženjem, za VEP pa so uporabili slikovni dražljaj na izmenjavo črno-belih kvadratov. Za odjem vseh potencialov so uporabljali kožne elektrode.*

Rezultati. *Pri vseh bolnikih sta bila elektrookulografsko razmerje svetloba/tema in val a ERG v mejah normalnih vrednosti, medtem ko vala b ni bilo mogoče izzvati ne z belim ne z modrim bliskovnim draženjem. Latenca vala P100 VEP na slikovni dražljaj je bila pri vseh pomembno podaljšana.*

Zaključek. *Rezultati testov kažejo, da je umestno elektrofiziološko vrednotenje delovanja vida pri juvenilni, na kromosom X vezani obliki retinoshize. Na nivoju mrežnice so podatki zanesljivi že z uporabo kožnih elektrod. Na kortikalnem nivoju pa se je pokazalo, da so zapozneli odzivi tudi lahko značilnost te bolezni.*

Ključne besede: *elektrookulogram; elektroretinogram; na kromosom X vezana retinoshiza; vidni evocirani potenciali*

VISUAL ELECTROPHYSIOLOGICAL TESTING OF YOUNG CHILDREN

ELEKTROFIZIOLOŠKO TESTIRANJE VIDA PRI OTROCIH

Anthony Kriss

Dept. Ophthalmology, Hospital for Sick Children, Great Ormond Street, London WC1N 3JH, Great Britain

Key words: *children; electroretinogram; hemisphere; optic chiasm; retina; visual evoked potential*

Abstract - *Recording the skin electroretinogram (ERG) and visual evoked potentials (VEPs) concurrently in young children is a simple yet powerful means of assessing visual pathway function. Rod and cone function can be assessed by testing under scotopic conditions, and using dim blue and red flashes, respectively. Monocular pattern-reversal stimulation and a common reference montage incorporating several electrodes placed across the occiput are important procedures, which will help identify post-retinal dysfunction localised to the chiasm or in one posterior hemisphere.*

Introduction

Electroretinographic (ERG) testing with contact lens or other types of corneal electrodes has a well established place in assessment of retinal function in co-operative subjects (1, 2, 3). Use of corneal electrodes in young children is more problematical and not universally adopted, since either the child is made unconscious with a sedative or general anaesthetic (and inevitably exposed to some risk), or alternatively forcible restraint has to be used almost invariably, while corneal electrodes are inserted and flash stimuli presented.

Visual evoked potential (VEP) testing has a proven role in assessment of post-retinal visual function (4). Flash stimulation is commonly used in paediatric visual appraisal, though it is increasingly recognised that pattern testing can be successfully accomplished in children (5, 6, 7); with the accompanying benefit that pattern stimulation tends to give more accurate information regarding the pathological process and the level at which dysfunction is occurring (4).

Many ophthalmology departments routinely record the ERG but not the VEP, whereas many clinical neurophysiology departments do the opposite, and routinely record the VEP but not the ERG. This article demonstrates that, in young children, there are strong advantages in recording both the skin ERG and VEP in the same recording session. We find that a reliable appraisal of cone and rod function can be obtained from skin ERGs, providing there is control and due account of physical and physiological factors which could lead to false interpretation (8). We test under fully darkened laboratory conditions, and first record transient responses to pattern-reversal in order to gauge macular pathway function. After a period of 10-15 minutes in the dark, flash stimulation is performed using bright white flash, and this elicits a mixed cone/rod ERG. If indicated, red and blue flash stimulation can then be used to separately gauge cone and rod function respectively (7, 9).

Monocular pattern-reversal stimulation gives reliable clues regarding the level of any post-retinal visual pathway dysfunction (4). Transient pattern-reversal or pattern-onset testing can also provide an estimate of visual acuity levels when a range of checksizes is presented (10, 11). Sweeping through a range of spatial frequencies using steady-state VEPs has been shown to be a rapid method of gauging visual acuity in infants (12). We have used sweep VEPs to gauge visual development in infants operated for congenital cataract (13, 14).

This article presents data from children with visual pathway dysfunction at the retinal, optic nerve, chiasmal and posterior hemisphere levels, in order to highlight the advantage of combined ERG/VEP recording in paediatric visual assessment.

Retinal disorders

Disorders affecting rod and/or cone function can be detected using skin ERGs, but it is vital to ensure that the adopted methodology is appropriate for obtaining well-defined responses. It is essential to have scotopic conditions in order to elicit rod mediated activity. A moderately bright flash (Grass PS22 photic stimulator: intensity 4, 3.7×10^5 candlepower) delivered under scotopic conditions will elicit a mixed cone/rod ERG, which, on average, has an a-b amplitude of 25 μV in subjects over 6 months of age without retinal disease (9). Red flash (peak transmission from 670 nm) will elicit a predominantly cone mediated ERG, and dim blue (peak transmission 450 nm) will elicit rod mediated responses (Grass intensity 1, 1.6×10^4 candlepower). The skin ERG electrode should be very near the eye - we place the active electrode centrally on the lower eyelid, about 1 cm below the rim. The reference is placed mid-frontally at Fz (10-20 system), and this is used as a reference for VEP recordings

Abbreviations: *ERG, electroretinogram; FVEP, flash visual evoked potential; PVEP, pattern-reversal visual evoked potential; VEP, visual evoked potential*

as well. Figure 1 shows flash ERG/VEP traces of a 15 week old patient with Leber's amaurosis, a clinical condition most usually isolated to the eye in which there is maldevelopment of both rods and cones. In most patients with Leber's amaurosis, no flash ERG or VEP activity is detectable (15). However, a minority have rudimentary perception-of-light or hand-movement levels of acuity, and will produce attenuated flash VEP activity (but not ERGs). Patients with some peroxisomal disorders affecting vision (e.g. infantile Refsum's, Zellweger's) will also produce no ERG and little or no flash VEP activity, but will also have evidence of neurological dysfunction, and abnormalities on biochemical testing of blood (thus distinguishing them from Leber's amaurosis (16)).

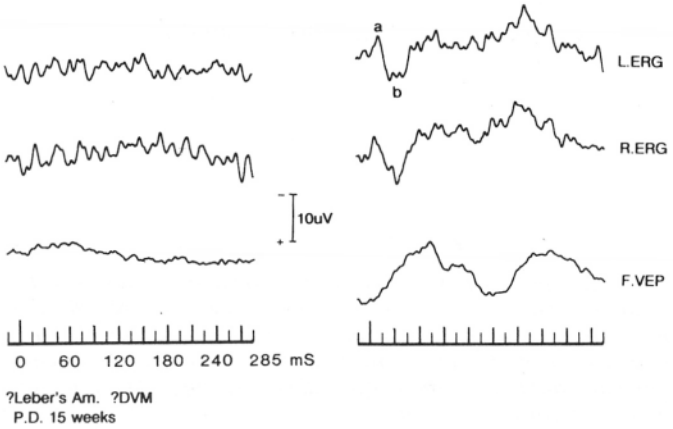


Fig. 1. *Flash ERG and VEP testing in a young infant with Leber's amaurosis (left) and a healthy infant of the same age (right). No visual responses were detectable in the patient (with permission from (9)).*

Sl. 1. *Bliskovni ERG in VEP pri otroku z Leberjevo amavrozo (levo) in pri enako starem zdravem otroku (desno). Pri bolniku ne moremo izvabiti vidnih potencialov (z dovoljenjem iz ref. 9).*

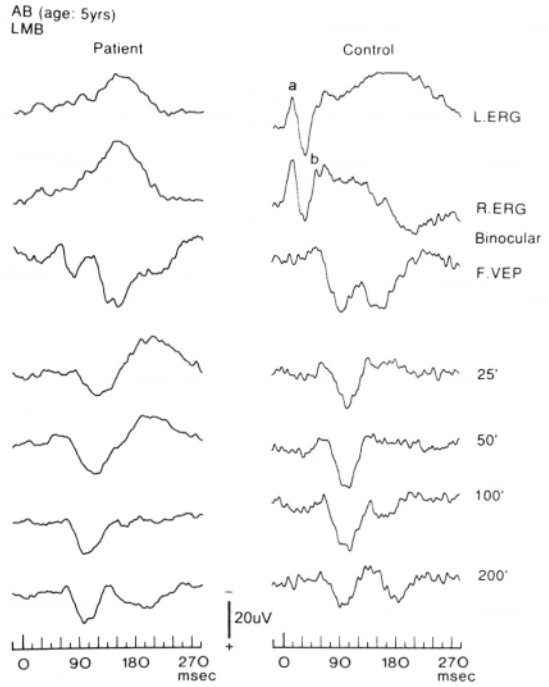


Fig. 2. *Flash ERGs and VEP, and binocular pattern-reversal VEPs to 25', 50', 100' and 200' checks in a 5yr old patient with Laurence-Moon-Biedel syndrome (left) and a control child (right). Note that no ERG activity is detectable in the patient, but VEP (macular) activity is relatively well preserved.*

Sl. 2. *Bliskovni ERG in VEP ter slikovni VEP po binokularnem draženju s 25', 50', 100' in 200' velikimi kvadrati pri pet let starem otroku s sindromom Laurence-Moon Briedel (levo) in pri zdravem otroku (desno). Pri bolniku ne registriramo ERG aktivnosti, medtem ko je VEP aktivnost (makularna) primerno ohranjena.*

Figure 2 demonstrates the flash ERGs, and VEPs, from a 5-year-old patient with Laurence-Moon-Biedel. This syndrome is mainly characterised by obesity, kidney dysfunction, hypogonadism, mental retardation, polydactyly, and a progressive pigmentary retinopathy which, in infancy, is not always apparent on fundal examination. In early childhood, the typical ERG/VEP picture is that of non-detectable, or very attenuated, ERG activity (both rod and cone mediated); VEP activity is well preserved, both to flash and pattern-reversal stimulation, though the latter may be mildly delayed to small checksizes. A similar electrodiagnostic picture is observed in Joubert syndrome, which is characterised by cerebellar vermis hypoplasia, and clinically associated with infantile tachypnea, mental retardation, and pigmentary retinopathy (17). In congenital cone dysfunction (also called rod monochromatism or achromatopsia), rod mediated activity, evoked by dim blue (or green flashes) delivered under scotopic conditions, is well-preserved. However, cone mediated activity tested with red flash under scotopic conditions, and with 30/second flicker, is most commonly not detectable. Delayed flash VEPs can be recorded in patients with cone dysfunction, However, pattern VEPs are evident in about 50 % of patients only, and are commonly very attenuated and delayed (Fig. 3).

Optic nerve disorders

Combined ERG/VEP will indicate the visual pathway level and, in some conditions, the nature of the abnormality. Pattern VEPs are likely to be detectable when acuity is at good to moderate levels. In these situations, visual pathway dysfunction due to demyelination will give a VEP which is markedly delayed but has a well-preserved waveform; whereas in the presence of compressive or ischaemic abnormalities, the pattern VEP is likely to be degraded, attenuated and mildly delayed only (4). It is important to record VEPs to monocular stimulation, since it will help reveal whether the disease process is affecting the optic nerve, chiasm or posterior hemisphere. Independent testing of the lateral half-fields will improve the test sensitivity (4, 18) but it is not likely to be achieved easily in children under 4 years.

Congenital nystagmus almost invariably occurs when there is poor vision, or complete blindness, due to abnormalities of the eye or anterior visual pathway. In infancy, fundal examination of a patient with congenital nystagmus is often normal, and the nature of the disorder may not be apparent. Combined ERG/VEP recording is particularly valuable in the investigation of these patients, as it will suggest whether the disease process involves the retina and/or the post-retinal visual pathway (7, 9).

A normal ERG and non-recordable VEP (flash or pattern) is indicative of very severe compromise of the post-retinal pathway. Disorders, such as severe optic nerve hypoplasia, and optic atrophy secondary to compressive (e.g. chiasmal craniopharyngioma, glioma, advanced osteopetrosis) or neurometabolic disease (e.g. Tay-Sachs disease) processes, will often produce this electrodiagnostic picture (7, 19).

1. Optic nerve hypoplasia is not always easy to detect by ophthalmoscopic or imaging techniques in young children. The fundus can appear normal, and detection of the hypoplastic disc may be subtle and easily missed, particularly if child is unsedated and has conspicuous nystagmus. The combined

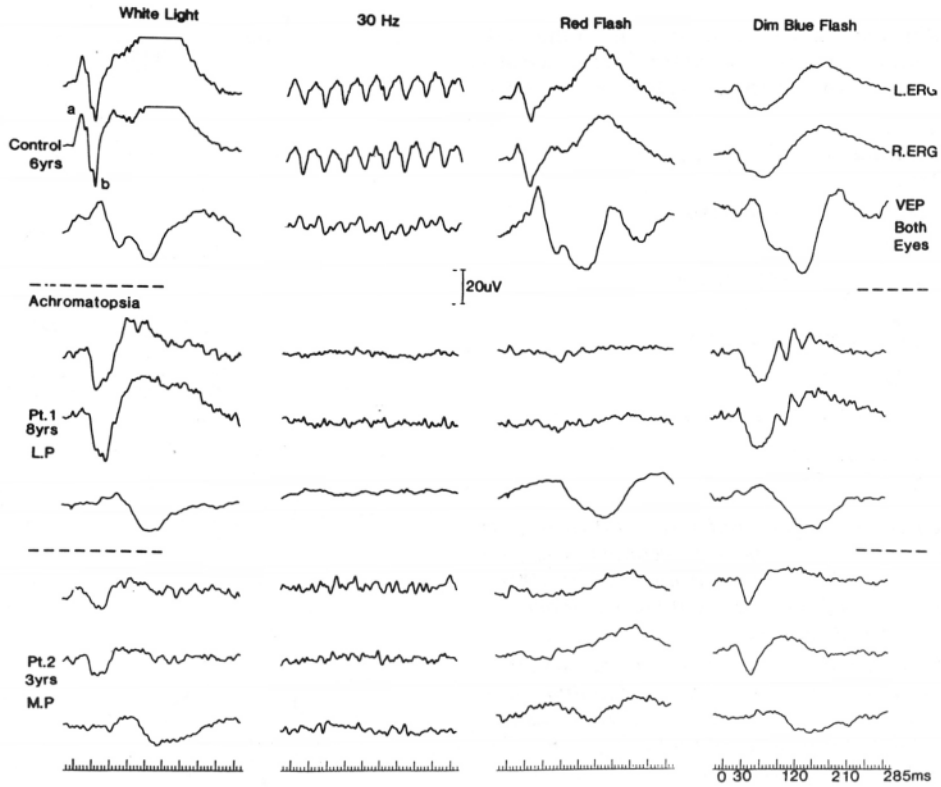


Fig. 3. *ERGs and binocular VEPs to bright white flash, 30/sec flicker, red flash and dim blue flash in 2 siblings with rod monochromatism (lower traces) and a 6yr old normal control (upper traces). Note that no ERG responses are detectable in either patient to cone function testing with 30/s flicker and red flash, but rod mediated activity is clearly detectable to testing under scotopic conditions with white and dim blue flash (with permission from (9)).*

Sl. 3. *ERG in binokularni VEP po svetlem, 30-sekundnem, rdečem in zatemnjenem modrem bliskovnem dražljaju pri sorodnih otrocih z monokromatizmom paličnic (spodnji posnetki) in pri šest let starem zdravem otroku (zgornji posnetki). Pri bolnikih po testiranju delovnaja čepnic s 30-sekundnim in rdečim bliskovnim dražljajem ne registriramo aktivnosti VEP, medtem ko po testiranju delovanja paličnic pod skotopskimi pogoji z belo in zatemnjeno modro svetlobo zaznamo aktivnost VEP (z dovoljenjem iz ref. 9).*

ERG/VEP picture (Fig. 4) usually shows a normal ERG (it is larger than average in severe cases (20) and very attenuated or no VEP activity (latency may be marginally increased, though not in all cases).

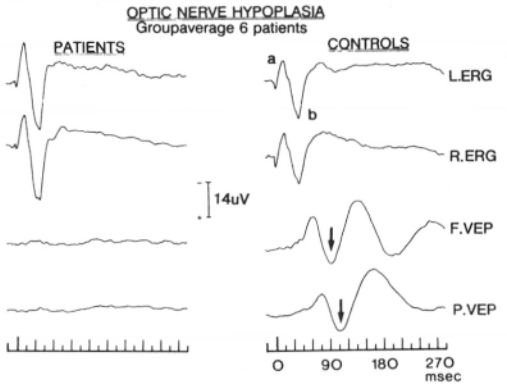


Fig. 4. *Group average responses from 6 patients with severe optic nerve hypoplasia (left) and healthy matched controls (right). Note that ERGs from the patients are larger than average, and neither flash (FVEP) nor pattern-reversal (PVEP) activity is detectable.*

Sl. 4. *Povprečeni odgovori 6 bolnikov s hudo hipoplazijo optičnega živca (levo) in zdravih kontrol (desno). ERG je pri bolnikih večji kot pri zdravih, bliskovni (FVEP) in slikovni VEP (PVEP) pa sta pri bolnikih s hudo hipoplazijo vidnega živca neizzivna.*

2. Infantile osteopetrosis. In this condition there is excessive deposition of bone and narrowing of foramina affecting cranial nerves, most notably optic and auditory nerves. Combined ERG/VEP recording (Fig. 5) is useful in assessing visual pathway status in this condition. VEP can provide an early sign of anterior visual pathway compression, and thus indicate the urgent need for bone marrow transplant, and possibly also optic nerve decompression, before the frank signs of optic atrophy are apparent.

Chiasmal abnormalities

Electrophysiological detection of chiasmal anomalies is optimally accomplished by way of independent left- and right-half field testing of each eye (4, 18). Although VEPs to stimulation of the two lateral half-fields tend to have opposite occipital distributions, they are not exact mirror images, since the neuro-anatomical arrangement of each hemisphere can be quite different in any subject. Half-field testing with VEPs is not normally achieved in young children, as it is not possible to hold their fixation for long enough throughout the averaging period.

Nonetheless, a marked occipital asymmetry on monocular testing which reverses in distribution when the other eye is tested (i.e. crossed asymmetry), is an important indicator of an anomaly involving optic fibres crossing at the chiasm. The asymmetry is of greatest significance when there is activity of opposite polarity on each side of the occipital midline. It is important to use widely

spaced electrodes, which are at least 4 cm away from the midline, and to adopt a monopolar derivation with the reference at a midfrontal location. Crossed asymmetry anomalies can be of two opposite forms:

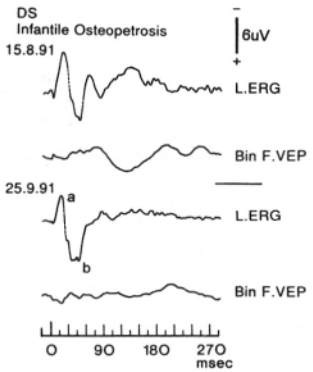


Fig. 5. *Normal mixed cone/rod ERG and flash VEP (arrowed) from young infant with infantile osteopetrosis recorded on the 6th week following birth (15. 8. 1991). Six weeks later (25. 9. 1991), the ERG was still normal though no consistent flash VEP activity was detectable.*

Sl. 5. *ERG aktivnost čepnic/paličnic in bliskovna VEP aktivnost (označena s puščico) je normalna pri dojenčku z infantilno osteopetrozo šest tednov po rojstvu (15. 8. 1991). Šest tednov kasneje (25. 9. 1991) je ERG aktivnost še v mejah normale, bliskovna VEP aktivnost pa ni izzivna.*

1. Those associated with compromise of fibres crossing at the chiasm, which is most commonly seen in children with glioma or craniopharyngioma. In chiasmal compression, VEP changes following pattern-reversal stimulation are clearer, and thus more reliable, than those to flash stimulation. Figure 6 shows the full-field pattern-reversal VEPs of a young boy who had had a craniopharyngioma removed and was left with a residual bitemporal visual field defect. Note that binocular testing is not revealing, but monocular testing shows a clear crossed asymmetry with opposite distributions for the two eyes.
2. Those due to excessive cross-over of fibres at the chiasm, which uniquely occurs in albinism. The pattern of crossed asymmetry is opposite to chiasmal compression (Fig. 7). In infancy, the albino crossed asymmetry is best shown with flash stimulation (in addition, ERG changes associated with albinism will also be detected) (21, 22). The vast majority of albinos have nystagmus and, in these circumstances, it is best to use large check sizes when using pattern-reversal stimulation, since smaller checksizes are not likely to produce reliable findings. However, albino VEP changes are best demonstrated with pattern onset stimulation in older children and adults (23, 24). (Fig. 8).

Unilateral posterior hemisphere dysfunction

In young children, both pattern and flash VEPs tend to show a conspicuous occipital asymmetry when there is dysfunction of one hemisphere involving the post-chiasmal visual pathway. The main positivity (P100) is seen in the midline and over the hemisphere with the dysfunction, and a negativity with peak latency around 100 ms is recorded over the opposite hemisphere. This asymmetry is seen on binocular stimulation, and is the same for independent stimulation of each eye (called an uncrossed asymmetry). It is postulated that the P100 distribution appears paradoxical, since electrodes over the hemisphere with the dysfunction are well placed to pick-up activity produced by dipole generators of the normally functioning hemisphere (25, 26). We have demonstrated in several previous studies the sensitivity of VEPs in hemisphere dysfunction where clinical signs have not been obvious (27, 28). Figure 9 shows VEP findings from an infant with a ventricular cyst in the posterior right hemisphere. Eye movement recordings (smooth pursuit and opto-kinetic nystagmus), and VEP studies, showed abnormalities indicative of right hemisphere dysfunction. Note that VEPs to *both* pattern-reversal and flash stimulation were markedly asymmetrical.

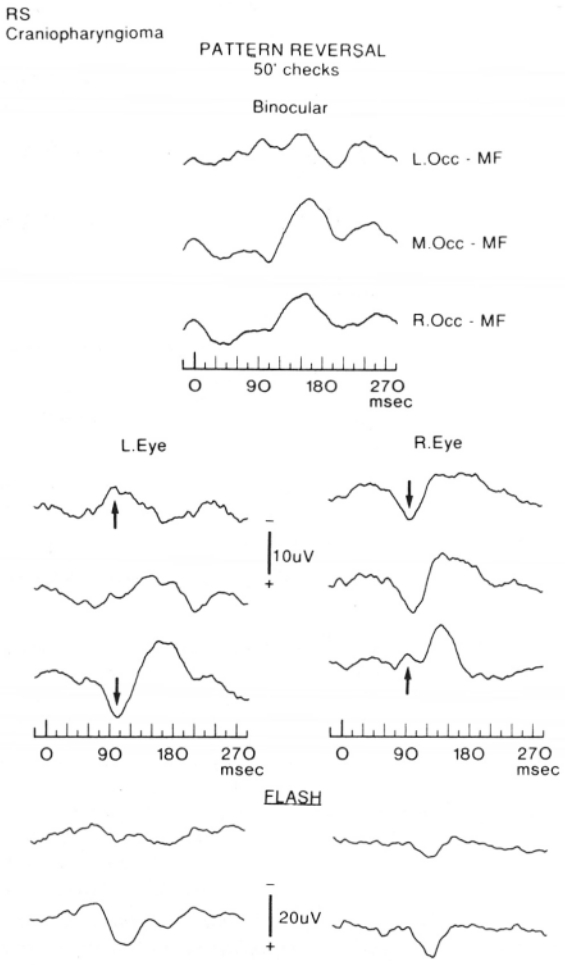


Fig. 6. *Bi- and monocular PVEPs, and monocular FVEPs in a child operated for removal of a craniopharyngioma. Full-field monocular PVEPs show a clear crossed asymmetry suggesting a bitemporal field defect. Note that in this situation binocular stimulation does not give useful information since there is cancellation due to summation of activity of opposite polarity in lateral channels.*

Sl. 6. *Bi- in monokularna slikovna VEP in monokularna bliskovna VEP aktivnost pri otroku, operiranem zaradi kraniofaringeoma. Monokularni slikovni posnetki VEP po draženju s celim poljem kažejo navzkrižno asimetrijo, kar je značilno za bitemporalni izpad v vidnem polju. Binokularna stimulacija zaradi izničevanja oziroma sumacije aktivnosti na stranskih kanalih ne daje dodatnih podatkov.*

Conclusion

Electrophysiological testing has much to offer paediatric neurologists or ophthalmologists assessing young children who appear to have poor vision. Recording ERG and VEP activity in the same

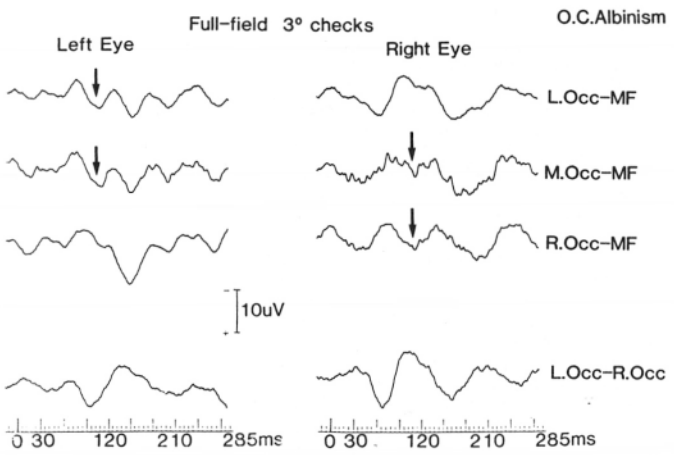


Fig. 7. *Full-field monocular pattern-reversal VEPs to 3 degree checks in a 7yr old patient with oculocutaneous albinism. Note the crossed asymmetry when comparing VEPs from each eye; the pattern of asymmetry is opposite to that associated with chiasmal compression, since in albinism most of the optic nerve fibres arising from one eye cross over at the chiasm and project onto the contralateral hemisphere.*

Sl. 7. *Monokularna slikovna aktivnost VEP po draženju s celim poljem in s tri stopinje velikimi kvadrati pri sedemletnem otroku z okulokutanim albinizmom. Navzoča je navzkrižna asimetrija, vendar je vzorec asimetrije nasproten tistemu, ki ga opazujemo pri hiazmalnih okvarah, saj se pri albinizmu večina vlaken iz enega očesa križa v hiazmi in projicira nad kontralateralno hemisfero.*

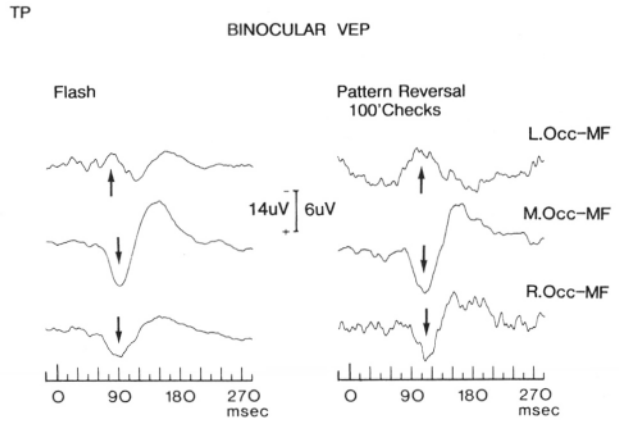


Fig. 9. *Binocular flash (left) and pattern-reversal VEPs (right) from an infant with a right occipital lesion. A marked occipital asymmetry evident on binocular and monocular stimulation is strongly suggestive of an occipital lesion in the hemisphere over which the P100 component is paradoxically recorded (see text for more details) (with permission from (28)).*

Sl. 9. *Binokularni bliskovni (levo) in slikovni VEP (desno) otroka z desno okcipitalno okvaro. Okcipitalna asimetrija, ki je vidna pri monokularni in binokularni stimulaciji, kaže na okcipitalno okvaro v hemisferi, nad katero paradoksalno registriramo komponento P100 (podrobnosti so razložene v besedilu) (z dovoljenjem iz ref. 28).*

session, as well as adopting appropriate stimulating techniques and recording methodology, provide powerful means of identifying the visual pathway level and possible nature of the disease

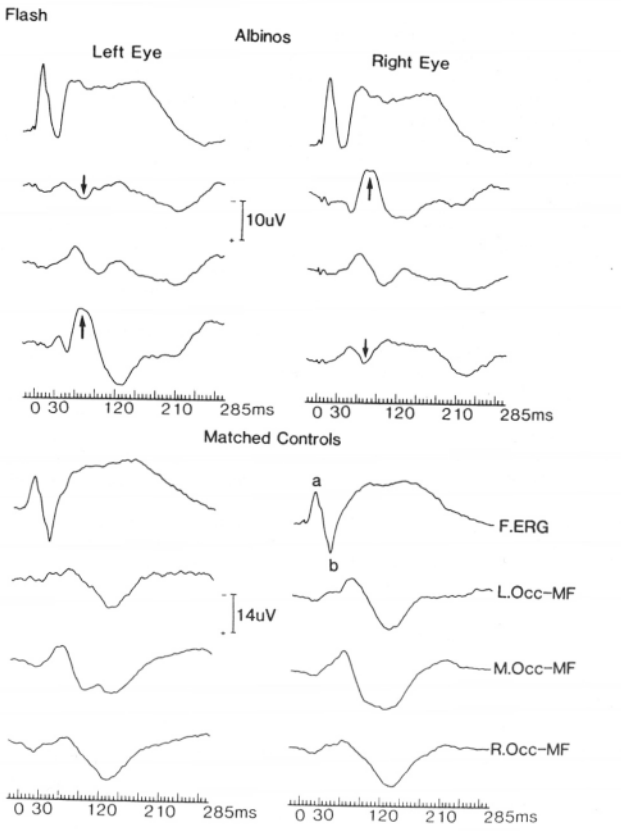


Fig. 8. *In infancy, flash stimulation is more effective stimulus mode for detecting albinism. Albinos give ERGs with enhanced a-waves, and a crossed asymmetry which is most conspicuous around 80 ms (arrowed) (with permission from (21))*

Sl. 8. *Pri dojenčkih je bliskovna stimulacija najučinkovitejši dražljaj za detekcijo albinizma. Albini imajo ERG z zvišanim valom a, in navzkrižno asimetrijo, ki je najočitnejša 80 ms po dražljaju (puščica) (z dovoljenjem iz ref. 21).*

process. Rod and cone function can be assessed by testing under scotopic conditions, and using dim blue and red flashes respectively. Monocular pattern-reversal stimulation and a common reference montage incorporating several electrodes placed across the occiput are important procedures, which will help identify post-retinal dysfunction localised at the chiasm or in one posterior hemisphere.

Acknowledgement. We thank the Iris Fund and the Wooden Spoon Society for their financial support.

References

1. Heckenlively JR, Arden GB. Principles and practice of clinical electrophysiology of vision. St. Louis: Mosby, 1991.
2. Marmor MF, Arden GB, Nilsson S-EG, Zrenner E. Standard for electroretinography. Arch Ophthalmol 1989; 107: 816-9.
3. Carr RE, Siegel IM. Electrodiagnostic testing of the visual system: a clinical guide. Philadelphia: Davis, 1990.
4. Halliday AM. Evoked potentials in clinical testing. Edinburgh: Churchill Livingstone, 1993.
5. Sokol S. Pattern evoked potentials: their use in paediatric ophthalmology. In: Sokol S ed. Electrophysiology and psychophysics: their use in ophthalmic diagnosis. Boston: Little Brown, 1980: 251-68.
6. Apkarian P, van Veenendaal W, Spekreijse H. Measurement of visual acuity in infants and young children by evoked potentials. Doc Ophthalmol Proc Ser 1986; 45: 168-89.

7. Kriss A, Russell-Eggitt I. Electrophysiological assessment of visual pathway function in infants. Eye 1992; 6: 145-53.
8. Kriss A. Skin ERGs: Their effectiveness in paediatric visual assessment; confounding factors, and comparison with ERGs recorded using various types of corneal electrode. Int J Psychophysiol 1993 (in press).
9. Kriss A, Jeffrey B, Taylor D. The electroretinogram in infants and young children. J Clin Neurophysiol 1992; 9: 373-93.
10. Sokol S. Measurement of infant acuity from pattern-reversal evoked potentials. Vision Res 1978; 18: 33-41.
11. Apkarian P, Spekreijse H. The use of the electroretinogram and visual evoked potentials in ophthalmogenetics. In: Desmedt JE ed. Visual evoked potentials. Amsterdam: Elsevier, 1990: 169-223.
12. Norcia A, Tyler CW. Spatial frequency sweep VEP: Visual acuity during the first year of life. Vision Res 1985; 25: 1399-408.
13. Thompson DA, Lloyd IC, Dowler J, et al. The development of spatial resolution measured by swept VEP and forced choice preferential looking techniques. Invest Ophthalmol Vis Sci 1993; 34: 1354.
14. Kriss A, Thompson DA, Lloyd IC, Russell-Eggitt I, Taylor D. Pattern VEP findings in young children treated for unilateral congenital cataract. Birth Defects 1993 (in press).
15. Lambert SR, Kriss A, Taylor D, Coffey R, Pembrey M. Follow-up and diagnostic reappraisal of 75 patients with Leber's congenital amaurosis. Am J Ophthalmol 1989; 107: 624-31.
16. Lambert SR, Taylor D, Kriss A. The infant with nystagmus, normal appearing fundi, but an abnormal ERG. Surv Ophthalmol 1989; 34: 173-86.
17. Lambert SR, Kriss A, Gresty M, Benton S, Taylor D. Joubert syndrome. Arch Ophthalmol 1989; 107: 709-13.
18. Brecelj J. A VEP study of the visual pathway function in compressive lesions of the optic chiasm. Full-field versus half-field stimulation. Electroenceph Clin Neurophysiol 1992; 84: 209-18.
19. Harden A, Pampiglione G. Visual evoked potentials, electroretinogram and electroencephalogram studies in progressive neurometabolic storage diseases of childhood. In: Desmedt JE ed. Visual evoked potentials in man. Oxford: Clarendon Press, 1977: 470-80.
20. Kriss A, Lloyd IC, Jeffrey BG, Russell-Eggitt I, Taylor DSI. Optic nerve hypoplasia: a role for ERG/VEP testing. Eye (submitted).
21. Russell-Eggitt I, Kriss A, Taylor D. Albinism in childhood: a flash VEP and ERG study. Br J Ophthalmol 1990; 74: 136-40.
22. Kriss A, Russell-Eggitt I, Taylor D. Childhood albinism: visual electrophysiological features. Ophthalmic Paediatr Genet 1990; 11: 185-92.
23. Apkarian P. A practical approach to albino diagnosis. VEP misrouting across the age span. Ophthalmic Paediatr Genet 1992; 13: 77-88.
24. Creel D, Spekreijse H, Reits K. Evoked potentials in albinos: Efficacy of pattern stimuli in detecting misrouted optic fibres. Electroenceph Clin Neurophysiol 1981; 52: 595-603.
25. Barrett G, Blumhardt LD, Halliday AM, Halliday E, Kriss A. A paradox in the lateralisation of the visual evoked response. Nature 1976; 261: 253-5.
26. Blumhardt LD, Barrett G, Kriss A, Halliday AM. The pattern-evoked potential in lesions of the posterior visual pathways. Ann NY Acad Sci 1982; 388: 264-89.
27. Lambert SR, Kriss A, Taylor D. Detection of isolated occipital anomalies during early childhood. Dev Med Child Neurol 1990; 32: 451-5.
28. Jacobs M, Shawkat F, Harris CH, Kriss A, Taylor D. Eye movement and electrophysiological findings in an infant with hemispheric pathology. Dev Med Child Neurol 1993; 35: 431-5.

ELEKTROFIZIOLOŠKO TESTIRANJE VIDA PRI OTROCIH

Anthony Kriss

Izvleček - *V številnih oftalmoloških oddelkih rutinsko snemajo samo elektroretinogram (ERG), medtem ko v oddelkih za klinično elektrofiziologijo snemajo le vidne evocirane potenciale (VEP). V preglednem prispevku je prikazano, da so prednosti sočasnega snemanja ERG in VEP pri otrocih zelo velike. Sistematično je predstavljeno zelo pomembno novo spoznanje, da lahko pri otrocih razmejimo lezije med več plastmi mrežnice, vidnim živcem, področjem hiazme in področjem vidne proge za hiazmo do primarne vidne možganske skorje. Prav tako je tudi prikazano, da že posnetki s površinskimi elektrodami odkrijejo okvare, ki prizadenejo funkcijo paličnic in ali čepnic. Izbrati je treba le pravo metodo: rdeči filter izvabi ERG, ki ga posredujejo čepnice, modri pa ERG paličnic. Nadalje so prikazani primeri prepoznavanja okvar vidnega živca ob sočasnem snemanju ERG in VEP in selektivno zapisovanje potencialov iz nitja, ki se križa v hiazmi. V zadnjem poglavju so obravnavane enostranske disfunkcije v področju vidne proge za hiazmo, ki se izražajo z nepravilno razporeditvijo VEP nad vidno možgansko skorjo.*

Zaključek. *Elektrofiziološko testiranje je lahko v veliko pomoč pediatričnima nevrologu in okulistu, ki želita oceniti stanje vida pri dojenčku ali malčku. Ob sočasnem snemanju ERG in VEP in s pravilno izbranimi tehnikami draženja in snemanja je možno oceniti tudi, v katerem nivoju vidnega sistema je okvara in kakšne narave je.*

Ključne besede: *elektroretinogram; možganska polobla; optična hiazma; otroci; vidni evocirani potencial*

ELECTROPHYSIOLOGY AS A DIAGNOSTIC AID IN PEDIATRIC OPHTHALMOLOGY

ELEKTROFIZIOLOGIJA KOT POMOČ PRI DIAGNOSTIKI V OTROŠKI OFTALMOLOGIJI

Branka Stirn Kranjc,[1] Jelka Brecelj[2]

[1] University Eye Clinic, Medical Centre, Zaloška 2, 61105 Ljubljana, Slovenia
[2] University Institute of Clinical Neurophysiology, Medical Centre, Zaloška 7, 61105 Ljubljana, Slovenia

Key words: *electrophysiology; electroretinography; pediatric ophthalmology; visual evoked potentials*

Abstract - Background. *Electrophysiological studies including electroretinography (ERG) and visual evoked potentials (VEP), which give information about functional integrity of the visual pathway, got evident impact on clinical pediatric ophthalmology.*

Methods and results. *Recordings of 252 electrophysiological examinations, performed in the past two years in 85 infants and young children with various neuro- and ophthalmological disorders, were analysed and compared to the young patients' clinical pictures. ERG and VEP signs were more specific to the disease entity in retinal dystrophies, ocular albinism, optic neuritis, chiasmal and retrochiasmal lesions, while the recordings in hydrocephalus, psychomotor retardation, epilepsy, hypoxia and other neurological disorders, chorioretinal and optic nerve colobomas, macular lesions, glaucoma or optic nerve trauma were nonspecific but pertinent to the clinical status. Using skin electrodes for the ERG and VEP testing, without sedation or pupil dilation, reliable results were obtained.*

Conclusions. *Normal ERGs and VEPs indicate well-preserved function of the retinocortical pathway, still the possibility of a dysfunction in other areas concerned with visual processing, attention and the eye movement is not excluded.*
Electrophysiological evaluation of the visual pathway is mostly and best performed in research laboratories for several reasons, such as time consummation, economic constraints and a scientist's special training, but in close co-operation with a clinician, so as to better understand the variety of visual pathway disorders, especially in children, and to better appreciate the information that can be derived from such tests.

Introduction

Assessment of the visual function is a complex task. Electrodiagnostic tests add new dimensions to our understanding of normal and abnormal visual development, and may clarify vague conditions and help in making diagnoses. They are especially valuable in preverbal children (1).
Among the wide variety of electrodiagnostic tests in children, electroretinograms to flash (FERGs) and pattern (PERGs) stimuli, as well as visual evoked potentials to flash (FVEPs) and pattern (PVEPs) stimuli are mainly recorded. All these recordings can be obtained in an alert child, using skin electrodes and no pupil dilatation. ERG testing provides information about the rod and cone system functions and can differentiate between them, if special conditions of the light and dark adaptation, as well as of different light intensities and color filters are applied. With the pattern stimulus, the function of the ganglion cell layer can also be assessed in children. VEP testing evaluates conduction from the eye to the primary visual cortex (2).
Congenital nystagmus is associated with a variety of visual sensory system, or with the ocular motor system disorders (3). Electrophysiology should be considered in infants with nystagmus to exclude albinism, cone dysfunction, congenital stationary night blindness, Leber's congenital amaurosis. The results of electrophysiological studies in these disorders can improve the clinician's certainty in diagnosis. They are variable in other, especially neurological or multisystem disorders, however, the application of electrophysiological tests in these infants' conditions is appropriate, since the results can be abnormal before the signs of a disease become evident (4). Visual maturation, optic neuritis, glaucoma, chiasmal and retrochiasmal lesions of the visual pathway are typical clinical problems where electrophysiology can aid in prognosis and follow-up, as well as in evaluation of the course of a disease, of its extent, and/or of therapeutic intervention.
In ophthalmogenetics, electrophysiology can detect carriers for some diseases like albinism, X-linked and autosomal retinal or optic nerve disorders (5). Electrophysiological responses cannot be directly correlated to the visual acuity measurements with optotypes or preferential looking tests, since their technique and response basis differ (6).
This paper is an attempt to present electrophysiological results obtained from infants and children with a variety of visual pro-

Abbreviations: *ERG, electroretinogram; FERG, flash electroretinogram; FVEP, flash visual evoked potential; PERG, pattern electroretinogram; PVEP, pattern-reversal visual evoked potential; VEP, visual evoked potential*

blems. FERGs, PERGs, FVEPs, and PVEPs were evaluated in relation to clinical findings. The value of visual electrophysiology is represented from the pediatric ophthalmologist's point of view.

Subjects and methods

We analyzed 252 electrophysiological examinations in 85 infants and young children, ranging from one month to 13 years of age, recorded in 1991-92. Electrophysiology as a diagnostic method in pediatric ophthalmology was used mainly for two purposes: to help us make diagnosis in vague clinical conditions, and to show how an obvious and known neuro- or ophthalmological disorder is reflected in electrophysiology. The results were analyzed according to seven groups of clinical problems: nystagmus (49 cases), retrobulbar neuritis or malingering (12), retinal dystrophy (9), macular degeneration (5), glaucoma (3), tumors (5), and trauma (2).

Amblyopia was excluded from the study, since extra methods and criteria would be necessary to comment on this clinical entity. Preterm infants were not tested prior to six months of age. Visual maturation was not studied either.

All electrophysiological recordings were obtained in alert children without pupil dilatation. ERGs were detected by conventional silver-silver chloride cup electrodes, attached to the lower eyelid, and referred to the ipsilateral temple electrode in older children (> 24 months), while in younger ones (< 24 months) it was referred to the Fz. VEP electrodes were applied to the posterior scalp; the midline electrode was placed above the inion (10 % of the nasion-to-inion separation) and the two lateral electrodes to either side of the first electrode (20 % of the left-to-right mastoid distance). They were referred to a common Fz reference (10-20 system).

Flash and pattern-reversal stimulation was performed. A Grass PS22 photic stimulator was used to deliver white flashes under darkened laboratory conditions. The intensity of white flashes 25 cm from the child's eye was 4.4 cd/m² (setting 4) and the stimulating rate was 2 Hz. Checkerboard stimuli were either projected onto a translucent screen (32 °r) or were presented on a television (25° horizontally and 20° vertically). Check size was 50' (projector) and 49' (TV set). Luminance 300 and 11.5 cd/m² for the projected white and black checks, and 120 and 2 cd/m² for the TV checks. The pattern-reversed at 2 Hz. Analysis time was 200 ms, bandpass from 1 to 250 Hz. A series of 100 responses were averaged and repeated at least twice.

The following electrophysiological criteria were used to define abnormality: for the FERG: the a-wave amplitude less than 4 μV, and the b-wave amplitude less than 6 μV; for the PERG: no response; for the FVEP: prolonged (> 112 ms) and/or attenuated (< 4 μV) or not recordable positive wave; and for the PVEP: prolonged (for 50' checks more 109 ms, for 49' checks more 112 ms) or not recordable

Results

Nystagmus

The largest group (49) of the referred infants and children had nystagmus as the predominant symptom, and/or neurological problem. Most typical disorders, which caused it, are presented.

Leber's congenital amaurosis. In 8 children (4 boys and 4 girls) with nystagmus, very poor vision and with quite normal funduscopic appearance, Leber's congenital amaurosis was suspected at the average age of 7.6 months. Their outer and anterior eye segments were unremarkable. The optic media were clear. They were all photophobic and 6 of them with very bad vision also had oculodigital reflex and sluggish pupils. Electrophysiological parameters, ophthalmological characteristics and associated systemic disorders (none of them severe) are presented in Table 1.

Tab. 1. *Clinical findings in Leber's congenital amaurosis related to electrophysiologic evaluation (first and last examination).*
Tab. 1. *Klinične spremembe pri Leberjevi kongenitalni amavrozi in elektrofiziološki rezultati (prvi in zadnji pregled).*

Case No. / Primer št.	Age months / Starost meseci	Optic n. pallor / Bledica očesnega živca	R. vascular attenuation / Zožitev mrežničnih žil	Macular reflex / Makularni refleks	Peripheral pigment / Pigmentacija periferije	Visual acuity / Vidna ostrina	Refractive error Dpt. / Refrakcijske napake Dpt.	Systemic disorders / Sistemske spremembe	FERG	FVEP ms	FVEP μV
1	3	-	-	±	-	L.P.	+ 6.50		-	**172**	17.2
	9	-	-	+	+	0.01	+ 6.0	-	-	**166**	**2.8**
2	5	-	-	+	-	L.P.	+ 3.50	skin, CNS koža, CŽS	-	106	**2.1**
	9	-	-	±	-	0.01?	+ 3.50		-	**173**	5.2
3	5	-	-	±	+	L.P.	+ 4.50 +2.0/90°	CNS CŽS	-	-	-
	10	-	-	±	+	0.01	+ 4.50 +2.0/90°		-	**160**	8.2
4	6	-	±	+	+	L.P.	+ 7.50	CNS CŽS	-	**143**	5.0
5	7	±	±	±	+	L.P.	+ 6.0	heart srce	-	-	-
	24	±	±	±	+	0.01?	+ 6.0		-	-*	-*
6	7	-	-	+	-	0.01	+ 3.50 +3.50/90°	-	-*	**125**	11.8
	24	-	-	+	-	0.03	+ 2.0 +3.0/90°		+	**155**	13.8
7	7	-	-	±	-	L.P.	+ 4.50	-	-	100	**2.2**
	15	-	+	±	+	0.02	+ 3.0		-	98	**1.4**
8	17	-	-	±	+	L.P.	+ 6.50	-	-	-	-
	47	-	±	±	+	0.02	+ 6.0	-	-	97	**2.4**

*-, not present; ±, moderate abnormality; +, present; *, artifact; CNS, central nervous system; L.P., light perception; bold script, abnormal values*
*-, ni prisotno; ±, zmerna sprememba; +, prisotno; *, artefakt; CŽS, osrednje živčevje; L.P., zaznavanje svetlobe; krepko tiskano, abnormne vrednosti*

Electrophysiological recordings were performed at least twice (except in the case 4). FERGs were not detectable in 7 out of 8 children. FVEPs to binocular stimulation were abnormal in all of them. In the first recording they were not detectable in 3, delayed in 3 and attenuated in 2 of the 8 children.

Hydrocephalus. Eight children (1-4 years of age) operated upon for hydrocephalus are presented in Table 2. The operation was performed prior to six months of age. They had been all given small doses of antiepileptic drugs. All had optic disc decoloration of various degree. Concomitant strabismus was noticed, while refractive errors were unremarkable.
In all children, FERGs tended to be within normal limits, while FVEPs were abnormal in 5 of the 8 children. PVEPs were recorded only in a 4 year-old girl, and were within normal limits (case 8).

Meningoencephalitis. Five children (1-7 years of age) with a history of severe meningoencephalitis were also treated for epilepsy. They all had concomitant convergent strabismus of various degree, three of them needed surgical correction. Their refractive errors were not significant, and their visual acuity was not severely affected. Their optic discs were still normal or slightly pale.
Electrophysiological recordings showed normal FERGs in all of them. Cortical responses to flash stimulation were delayed (120-142 ms) in 3 of the 5 children. The PVEPs elicited in two preschool children with normal FVEPs were delayed (118-129 ms).

Other neurological disorders. In 11 infants and children (8 months - 10 years of age) with various neurological disorders (epilepsy and certain degree of psychomotor retardation due to

Tab. 2. *Clinical parameters and FVEPs after the operation for hydrocephalus.*
Tab. 2. *Klinični parametri in FVEP po operaciji hidrocefalusa.*

Case No.	Age years	Visual acuity R. eye	Visual acuity L. eye	Optic nerve pallor R. eye	Optic nerve pallor L. eye	FVEP R. eye ms	FVEP R. eye µV	FVEP L. eye ms	FVEP L. eye µV
Primer št.	Starost leta	Vidna ostrina D. oko	Vidna ostrina L. oko	Bledica očesnega živca D. oko	Bledica očesnega živca L. oko	D. oko		L. oko	
1	1	0.1?	0.1?	c/d 0.5	c/d 0.5	98	9.7	78	7.4
2	1	0.1?	0.05	temporal	temporal	95	28.5	89	19.1
3	2	L.P.	L.P.	total ++	total ++	**139**	12.5	**141**	1.9
4	2	0.1	0.1	temporal	total +	102	**3.7**	**124**	7.4
5	2	0.05	0.05	total +	total +	111	**2.8**	**120**	5.7
6	2	0.1	0.1	total ++	total +	100	**1.1**	**122**	**2.0**
7	2.5	L.P.	0.01	total +++	total +++	**130**	8.4	**120**	4.1
8	4	0.1	0.3	temporal	temporal	84	46.8	82	38.5

+, minor; ++, moderate; +++, severe; c/d, cupping of the optic disc diameter; L.P., light perception; bold script, abnormal values
+, blaga; ++, zmerna; +++, huda; c/d, premer poglobitve papile očesnega živca; L.P., zaznavanje svetlobe; krepko tiskano, abnormne vrednosti

hypoxia, hemorrhage or organic abnormality), nystagmus and some degree of optic disc pallor were seen at clinical examination. Their corrected visual acuities were more than 0.1.
Electrophysiological recordings showed normal FERGs and abnormal FVEPs in 4 out of 11 tested children, and abnormal PVEPs (delayed and/or attenuated) in 6 out of 9.

Idiopathic nystagmus. This group of 5 children (1-7 years of age) without any other ophthalmological or neurological disorder but nystagmus had corrected visual acuities at least 0.1 or more.
FERG recordings did not show any distinct abnormality. FVEPs were delayed in one of the children (both eyes). PVEPs to binocular stimulation were abnormal in 4 of them. In 3 children, they were very attenuated or not recordable, and in one child, they were delayed (138 ms).

Colobomas. Ten children with intraocular colobomas presented the most inconsistent group of ophthalmological appearance and associated systemic disorders. Eight of the children were mentally retarded.
Seven children (1 month - 10 years old) had the iris, choroidal and optic nerve involvement, and 3 of them mild microphthalmos without a retrobulbar cyst, but with lens involvement (inferior partial coloboma, mild diffuse opacities). The electrophysiological results showed still normal FERGs, while FVEPs were mostly attenuated in all affected eyes. However, PVEPs recordings were not successful, especially at monocular testing.
In 3 children (1-3 years of age) only the optic nerves were affected. In two girls, large typical unilateral optic disc colobomas were found, and were not associated with systemic complications in one case, the other girl had epilepsy. Their visual acuities were 0.08-0.1 in the affected eyes. FERGs were normal. FVEPs and PVEPs were abnormal in both affected eyes. In one girl, FVEPs were delayed (139 ms), while PVEPs were attenuated (68 % compared to the other eye). In the other case, FVEPs were attenuated (60 % compared to the other eye), while PVEPs were delayed (141 ms). The third child, a one year old boy with severe bilateral optic nerve hypoplasia (diameter about one third of a normal disc) and associated brain disorder (hypopituitarism), even had questionable light perception. His FERGs were well formed (bigger amplitude), while cortical responses were unrecordable, even to robust flash stimulus.

Albinism. Two albino children, first a boy of obvious oculocutaneous albinism, was seen at the age of 13 months, and the second, a boy with ocular albinism, was seen at the age of 17 months. The first one had an attenuated (b wave), the second one normal FERGs. In both, FVEPs showed reversed asymmetry. At the latency around 80 ms, a pronounced negativity on the contralateral side of the scalp, and attenuated positivity at the ipsilateral side of the scalp to the stimulated eye was seen. The reversed left and right eye asymmetry was best seen in the trace where a potential was derived by subtracting the left occipital response from the right one (difference potential).
Recordings were also made on the carrier mother of the boy with ocular albinism. She had normal FERGs, while FVEPs showed asymmetric distribution, but not as evident as in her son.

Retrobulbar neuritis or malingering

Twelve children (7-13 years of age) were referred to us because of retrobulbar neuritis. After clinical examination with repeated visual acuity testing, examination of visual fields, colour testing,

pupillary reactions and fundi examination, we suspected bilateral retrobulbar neuritis only in four cases. These children's vision couldn't be corrected to normal distance, and they had small central scotomas or narrower visual fields, but with great fluctuations. A 13 years old boy had visual acuity reduced to 0.5, and central visual field deterioration in his right eye. He had unilateral optic neuritis (papillitis).
PERGs were normal in all children. PVEPs to full-field and half-field stimulation were within normal limits in 7, and abnormal in 5 of the 12 children. In 3 of the latter, VEP abnormalities were found to full-field stimulation (in 2 to stimulation of either eye), while in the other 2, abnormalities were revealed only to half-field stimulation.
After several months of follow-up for 3 of the 5 children with abnormal PVEPs, the children still had abnormal PVEPs, even though they had no visual complaints, had normal visual acuities, visual fields, colour tests and pupillary reactions. Only a minor temporal pallor of the optic discs remained in two girls, in whom also a greater delay of PVEPs was recorded. According to their neurological status and follow-up, multiple sclerosis was suspected.
The 7 children (all girls) with normal PVEPs could have been malingerers because of completely normal ophthalmological and neurological status, functional tests and also electrophysiological examination.

Retinal dystrophy

It was diagnosed in four children with profound night blindness. None of them had a family history of the disease.
A 12 year-old girl had clinically typical retinitis pigmentosa, with bone corpuscles and still normal visual acuity. Her FERG was not recordable, and PVEPs were normal.
A 2.5 year-old boy had reduced visual acuities (0.2 in his right and 0.1 in his left eye), minor optic disc pallor, attenuated retinal vessels, retinal pigment clumping at the central and peripheral retina. His FERG was not recordable, and FVEPs were normal.
Another 7 year-old girl had a similar clinical picture but more reduced visual acuity (0.1 in both eyes). Her FERG was extinguished, cortical responses were elicited only to flash stimuli (more to white, blue flash).
We diagnosed Laurence Bardet Moon Biedel syndrome in a 7 year-old girl with visual acuities of 0.3 (myopic correction) in both eyes, narrower visual fields, pale optic discs, attenuated retinal vessels, pigment clumping at the posterior pole and retinal periphery, but no typical bone corpuscles. She had no ERG responses, and abnormally shaped and delayed VEPs (147-156 ms).
In 5 other cases referred to us because of minor retinal changes, such as small pigmentations or depigmentations at the retinal posterior pole or periphery, no clinical functional or electrophysiological changes were found.

Macular degeneration

We saw two cases of macular degeneration with a positive family history. A 5 year-old boy had a vitelliform Best macular dystrophy (stage IV and visual acuity 0.04 in his right eye, stage II-III and visual acuity 0.6 in his left eye). Electrophysiological recordings showed normal retinal responses (FERGs and PERGs). PVEPs were abnormal in both eyes: from the left eye they were well formed, but with an abnormal interocular latency difference (11 ms), those from the right eye had significantly reduced P100 amplitude. The second was an 11 year-old boy with mild changes in the appearance of the macular reflexes and corrected visual acuities 0.75 in both eyes. Macular changes were not reflected in the PERGs. However, PVEPs were abnormal in both eyes (P100 latency 119 and 122 ms).
In 3 cases with an abnormal look of the maculas (changes in the distribution of the retinal pigment epithelium), all with the visual acuities still within normal range, no electrophysiological abnormalities could be registered.

Glaucoma

We followed up 2 glaucoma suspects (slight mesodermal dysgenesis and some cupping of the disc, larger but clear corneas) and a preschool boy operated on for bilateral congenital glaucoma. Their intraocular pressures, visual acuities and visual fields were within normal limits, their electrophysiologic recordings were normal too, except in one trial where PERG amplitude was reduced to 0.33 μV.

Tumors

Four children (1-12 years of age) were followed up clinically (Tab. 3) and electrophysiologically (Tab. 4) because of unilateral lacrimal gland tumor, optic nerve astrocytoma, suprasellar tumor and temporobasal astrocytoma.

Tab. 3. *Clinical changes in tumors along the visual pathway.*
Tab. 3. *Klinične spremembe pri tumorjih v vidni poti.*

Case No. / Primer št.	Diagnosis / Diagnoza	Age years / Starost leta	Fundi / Očesno ozadje	Reduced visual acuity / Zmanjšanje vidne ostrine R. eye / D. oko	L. eye / L. oko	Remark / Opombe
1	Left eye lacrimal gland tumor Tumor leve solzne žleze	9	folds gube	-	-	protrusion protruzija
2	Right eye optic nerve astrocytoma Astrocitom desnega očesnega živca	1	normal normalno	+	-	protrusion protruzija
	After R. eye enucleation Po odstranitvi desnega zrkla	1.5				-
3	Suprasellar tumor Supraselarni tumor	5	pallor, R. eye bledica, D. oko	+++	-	squint škiljenje
4	Left temporobasal astrocytoma Temporobazalni astrocitom levo	12	temporal pallor, L. and R. eye temporalna bledica, L. in D. oko	-	-	R. hemianopsia desnostranska hemianopsija

-, not present: +, minor reduction; +++, severe reduction;
-, ni prisotno; +, minimalno zmanjšanje; +++, izrazito zmanjšanje

PERGs were normal (not done in case 2) while PVEPs to full-field stimulation indicated dysfunctions in all cases. Half-field stimulation also helped to localize the lesions, especially in the case of suprasellar tumor, where PVEPs were not recordable from the left eye to temporal half-field stimulation. In the case of temporobasal astrocytoma too, the uncrossed asymmetry of PVEPs to full-field stimulation was in agreement with more evident right half-field abnormalities and with the right homonymous hemianopsia.
Another 7 year-old girl was treated for leukemia with leukemic retinopathy and optic nerves involvement. Her visual acuity was severely reduced in both eyes. FERGs were normal, while FVEPs were delayed (139 and 152 ms).

Tab. 4. *VEP changes (P100 latencies and amplitudes) in tumors along the visual pathway.*

Tab. 4. *Spremembe VEP (latenc in amplitud vala P100) pri tumorjih vzdolž vidne poti.*

Case No. / Primer št.		Full-field stimulation / Draženje s celim poljem		Half-field stimulation right half-field / Draženje s polovicama polja desno polpolje		left half-field / levo polpolje	
1	R. eye D. oko	94 ms	37.0 µV	97 ms	13.2 µV	99 ms	12.5 µV
	L. eye L. oko	97 ms	27.5 µV	102 ms	8.5 µV	105 ms	8.9 µV
2	R. eye D. oko	**115** ms	41.2 µV				
	L. eye L. oko	108 ms	24.2 µV				
	postoperatively: po operaciji:						
	R. eye D. oko	-	-				
	L. eye L. oko	**116** ms	11.4 µV	104 ms	6.3 µV	**110** ms	6.0 µV
3	R. eye D. oko	-	-				
	L. eye L. oko	**120** ms	10.7 µV	**117** ms	7.0 µV	-	-
	postoperatively: po operaciji:						
	R. eye D. oko	**175** ms	7.0 µV				
	L. eye L. oko	**110** ms	7.5 µV	**116** ms	5.7 µV	-	-
4	R. eye D. oko	109 ms	6.0 µV	**140** ms	3.3 µV	**111** ms	2.9 µV
	L. eye L. oko	**119** ms	5.0 µV	**115** ms	**1.3** µV	**124** ms	2.2 µV

abnormal values in bold script
abnormne vrednosti tiskane krepko

Trauma

A 13 year-old boy survived blunt trauma to his right side of the head with an orbital roof fracture. He was referred to us a few weeks after the injury, when the right optic nerve atrophy was evident. His right eye retinal responses (FERGs and PERGs) were normal, but his cortical responses deteriorated (FVEPs attenuated, PVEPs not recordable).
A 5 year-old boy suffered a right temporoparietal traumatic brain damage, a year prior to our examination. We registered normal visual acuities in both eyes, horizontal nystagmus and normal fundi. Retinal responses (PERGs) from both eyes were normal, while cortical responses (PVEPs) to full-field stimulation had an asymmetric distribution. Half-field stimulation revealed a distorted left, but normal right half- field waveform, which indicated a lesion affecting the retrochiasmal visual pathway.

Discussion

It is important to establish the diagnosis as soon as possible, especially in early childhood, for an appropriate therapy (metabolic disease, compressive lesion, organic disorder), adequate low-vision rehabilitation and genetic counselling. Electrophysiological examinations, when performed by an experienced electrophysiologist, can shorten the time to proper diagnosis of some pediatric visual disorders.
In infants with nystagmus and a variety of ophthalmological and neurological impairments, concurrent ERG/VEP recordings can give useful information about the visual pathway function. ERG abnormalities can precede clinical signs, even when the fundus appearance is normal (2, 7). However, electrophysiological testing in these children may not provide significant information, if only pattern-reversal stimulation is performed. Nystagmus attenuates the pattern-reversal VEPs, as also found in our cases with poor fixation and large amplitude nystagmus. Thus, in these conditions, the pattern-reversal VEPs were not always helpful in solving the diagnostic problem. However, the latency prolongation may still be a reliable indicator of a dysfunction.
Optic nerve pallor of various degree is often accompanied with optic nerve lesions and neurological disorders, however, it is a rather nonspecific sign in interpreting the severity of the visual pathway damage. Usually delayed and attenuated VEPs in these patients give an approximate estimation of the visual function when behavioural tests are not possible. In our children with various neurological impairments and some degree of optic disc pallor, VEP testing showed that the problem was postretinal, but it didn't indicate the pathology. Nystagmus in this group of children attenuated the PVEP amplitudes. Other clinical methods and assessments need to be carried out on these patients to exclude organic lesion.
Leber's congenital amaurosis patients have demonstrated clinical heterogeneity (8). Our clinical diagnostic criteria for Leber's congenital amaurosis were consistent with those in the references (3, 7), with sluggish pupillary reflexes, high hyperopia and oculodigital reflex described as associated findings (9, 10). The disease is a retinal dystrophy affecting both rods and cones. No detectable FERGs are thus expected and, very rarely, attenuated FERGs could be registered (4, 8, 10, 11). In the majority of cases, PVEPs are not elicitable, neither are FVEPs (11, 12). In the study of Kriss (11), FVEPs were not discernible in 56 % of the children, in the remaining 44 %, they were markedly reduced. In our group of 8 children, FERGs were not detectable in 7 and FVEPs in 2 of them. In the remaining 6 children FVEPs were abnormal (delayed, attenuated).
An ERG/VEP picture, similar to the one in Leber's congenital amaurosis, is recorded in several systemic conditions of the early childhood associated with the rod and/or cone dysfunction (paroxysmal disorders, Batten's disease, Senior-Loken syndrome, congenital stationary night blindness, achromatopsia, infantile onset retinitis pigmentosa and infantile Refsum's disease), therefore sophisticated techniques of electrophysiological, neuroradiological and biochemical testing are recommended (7, 10, 11). We didn't find any cases of stationary night blindness or cone dystrophy in our group of children. Multisystem metabolic syndromes were not found either.
In our cases of chorioretinal colobomas, FERG recordings were not significant, whether they involved the macula or not. Localized lesions at the retinal posterior pole (dystrophies, scars) didn't show any FERG changes either. This was expected, since FERGs test the function of large retinal areas, dominated by sco-

topic responses (13). In those cases, the dysfunctions were indirectly reflected in FVEPs. In a case of bilateral severe optic nerve hypoplasia, FERGs were pronounced, FVEPs, on the other hand, were extinguished. These findings were also reported by Kriss et al. (11). To their experience, less severe optic nerve hypoplasia might have attenuated FVEPs, usually of normal latencies, or within normal limits.

Albinism is genetically determined heterogeneous group of at least 10 forms of disorders (11, 14, 15, 16). Hypopigmentation as well as misrouting can be detected very early with flash stimulation. In the oculocutaneous albino patients an attenuated FERG b-wave has been described (5, 11, 14, 15). Moreover, it has been shown that FVEP changes are pathognomonic for albinism. Monocular flash stimulation produces a distinct crossed asymmetry distribution of the responses. This is seen as a negativity (around 80 ms) on the side of the scalp contralateral to the stimulated eye, and as a positivity about the same latency on the ipsilateral side. In one of our albinos, attenuated FERGs were recorded, but not in his carrier mother. In both our albinos FVEPs were consistent with the electrophysiological evidence of the albino misrouting.

In 4 of our children with night blindness, a retinal disorder associated with different clinical signs and reduced vision or visual field deterioration was confirmed with the non-detectable FERGs. Recordable PVEPs identified the conditions where macular function was preserved.

Macular degenerations in children differ from senile degenerations clinically, and probably also in the electric activity. PERG is likely to be abnormal with reduced amplitude or absence in most maculopathies in adults (13). In our case of the vitelliform Best macular dystrophy, electrophysiological results showed that the function of distal retinal layers, as assessed by PERGs, were within normal limits, while cortical responses were abnormal. Thus, macular changes were not reflected in PERGs.

In glaucoma follow-up, PERG could be one of the examination methods, especially in young children, where visual field testing is not possible or reliable. However, it is known from the studies with adults (17, 18, 19) that PERG amplitude is not equally sensitive to the reduction of the number of ganglion cells and to the damage of the optic nerve fibers caused by prolonged influence of an elevated intraocular pressure. The technique of the recording might influence the results, especially the use of skin electrodes, which are comfortable for the patient, and the resolution power of the method could still give predictive value in glaucomatous eyes in adults. In young children, recording of PERGs can be problematic if a child is not cooperative long enough to obtain responses of low amplitude by the skin electrodes. We found somehow attenuated PERGs in one child's glaucomatous eye, which is in our opinion not conclusive abnormality, if recorded only once.

In detecting dysfunctions of the optic nerve, optic chiasm and retrochiasmal pathway, VEP testing is successful. It has been reported that half-field stimulation contributes to the evaluation of the visual pathway in children as well (20, 21, 22, 23). We confirmed that PVEPs provide reliable indication of dysfunctions affecting the optic chiasm as well as the retrochiasmal visual pathway. Furthermore, we have shown that simultaneous, recordings of PERGs and PVEPs in children, referred for optic neuritis, could be even more helpful in differentiating the visual problems. With normal PERGs and normal PVEPs malingering could be suspected.

We found that follow-up was valuable in all groups of children we examined. First, it was not always possible to complete the electrophysiological recordings in one session. Second, in some conditions, e.g. in optic neuritis and compressive lesions of the visual pathway, monitoring the visual problem was helpful to the clinician.

We conclude that visual electrophysiological testing can provide valuable information to the pediatric ophthalmologist. We confirmed the observation of others (1, 4, 5, 11, 14, 24) that, in early childhood, disorders such as Leber's congenital amaurosis, night blindness, ocular albinism, optic nerve hypoplasia can be distinguished electrophysiologically. Our experience is that in several disorders (idiopathic nystagmus, hydrocephalus, meningoencephalitis, colobomas, maculopathies, glaucoma), especially in mentally retarded children, the electrophysiological recordings are not yet reliable enough to provide significant information. One of the reasons could be that the selected electrophysiological test may not be selective enough. The clinician should not forget that normal ERGs and VEPs indicate well preserved function of the primary retinocortical pathway, however, such an electrophysiological finding does not exclude the possibility of a dysfunction of other areas concerned with visual processing, attention and the eye movements (14).

Acknowledgement. We are grateful to Mr. Tone Žakelj for his help with preparing the manuscript.

References

1. Carr RE. Electrodiagnostic tests of the retina and higher centers. In: Harley RD ed. Pediatric ophthalmology. 2nd ed. Vol 1. Philadelphia: Saunders, 1983: 189- 206.
2. Fulton AB, Hartmann EE, Hansen RM. Electrophysiologic testing techniques for children. Doc Ophthalmol 1989; 71: 341-54.
3. Weiss AH, Biersdorf ER. Visual sensory disorders in congenital nystagmus. Ophthalmology 1989; 96: 517-23.
4. Day S. History, examination and further investigation. In: Taylor D ed. Pediatric ophthalmology. Oxford: Blackwell, 1990: 47-64.
5. Apkarian P, Spekreijse H. The use of the electroretinogram and visual evoked potentials in ophthalmogenetics. In: Desmedt JE ed. Visual evoked potentials. Elsevier: Scientific Publishers B.V., 1990: 169-223.
6. Gottlob I, Fendick M, Guo S, Zubcov A, Odom JV, Reinecke RD. Visual acuity measurements by swept spatial frequency visual evoked cortical potentials (VECPs): Clinical application in children with various visual disorders. J Ped Ophthalmol Strab 1990; 27: 40-7.
7. Lambert SR, Kriss A, Taylor D, Coffey R, Pembrey M. Follow-up and diagnostic reappraisal of 75 patients with Leber's congenital amaurosis. Am J Ophthalmol 1989; 107: 624-31.
8. Schroeder RM, Maumenee IH. Leber's congenital amaurosis. Arch Ophthalmol 1987; 105: 356-9.
9. Dagi LR, Leys MJ. Hyperopia in complicated Leber's congenital amaurosis. Arch Ophthalmol 1990; 108: 709-12.
10. Heher KL, Traboulsi EI, Maumenee IH. The natural history of Leber's congenital amaurosis. Ophthalmology 1992; 99: 241-5.
11. Kriss A, Jeffrey B, Taylor D. The electroretinogram in infants and young children. J Neurophysiol 1992; 9 (3): 373-93.
12. Jan JJ, Greonveld M, Sykanda AM. Diagnostic criteria for Leber's congenital amaurosis. Arch Ophthalmol 1987; 105: 1320-3.
13. Arden GB, Carter RM, Macfarlan A. Pattern and ganzfeld electroretinograms in macular disease. Br J Ophthalmol 1984; 68; 878-84.
14. Kriss A, Russell-Eggitt I. Electrophysiological assessment of visual pathway function in infants. Eye 1992; 6: 145-53.
15. Russell-Eggitt I, Kriss A, Taylor D. Albinism in childhood: a flash VEP and ERG study. Br J Ophthalmol 1990; 74: 136-40.
16. Kriss A, Russell-Eggitt I, Taylor D. Childhood albinism: visual electrophysiological features. Ophthalmic Paediatr Genet 1990; 11: 185-92.
17. Hawlina M, Štrucl M, Stirn B, Finderle Ž. Pattern ERG recorded by skin electrodes in early ocular hypertension and glaucoma. Doc Ophthalmol 1989; 73: 183-91.
18. O'Donaghue E, Arden GB, O'Sullivan F, Falcao-Reis F, Moriartry B, Hitchings RA et al. The pattern electroretinogram in glaucoma and ocular hypertension. Br J Ophthalmol 1992; 76: 387-94.
19. Papst N, Bopp M, Schnaudigel OE. The pattern electroretinogram associated with elevated intraocular pressure. Albrecht von Graefes Arch Clin Exp Ophthalmol 1984; 222: 34-7.
20. Borda RP. Visual evoked potentials to flash in the clinical evaluation of the optic pathway. In: Desmedt JE ed. Visual evoked potentials in man. Oxford: Clarendon Press, 1977: 481-9.
21. Feinsod M, Hoyt WF, Wilson BM, Spire JP. The use of visual evoked potentials in patients with multiple sclerosis. In: Desmedt JE ed. Visual evoked potentials in man. Oxford: Clarendon Press, 1977: 458-61.
22. Brecelj J. Visual evoked potentials and the localization of visual pathway lesions. Spektrum Augenheilk 1991; 5: 114-23.
23. Brecelj J, Stirn B. Electrophysiologic evaluation of the visual pathway in children. Doc Ophthalmol 1992; 79: 313-23.
24. Sokol S. The pattern visual evoked potential in the evaluation of pediatric patient. In: Desmedt JE ed. Visual evoked potentials. Elsevier Scientific Publishers B.V., 1990: 115-22.

ELEKTROFIZIOLOGIJA KOT POMOČ PRI DIAGNOSTIKI V OTROŠKI OFTALMOLOGIJI

Branka Stirn Kranjc, Jelka Brecelj

Izvleček - Izhodišča. *Elektrofiziološke preiskave z elektroretinogramom (ERG) in vidnimi evociranimi potenciali (VEP) dajejo informacije o morebitni prizadetosti delovanja vidne poti in so pridobile pomembno veljavo v klinični otroški oftalmologiji.*

Metode in rezultati. *Analizirali smo posnetke 252 elektrofizioloških preiskav iz zadnjih dveh let, opravljenih pri 85 dojenčkih in otrocih z različnimi nevro- in oftalmološkimi obolenji. Po klinični sliki in problematiki smo jih razvrstili v naslednje skupine: I. nistagmus - 49 otrok (kongenitalna Leberjeva amavroza, stanje po operaciji hidrocefalusa, po prebolelem meningoencefalitisu, po hipoksičnih in drugih okvarah možganov, idiopatski nistagmus, kolobomi horioretine in očesnega živca, albinizem); II. retrobulbarni nevritis in agravacija - dvanajst otrok; III. distrofija mrežnice - devet otrok; IV. makularna degeneracija - pet otrok; V. glavkom - trije otroci; VI. tumorji - pet otrok; VII. poškodba - dva otroka.*

- *Vsi otroci z Leberjevo amavrozo so imeli zelo slab vid (0,03 in manj), normalno očesno ozadje ali pa nekoliko ožje žile in nakazano pregrupacijo pigmenta proti periferiji. ERG na bliskavico (FERG) ni bil izziven pri sedmih od osmih primerov; VEP na bliskavico (FVEP) ni bilo v enem primeru, pri ostalih pa so bili močno podaljšanih latenc (do 173 ms) oz. manjše amplitude (do 2,1 mV). Pri vseh otrocih, ki so bili operirani zaradi hidrocefalusa, je bil FERG po kirurškem posegu normalen, FVEP pa abnormen pri petih od osmih otrok, predvsem na račun podaljšanih latenc, pa tudi nižjih amplitud.*
- *Po prebolelem meningoencefalitisu in po hipoksičnih in drugih okvarah možganov rezultati elektrofizioloških raziskav niso bili dovolj specifični, da bi omogočili oceno stanja vidne poti.*
- *Otroci z intraokularnimi kolobomi so bili najbolj nehomogena skupina z zelo različno klinično sliko in največ tehničnimi problemi pri elektrofizioloških preiskavah, povezanih tudi z duševno zaostalostjo. V FERG nismo našli sprememb, amplitude FVEP pa so bile manjše pri vseh, vendar je vrednotneje nezanesljivo. Enostranski kolobomi ali huda hipoplazija papil so dali elektrofiziološke rezultate (spremembe FVEP) v skladu s klinično sliko.*
- *Pri otrocih z okulokutanim ali le okularnim albinizmom smo iskali tipično asimetrijo VEP. Našli smo jo tudi pri eni materi - prenašalki. Tudi val b v FERG je bil pri enem otroku nižji.*
- *V 11 primerih, ko je bila diagnoza retrobulbarni nevritis negotova tako klinično kot po funkcijskih preiskavah, jo je v štirih primerih potrdila najdba zapoznelega slikovnega VEP (pattern VEP, PVEP) ob normalnem slikovnem ERG (pattern ERG, PERG - v vseh primerih), normalni PVEP in PERG pa so jo zavrnili v preostalih sedmih primerih. Okvare vidne poti tu nismo mogli dokazati ne z oftalmološkimi, nevrološkimi in ne z nevrofizioloških preiskavami, zato dopuščamo možnost agravacije.*
- *Pri štirih distrofijah mrežnice z nočno slepoto in različno klinično sliko nismo dobili odzivov FERG, VEP pa je bil spremenjen v skladu z okvaro vidne ostrine. Napredovalo enostransko in začetno drugostransko viteliformno makularno distrofijo Best smo našli v enem primeru, ko so bili odzivi FERG in PERG normalni, PVEP pa daljši in nižji pri očesu z manjšo vidno ostrino.*
- *Pri dveh otrocih s sumom na kongenitalni glavkom z minimalno mezodermalno disgenezo, večjimi, a še prozornimi roženicami in nakazano začetno ekskavacijo papil, znotrajočesnim tlakom na zgornji meji normale in pri enem operiranem otroku smo le v enem primeru dobili nižje odzive PERG.*
- *Pri petih otrocih smo diagnosticirali tumorje vzdolž vidne poti (enostranski tumor solzne žleze, astrocitom očesnega živca, levkemija z zajetjem očesnih živcev, supraselarni tumor, temporobazalni astrocitom), nato pa jih tudi elektrofiziološko spremljali. ERG so bili normalni v vseh primerih, PVEP pa spremenjeni v skladu z lokalizacijo kompresijske lezije.*
- *Poškodba očesnega živca se je odrazila s podaljšanim in nižjim FVEP, pri udarnini možganov temporoparietalno pa so PVEP pokazali retrohiazmalno okvaro z abnormnimi potenciali na draženje v levih polovicah polj in normalne odgovore po stimulaciji desnih polovic polj.*

Zaključki. *Vidno pot elektrofiziološko večinoma vrednotijo elektrofiziologi v raziskovalnih laboratorijih, kar je tudi najbolje zaradi precejšnje zamudnosti preiskav, zaradi ekonomskih omejitev in nujne usmerjene strokovnosti. Sodelovanje klinika pri tem pa je nujno, saj izboljša razumevanje različnih okvar vidne poti, zlasti pri otrocih, in vrednotenje informacij, dobljenih z opravljenimi testi. Normalna ERG in VEP kažeta na ohranjeno funkcijo primarne retinokortikalne vidne poti, vendar ne izključujeta možnosti disfunkcije drugih predelov v zvezi z vidnim procesom, pozornostjo in gibi oči.*

Ključne besede: *elektrofiziologija; elektroretinografija; pediatrična oftalmologija; vidni evocirani potenciali*

ELECTROPHYSIOLOGICAL ASSESSMENT OF FUNCTIONAL IMPAIRMENTS IN A SPECTRUM OF OPTIC NERVE COLOBOMA

ELEKTROFIZIOLOŠKO OCENJEVANJE FUNKCIJSKIH MOTENJ PRI KOLOBOMU OPTIČNEGA ŽIVCA

Márta Janáky,[1] Zsuzsanna Pelle,[1] Ágnes Szabó,[1] György Benedek[2]

[1] Department of Ophthalmology and
[2] Department of Physiology, Albert Szent-Györgyi Medical School, H-6720 Dóm tér 10, Szeged, Hungary

Key words: *electroretinogram; optic nerve coloboma; visual evoked response*

Abstract - *Electroretinograms (ERGs) and visual evoked potentials (VEPs) of 10 children with different degrees of optic nerve coloboma are presented. The amplitude of the ERG waves was found to be reduced, and this reduction correlated well with the extent of the retinal changes. The amplitude of the VEP also depended on the degree of involvement of the optic nerve. The ophthalmoscopic findings, however, did not always correlate with the visual loss. Electrophysiological methods seem to provide substantial aid in the assessment of functional impairment in colobomatous defects. They provide a correct prognosis, before accompanying retinal or cerebral alterations reduce the vision further.*

Introduction

Coloboma is a common name for ocular abnormalities caused by incomplete closure of the embryonic fissure. The defect may affect the iris, ciliary body, choroid, retina or optic nerve. The most serious cases involve microphthalmus with cyst formation (1, 2, 3, 4). The accompanying ophthalmological findings include strabismus, amblyopia, nystagmus and retinal detachment (5, 6). Colobomas may be associated with a variety of single gene disorders and malformation syndromes (7, 8). There have been many reports on the combination of colobomas with systemic findings, such as mental retardation, oligophrenia and craniofacial and skeletal abnormalities (9).

In colobomatous cases, the visual acuity ranges from fairly good vision to total blindness, and does not always correlate with the ophthalmoscopic findings. Electrophysiological assessment of the retinal and optic nerve function has not been extensively performed. Therefore we report ten cases of colobomatous defects of different degrees, particularly from an electrophysiological aspect.

Subjects and Methods

The clinical and electrophysiological data on 10 patients (7 females and 3 males, age range: 10 months - 14 years) with optic nerve coloboma were studied. The severity of anatomical alterations was determined by ophthalmoscopic picture and ultrasound examinations. The ultrasonographic findings are to be published elsewhere. Various electrophysiological examinations such as pattern-reversal VEP (PVEP), flash VEP, light-emitting diode elicited VEP (LED-VEP), scotopic ERG and LED-ERG were carried out for objective examination of the retinal and optic nerve functions. The ERG examinations were performed under scotopic conditions, with monochromatic blue filters. For flash stimulation, a stroboscopic bulb (light intensity 0.1 W) was employed, which shed its light onto a Ganzfeld screen. For mentally retarded children and those below 3 years of age, a NIC-107 LED stimulator (Nicolet, USA) was used. Fifty responses were averaged. Every trial was repeated at least twice for reproducibility.

ERG recordings were generally obtained with a skin electrode (Senso-Medics, USA) attached to the middle of the lower eyelid, with a reference electrode clipped to the linked earlobes.

The pattern stimulation for VEP was delivered by a black-and-white checkerboard pattern, appearing on a TV screen with a checksize of 20 or 40 min. The checks were alternated at a rate of 1.8 Hz to give a reversing display with a constant luminance of 20 cd/m^2. In each trial, 100 stimuli were processed by an amplifier and a signal averager. The band-pass filters were set at 0.3 Hz and 100 Hz.

Results

We present the clinical and electrophysiological data on 10 children with optic coloboma. We used routine ophthalmological tests and electrophysiological methods, in order to assess the functional impairments, and stress the presence of consecutive, additional, factors that contribute to the functional alterations, as well as to the possibilities for their prevention.

Tables 1 and 2 detail the refractive errors, visual acuity and other ophthalmological and non-ophthalmological alterations in the group. The ERG and VEP alterations are presented in Table 3.

The patients can be divided into two groups on the basis of their electrophysiological and clinical findings. The first group comprises the five patients (cases 1-5) for whom the electrophysio-

Abbreviations: *ERG, electroretinogram; LED, light-emitting diode; PVEP, pattern-reversal visual evoked potential; VEP, visual evoked potential*

Tab. 1. *Refractive errors and visual acuity in 10 children with optic coloboma.*

Tab. 1. *Refrakcijske napake in vidna ostrina pri 10 otrocih s kolobomom optičnega živca.*

No. Št.	Age Starost	Refractive error Refrakcijska motnja OD/DO	OS/LO	Visual acuity Ostrina vida OD/DO	OS/LO
1.	10 mths/mes.	-0.3	+3.0	O.P.	O.P.
2.	3 yrs/let	-1.0	-1.0	O.P.	O.P.
3.	8 yrs/let	-4.0	-2.0	0.6	0.6
4.	9 yrs/let	+6.0	+6.0	1.0	0.2
5.	9 yrs/let	-11.0	-11.0	1.0	0.1
6.	1 yr/leto	+4.0	+5.0	O.P.	O.P.
7.	6 yrs/let	+5.0	-6.0	no visual attention odsotnost vidne pozornosti	
8.	14 yrs/le	non measurable nemerljivo		CF 0.5 m	CF 3 m
9.	2 yrs/let	+2.0	+1.0	L.P. ?	O.P.
10.	10 mths/mes.	-4.0	-4.0	L.P. ?	O.P.

O.P., object perception; L.P., light perception; C.F., counting fingers
O.P., zaznava predmetov; L.P., dojem svetlobe; C.F., štetje prstov

logical findings were close to normal. The children in this group had rather good visual acuity, and they can expect a fairly good prognosis, even in the case of a mild microphthalmus or hypoplasia of the optic nerve. The fairly severe refractive error, which ranged between +6.0 D and -11.0 D, did not have a profound effect on the visual ability. The correction reduced the nystagmus and alleviated the symptoms of strabismic amblyopia. The mental development of the children was greatly promoted upon the increased access to information due to the enhanced visual acuity. (Fig. 1).

Tab. 2. *Ophthalmological and other complication in 10 children with optic coloboma.*

Tab. 2. *Oftalmološke in druge nepravilnosti pri 10 otrocih s kolobomom optičnega živca.*

No. Št.	Diagnosis Diagnoza	Ophtalmol. complications Oftalmološke nepravilnosti	Other complications Druge nepravilnosti
1.	Colob. n. optici O.S.	anisometria strabismus	-
2.	Megalopapilla O.D. Colob. n. optici O.S.	-	
3.	Colob. n. optici et choroid. O.U. Hypoplasia n. optici O.U.	nystagmus astigmatism	-
4.	Colob. n. optici O.S.	strabismus hyperopia	mental retardation/ duševna zaostalost
5.	Colob. n. optici O.U.	nystagmus myopia	autism / avtizem Rh incompatibility?/ inkompatibilnost Rh?
6.	Colob. n. optici, choroid., iridis O.U.	hyperopia	faux lupina; hydrocephalus int. (prepartum industrial toxic exposition) / predporodna izpostavljenost toksičnim vplivom
7.	Colob. n. optici, choroid., iridis O.U.	nystagmus	somatomental retardation, anisometropia,telesna in duševna zaostalost, microcephalus, spasmus nutans (chromosomal anomaly) (kromosomska anomalija)
8.	Colob. n. optici, choroid. iridis Microphthalmus O.U.	nystagmus glaucoma	-
9.	Colob. n. optici with orbital cyst O.D. Colob. n. optici O.S. Microphthalmus O.U.	nystagmus	-
10.	Colob. n. optici et choroid. O.U.	nystagmus strabismus	dyscrania microcephalia

Tab. 3. *The ERG and VEP alterations in 10 children with optic coloboma.*

Tab. 3. *Spremembe ERG in VEP pri 10 otrocih s kolobomom optičnega živca.*

No.	VEP	ERG
1.	normal O.U. normalni obojestransko	normal O.U. normalni obojestransko
2.	normal, without significant side differences normalni obojestransko, brez statistično pomembnih razlik	normal O.U. normalni obojestransko
3.	prolonged latencies podaljšane latence normal amplitudes O.U. normalnih amplitud obojestransko	normal O.U. normalni obojestransko
4.	normal O.D. desno normalni subnormal O.S. levo subnormalni	normal O.U. normalni obojestransko
5.	prolonged latency O.D.; desno podaljšana latenca prolonged latency, reduced amplitude O.S. levo podaljšana latenca, nižja amplituda	normal O.U. normalni obojestransko
6.	irregular waveforms neregularnih oblik no reproducible response O.D. desno neponovljivi reproducible O.S. levo ponovljivi	subnormal O.U. na obeh straneh subnormalni
7.	subnormal, hardly reproducible O.U. subnormalni, obojestransko komaj ponovljivi	normal O.U. normalni obojestransko
8.	subnormal, hardly reproducible O.U. subnormalni, obojestransko komaj ponovljivi	subnormal O.U. obojestransko subnormalni
9.	no reproducible O.D. desno neponovljivi hardly reproducible O.S. levo komaj ponovljivi	extinguished O.D. desno neizvabljivi subnormal O.S. levo subnormalni
10.	no reproducible O.D. desno neponovljivi reproducible O.S. levo ponovljivi	normal O.U. obojestransko normalni

For the other five children (cases 6-10) the electrophysiological findings revealed serious functional impairments. Subnormal and distorted ERGs, and greatly impaired VEPs were obtained. The visual acuity was further impaired by the accompanying cerebral damage (hydrocephalus in case 5, microcephalus in case 6, dyscrania in case 10), or by a severe ocular deformity (e.g. orbital cyst in case 9), microphthalmus (case 8), or because of consecutive functional disturbances such as nystagmus or amblyopia (Fig. 2).

In these cases, no substantial improvement in the visual acuity can be achieved. Still, due treatment of the secondary glaucoma (as in case 8), or surgical intervention to prevent optic nerve atrophy caused by the elevated intracranial pressure in hydrocephalus, or in dyscrania, can hold off further impairments.

Discussion

Our results prove that a wide variety of functional disturbances accompany optic nerve coloboma. They provide evidence necessary for a thorough functional examination of colobomatous eyes. Interestingly enough, most of the studies dealing with colo-

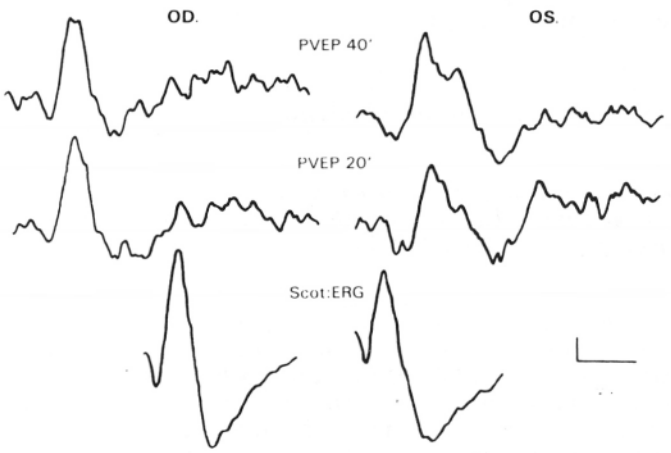


Fig. 1. *VEP (top) and ERG records (bottom) in case 4 (diagnosis: coloboma n. optici sin.). Visual acuity: LD 1.0 with a correction of +6 D sph, LS 0.2 with a correction of +6 D sph. The VEPs are fairly intact, even at the side of the coloboma. This suggests a non-colobomatous origin of the visual impairment (amblyopia?). Calibrations: 10 µV, 100 ms.*

Sl. 1. *VEP (zgoraj) in ERG (spodaj) pri bolniku 4 (diagnoza: coloboma n. optici sin.) Visus: DO 1.0 s korekcijo +6 D sph, LO 0.2 s korekcijo +6 D sph. Posnetki VEP so dokaj normalni celo na strani koloboma. To nakazuje, da izvor motnje vida verjetno ni povezan s kolobomom (amblyopia?). Kalibracija: 10 µV, 100 ms.*

bomatous deformities have concentrated on the pathological alterations, and not much attention has been paid to the functional abilities. The textbooks note an "invariably diminished" (2) - or "severely reduced" (1) visual acuity. Some reports, however, mention close to normal visual functions for patients with morning glory syndrome (10). As regards the assessment of the visual functions, our results stress the importance of the electrophysiological methods in congenital disturbances of the eye, such as colobomatous deformities of the optic nerve. The ophthalmologist can not only assess the damage upon the pathology, but also follow the changes in the visual functions during the course of the disease. This lends therapeutic significance to these examination methods.

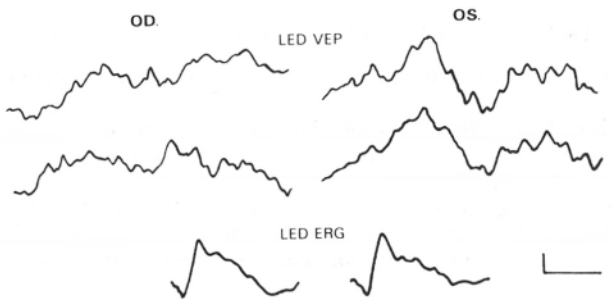


Fig. 2. *VEP (top) and ERG records (bottom) in case 6 (diagnosis: coloboma n. optici, choroid and iridis o.u., hydrocephalus). Reproducible responses can be elicited only upon stimulation of the left eye. Calibrations: 10 µV, 100 ms.*

Sl. 2. *VEP (zgoraj) in ERG (spodaj) pri bolniku 6 (diagnoza: coloboma n. optici, choroideae et iridis o.u., hydrocephalus). Ponovljive odgovore smo registrirali samo pri draženju levega očesa. Kalibracija: 10 µV, 100 ms.*

References

1. Nelson LB. Pediatric Ophthalmology. Vol 25. Major problems in clinical pediatrics. Philadelphia: W.B. Saunders Company, 1984: 80-2.
2. Duke-Elder S. System of Ophthalmology. Vol III. Part 2. Edinburgh: Henry Kimpton, 1964: 456-88.
3. Rintoul AJ. Colobomatous cupping of the optic disc. Br J Ophthalmol 1971; 55: 396-9.
4. Wiggings RE, Von Norden GK, Boninh M. Optic nerve coloboma with cyst: a case report and review. J Pediatr Ophthalmol Strab 1991; 28: 274-7.
5. Bochow TW, Olk RJ, Knupp JB, Smith ME. Spontaneous reattachment of a total retinal detachment in an infant with optic nerve coloboma. Am J Ophthalmol 1991; 112: 347-8.
6. Brown GC. Optic nerve hypoplasia and colobomatous defects. J Pediatr Ophthalmol Strab 1982; 19: 90-3.
7. Rosenberg LF, Burde RH. Progressive visual loss caused by an arachnoidal brain cyst in a patient with an optic nerve coloboma. Am J Ophthalmol 1988; 106: 322-5.
8. Savell J, Cook JR. Optic nerve colobomas of autosomal-dominant heredity. Arch Ophthalmol 1976; 94: 395-400.
9. van Dalen JTW, Delleman JW, Yogiantoro M. A discussion of 61 cases of optic nerve coloboma. Doc Ophthalmol 1983; 56: 177-81.
10. Guiffré G. Morning glory syndrome. Clinical and electrofunctional study of three cases. Br J Ophthalmol 1986; 70: 229-36.

ELEKTROFIZIOLOŠKO OCENJEVANJE FUNKCIJSKIH MOTENJ PRI KOLOBOMU OPTIČNEGA ŽIVCA

Márta Janáky, Zsuzsanna Pelle, Ágnes Szabó, György Benedek

Izvleček - *Izhodišča. Avtorji so želeli prikazati pomembnost elektrofiziološkega ocenjevanja funkcijske prizadetosti pri otrocih s kolobomom optičnega živca različnih stopenj in etiologij.*

Metode. *V skupini desetih bolnikov (starost: 10 mesecev - 14 let) s kolobomom optičnega živca so določili obsežnost anatomskih sprememb z oftalmoskopijo in ultrazvočno preiskavo. Funkcijo mrežnice in optičnega živca so ocenjevali z elektroretinografijo (ERG) in vidnimi evociranimi potenciali (VEP). ERG meritve so izvedli v skotopičnih pogojih z bliskovno stimulacijo, za VEP pa so uporabili slikovni dražljaj.*

Rezultati. *Po rezultatih elektrofizioloških testov so lahko razdelili bolnike v dve skupini. V prvi skupini so bili bolniki z elektrofiziološkimi izvidi, ki so bili blizu normalnim. Otroci v tej skupini so imeli dobro ostrino vida in so lahko pričakovali ugodno prognozo. S korekcijo vida so ublažili nistagmus in odpravili simptome ambliopije zaradi strabizma. Zaradi boljšega dostopa do vidnih informacij so se ti otroci tudi uspešneje duševno razvijali. Pri otrocih druge skupine so z vidnimi elektrofiziološkimi testi odkrili hudo funkcijsko prizadetost. Vidno ostrino so dodatno prizadele spremljajoče možganske poškodbe, deformiranosti očesa, mikrocefalija ali nistagmus in ambliopija. V teh primerih niso uspeli doseči pomembnega izboljšanja vidne ostrine. Kljub temu pa lahko zdravljenje sekundarnega glavkoma ali kirurški posegi, ki preprečujejo atrofijo vidnega živca zaradi zvišanega intrakranialnega pritiska, zaustavijo napredovanje izpadov.*

Zaključek. *Rezultati študije poudarjajo pomen elektrofizioloških testov pri prirojenih očesnih motnjah, kot je kolobom optičnega živca. Oftalmologu omogočajo ne samo oceniti funkcijski izpad, ampak tudi spremljati vidno funkcijo v poteku bolezni, kar dodaja tem preiskovalnim metodam tudi prognostični pomen.*

Ključne besede: *elektroretinogram; kolobom optičnega živca; vidni evocirani potencial*

PATTERN-REVERSAL VEP IN OPTIC DISC DRUSEN

CASE REPORT

SLIKOVNI VIDNI EVOCIRANI POTENCIAL PRI BOLNIKU Z DRUZAMI OPTIČNEGA DISKA

PRIKAZ PRIMERA

Vladimir Juvan

Eye Department, General Hospital, Meštrovićeva ul., HR-42000 Varaždin, Croatia

Key words: *optic disc drusen; visual evoked potentials*

Abstract - *A case of bilateral optic disc drusen in a young man, aged 21, is described. Visual acuity was normal, there were irregular visual field defects, and pattern-reversal VEP showed a significant delay of the P1 and N2 waves. These findings match well with the recent reports in the literature. Pathophysiology of drusen and possible causes for this delay are discussed.*

Introduction

Drusen, or colloid bodies of the optic nerve, is a slowly progressive disease, characterized by visual field defects due to compressive optic neuropathy. They are either visible by retinoscopy as roughness and pallor of the optic disc surface, or buried in deeper layers of the optic nerve head. In this case they can be identified by echography and CT scans. Drusen show autofluorescence when observed through appropriate filters for fluorescein angiography. Reports about VEP changes in optic nerve drusen were rather controversial in earlier literature (1, 2, 3), but recent reports (4) seem to confirm the delay of P1 wave.

Methods

We performed pattern-reversal VEP with checkerboard pattern, contrast 97 %, check size 50' and 25' on a TV monitor at frequency of 1 Hz (2 reversals/s), the stimulating field subtended 12 degrees. The montage consisted of five electrodes positioned in a horizontal row, 5 cm above inion, according to Queen Square system. Reference electrode was placed at Fz, and neutral electrode on the front. We used silver-silver chloride disk electrodes, and the impedance was kept below 5 kiloohms. The recording was done on 5 channels.

Case report

A young man, aged 21, otherwise healthy, visited our out-patient clinic in July 1991 for a routine pre-employment ophthalmologic examination. Visual acuity was 1.0 (6/6) in both eyes, but the visual fields assessed by kinetic Goldmann perimetry showed bilaterally irregular field defects, more pronounced in the nasal halves of the visual field (Fig. 1 and 2). Retinoscopy showed bilaterally a certain pallor and roughness of the optic disc surface and autofluorescence when observed with filters. Echography demonstrated intense echoes within the optic disc regions on both sides, and CT-scan of the orbit and brain confirmed these findings and excluded other possible causes of visual field defects.

Pattern-reversal VEP (Fig. 3 and 4) demonstrated a significant bilateral delay of the P1 and a notable delay of the N2 wave (beyond two standard deviations). Amplitude values were just within normal limits. Neurological examination showed no abnormalities, and cerebro-spinal fluid analysis was normal.

Discussion

Reports about flash and pattern VEP in optic nerve drusen were controversial in earlier literature. While some authors (1) obtained normal values, others (2, 3) demonstrated a delay of the P1 wave.

In a recent survey performed by Scholl and coworkers (4), about 41 % of patients had a delay of the P1 wave. PERG performed by the same group of authors showed normal P50 wave, and reduced amplitude or absence of the N95 wave.

Our result also shows a delay of P1 wave in optic nerve drusen. It has been established that other compressive optic neuropathies may also cause a delay of the P1 wave, as well as gross distortion of the waveform. This delay is, as a rule, small compared to the delays in multiple sclerosis, and it is accompanied by reduced amplitude (5).

Pathophysiologically, it is not quite clear whether in case of optic nerve drusen there is direct compression of the nerve fibres or the changes are secondary to circulatory disturbances. Histological

Abbreviations: *PERG, pattern electroretinogram; VEP, visual evoked potential*

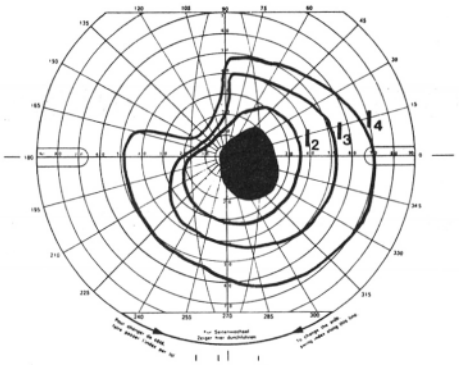


Fig. 1. *Visual field - right eye.*
Sl. 1. *Vidno polje desnega očesa.*

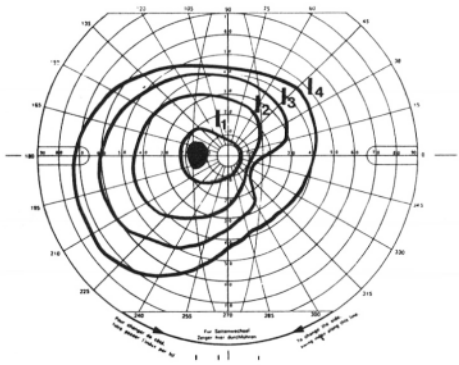


Fig. 2. *Visual field - left eye.*
Sl. 2. *Vidno polje levega očesa.*

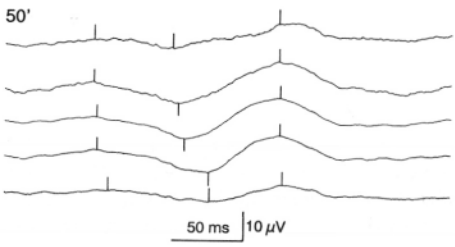


Fig. 3. *Pattern-reversal VEP - right eye.*
Sl. 3. *Slikovni VEP - desno oko.*

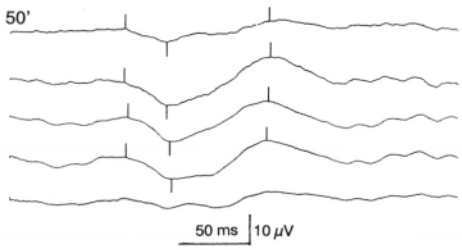


Fig. 4. *Pattern-reversal VEP - left eye.*
Sl. 4. *Slikovni VEP - levo oko.*

studies demonstrate axonal degeneration and intracellular mitochondrial calcification with consequent rupture of the axons (6). To conclude, in our case this type of optic neuropathy produced a delay of both P1 and N2 wave.

References

1. Mustonen E, Sulg I, Kallanranta T. Electroretinogram (ERG) and visual evoked response (VER) studies in patients with optic disc drusen. Acta Ophthalmol 1980; 58: 539-49.
2. Bishara S, Feinsod M. Visual evoked response as an aid in diagnosing optic nerve head drusen. Case report. J Pediatr Ophthalmol Strabismus 1980; 17: 396-8.
3. Stevens RA, Newman NM. Abnormal visual evoked potentials from eyes with optic nerve head drusen. Am J Ophthalmol 1981; 92: 857-62.
4. Scholl GB, Song HS, Winkler DE, Wray SH. The pattern visual evoked potential and pattern electroretinogram in drusen-associated optic neuropathy. Arch Ophthalmol 1992; 110: 75-81.
5. Halliday AM. Evoked potentials in clinical testing. Edinburgh, London, Melbourne, New York: Churchill Livingstone, 1982: 225-33.
6. Miller NR. Walsh and Hoyt's clinical neuro-ophthalmology 4th ed. Vol. 1. Baltimore, London: Williams & Wilkins, 1982: 355-65.

SLIKOVNI VIDNI EVOCIRANI POTENCIAL PRI BOLNIKU Z DRUZAMI OPTIČNEGA DISKA. PRIKAZ PRIMERA

Vladimir Juvan

Izvleček - Izhodišča. *Avtor prikazuje, kako se spremeni slikovni evocirani potencial pri bolniku z retinoskopsko, ehografsko in tomografsko dokazanimi druzami v optičnem živcu.*

Metoda. *Slikovne evocirane potenciale je izvabljal z vzorcem črno-belih kvadratkov s kontrastom 97 odstotkov in velikostjo 50 ter 25 minut vidnega kota. VEP je snemal prek petih elektrod v horizontalni črti 5 cm nad inionom.*

Rezultati. *Bolnik v starosti 21 let je imel ob pregledu normalno vidno ostrino na obeh očeh, toda kinetična Goldmannova perimetrija je prikazala bilateralni nepravilni izpad vidnega polja, bolj izražen v nazalni polovici. Oftalmoskopija je prikazala bledo in grobo površino papile in avtofluorescenco pri opazovanju skozi filter. Ehografija je prikazala močan odboj v predelu optičnih diskov. Računalniška tomografija orbit in možganov je potrdila diagnozo in izključila druge vzroke izpada vidnega polja. Slikovni VEP je imel sicer normalne amplitude vrhov, toda pomembno zapoznela vala P1 in N2.*

Zaključek. *Pri obravnavanem bolniku z druzami optičnega diska je avtor ugotovil podaljšanje tako vala P1 kot vala N2 VEP.*

Ključne besede: *druze optičnega diska; vidni evocirani potenciali*

ELECTRORETINOGRAPHIC SYSTEM

SISTEM ZA ELEKTRORETINOGRAFIJO

Milan Grgič, Blaž Konec, Marjan Mihelin, Ignac Zidar
University Institute of Clinical Neurophysiology, Medical Centre, Zaloška c. 7, 61105 Ljubljana, Slovenia

Key words: *dome stimulator; electroretinography; integral luminance; standardization*

Abstract - *At the University Institute of Clinical Neurophysiology in Ljubljana, the system for clinical retinography has been based for years on an old Medelec MS6 machine, connected with a photostimulator KAISER, and internal normative data were used for the routine clinical use. In 1989, Standard for Clinical Electroretinography was published in the Archives of Ophthalmology by the International Standardisation Committee. Five standard types of measurements were defined along with stimulation parameters, types of electrodes and other acquisition parameters. In order to improve the measurement system and to adjust the laboratory to the proposed standards, a new acquisition system and a new stimulator were arranged. The acquisition system, based on an HP 9000 computer with a powerful analog-to-digital conversion system, standard computer peripheral units, and home written computer programmes, have proved to be a good solution. Medelec Ganzfeld BS-02 stimulator, triggered by the computer through its digital output card, was chosen. After the initial hardware and software setup was made, a set of calibration measurements was done in order to achieve the parameters according to the proposed standards. New normative data are being gathered and concurrently analysed.*

Introduction

At the Ljubljana Institute of Clinical Neurophysiology electroretinographic (ERG) measurements have been performed for more than 20 years. Internal standards have been established and tables of normative ERG parameters values made according to reccomendations of that time to evaluate routine recordings (1, 2, 3).

In 1989, the International Standardisation Committee published in the Archives of Ophthalmology (4) its Standards for Clinical Electroretinography proposing standards for 5 commonly performed measurements. They were to be followed in all the electroretinographic laboratories throughout the world, so as to allow reasonable comparison of the results obtained in any of them. Types of the stimuli for eliciting ERG activities, recording electrodes, amplification and other parameters which determine the form of an ERG recording were proposed.

Being aware of the importance of unified protocols and the technique of recording the ERGs, we at the Institute decided to follow the recommendations and to adjust our measurements to the new standards. The weakest point of our equipment turned out to be the stimulator, therefore, we had to replace it. We chose the recommended dome full-field Ganzfeld BS-02 stimulator and incorporated it in the acquisition system we have been using for the evoked potentials, since it was flexible enough to allow adjustments also to the standard ERG recordings.

The dome stimulator

Providing uniform illumination of the retinal area, the Medelec Ganzfeld BS-02 stimulator is superior to common photo-flashes, which are basically focal sources of light. Three intensities determining the energy released in the moment of a flash (1 J, 10 J, and 80 J) can be chosen from whith a knob on its housing. With any of them, the flash lasts less than 5 ms, thus complying with the demand of the standard, that a flash should last less than the integration period of the fastest photoreceptor.

Since it reacts fast enough to such a short stimulus, a gas photocell was used to measure the flash duration. The photo-cell electric output, analogous to the flash intensity by its time course, was monitored on the oscilloscope. To measure the integral luminance of the stimulator, we used an instrument UDT Model 81 RADIOMETER/PHOTOMETER. At 1 J, the integral luminance was 1.46 cd s/m^2, close enough to the lowest value allowed by the standard (1.5 cd s/m^2) to make us choose the 1 J strength to be the standard of our flash stimulus.

Integral luminance of the stimulator can be changed also by setting the two flash filters in the dome of the stimulator. Each of them attenuates the luminance by different levels, the sum attenuation being the multiplication of filter reduction. Combining the two individual filter settings, an attenuation (proposed by the standard for some examinations) of the standard flash can be achieved.

Abbreviation: *ERG, electroretinogram*

In addition to producing flashes, the stimulator provides a luminance which has a steady time distribution and is even accross the full field, the so called background luminance. It can be adjusted to the stimlus by means of colour and colourless filters. Maximal colourless filtering does not attenuate the background luminance enough, so that, additionally, we use the blue filter. It renders the background bluish and lowers its luminance to 19 cd/m², which is close to the standard lowest value of 17 cd/m². As our flash intensity is close to the lowest value allowed, the background luminance is accordingly low as well: in the ERG measurements, the ratio of the two luminances is namely important.

Luminance and integral luminance measurements

The luminance meter is calibrated for the use with a photometric filter and an attachement reducing the visual angle to 15°. The photometric filter has the transparency in accordance with the photopic luminous efficiency function (photopic luminosity curve) and that is why the light flow to the filter is not measured in physical (W) but in a physiological unit called lumen (lm). From the light flow measured and the geometry of the attachement (15°) taken into account, the luminance of the light source could be calculated (Fig. 1). The calculation is performed by the meter itself, if set to the luminance measuring mode. However, one should be aware that the instrument is adjusted to the ideal Lambert's light source and that, therefore, the exactness of measurement depends on whether the measured source also complies with Lambert's law.

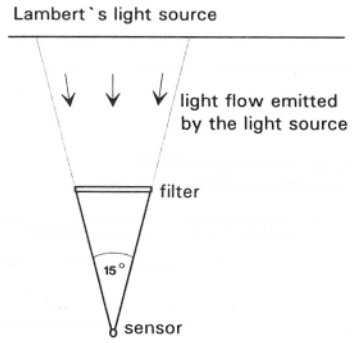


Fig. 1. *Luminance measurement of an ideal Lambert light source.*
Sl. 1. *Meritev svetlosti idealnega Lambertovega svetila.*

Lambert's light sources are those which are seen equally bright if viewed from any angle. An example of such a light source is a rough white wall. The result of its luminance measurement is the same, regardless of the distance between the source and the meter; the light flow is namely always the same, if only the source is large enough to cover the whole perimeter of the sensor.
The measurement of the luminance of the stimulator dome is shown in Figure 2: behind the dome there is an imaginary Lambert's light source. If the luminance of a small enough dome area is measured, the reading corresponds well to the dome luminance. The measured area is the smaller, the narrower the angle of the instrument, and the closer it is to the surface of the dome. However, it shouldn't be so close as to cast its shadow on the measured surface.
For the luminance measurements of the stimulator dome, we placed the instrument in the position of an eye during an ERG recording. By setting the meter to an individual flash metering we read also the integral luminance of a flash.

Other components of the ERG measuring system

The stimulator is the main and specific component of any ERG measuring system. Its other elements for data acquisition and processing, and the output components for data storing or/and displaying in the graphic or alphanumeric mode need not be specific.

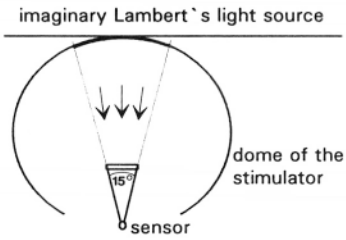


Fig. 2. *Measuring the stimulator dome luminance.*
Sl. 2. *Meritev svetlosti kupole stimulatorja.*

Our system for data acquisition is based on a powerful HP 9000 computer with a programmable Hewlett Packard subsystem "Multiprogrammer HP 98633A", which consists of analogue-digital and digital-analogue converters, a timer, counter and some other modules. Providing up to 16-channel recordings, it is also used for more sophisticated evoked potentials recordings and measurements. The software for the integration of the modules into the system is our own product (5). Another crucial element of the system is a 16-channel amplifier which (for reasons of safety) is a professional medical equipment, specifically made for the work with patients: its power supply is galvanically separated from its input stage and other electronic components. Parameter setting (amplification, band-pass, filters slopes, electrodes interconnections) can be changed either manually, or via the computer to which it is connected.
Manipulation with the system is made quite simple. Choosing a type of measurement from the screen menu makes the computer read the needed parameter values from the files on the computer-disk into all the devices active in the chosen measurement. Any parameter can be manually overriden, but it is not done in routine examinations, which should be performed uniformly. Their uniformity is best secured with the automatic parameter setting. After acquisition and processing, signals can be stored on a magnetic computer disk, and plotted or/and transferred through a network to other computers.

Five standard electroretinographic measurements

We use two types of detecting electrodes for the ERG recordings: the HK loop (6) and the silver cup electrodes. The active one (HK) is placed on the lower eyelid, the referential close to the lateral angle, and the ground electrode on the forehead.
Since it is most sensitive to light adaptation, we start any ERG recording with the rod response (scotopic ERG), after initial 20 minutes of dark adaptation. Further recordings are made in the order shown (with corresponding parameters) in Table 1. The flicker response, recorded at the end, is elicited with the Grass flash, as the Ganzfeld flicker is limited to 20 Hz, not complying with the 30 Hz recommendation. The luminance of the Grass stimulator is 2.12 cd·s/m². We place it 25 cm in front of the patient's eyes.

Tab 1. *The sequence of the ERG recordings with corresponding parameters.*
Tab 1. *Potek ERG meritev s pripadajočimi parametri.*

Response Odziv	Electrodes reference Elektrode referenčna	 active aktivna	LFF SFM Hz	HFF ZFM Hz	Ampli-fication Ojača-nje	Analysis time Čas meritve ms	Samp. time Vzorč. čas ms	Acquis. rate Ponav. frek. Hz	Average number Število povpreč.	Stimulation Stimulacija
20-minute dark adaptation / 20-minutno prilagajanje na temo										
Rod response Odziv paličnic	orb. rim	HK	0.5	250	6000	200	0,4	0.5	20	Ganzfeld: SF ND2.6
Maximal response Maksimalni odziv	orb. rim	HK	0.5	250	6000	200	0,4	0.2	20	Ganzfeld: SF ND0.
Oscillatory pot. Oscilatorni odziv	orb. rim	HK	50	250	30000	100	0,2	1/15	10	Ganzfeld: SF ND0.
10-minute light adaptation / 10-minutno prilagajanje na svetlobo										
Cone response Odziv čepnic	orb. rim	HK	0.5	250	30000	200	0,4	3	50	Ganzfeld: SF ND0.*
Flicker response Odziv na 30 Hz	orb. rim	HK	1	70	12000	200	0,4	3	50	Grass: 2.12 cd s/m^2

*LFF, low frequency filter; HFF, high frequency filter; SF ND0, standard flash without attenuation (1,46 cd s/m^2); ND2,6, 500-times attenuation (log 500≡ 2,6 or 10^{2,6} ≡ 500); *, background illumination*
*SFM, spodnja frekvenčna meja; ZFM, zgornja frekvenčna meja; SF ND0, standardni fleš brez slabljenja ND2,6, 500-kratno slabljenje; *, svetilnost ozadja*

References

1. Karpe G. A routine method of clinical electroretinography. Acta Ophthal 1962; 70: Suppl: 15-31.
2. Burian HM, Pearlman JT. Evaluation of the amplitude of the b-wave of the human electroretinogram. Amer J Ophthal 1964; 58: 210-16.
3. Ruedeman AD. Normal human electroretinogram. Amer J Ophthal 1965; 60: 865-78.
4. International Standardization Committee. Standard for Clinical Electroretinography. Arch Ophthalmol 1989; 107: 816-9.
5. Grgič M, Mihelin M, Zidar I. Evoked potentials measurement system based on computer HP9000. In: Postgraduate Course and 32nd International Neuropsychiatric Symposium, June 14th - 20th, 1992, Graz, Austria. Zagreb: Proceedings, 1992: 83.
6. Hawlina M, Konec B. New noncorneal HK-loop electrode for clinical electroretinography. Doc Ophthalmol 1992; 81: 253-9.

SISTEM ZA ELEKTRORETINOGRAFIJO

Milan Grgič, Blaž Konec, Marjan Mihelin, Ignac Zidar

Izvleček - Izhodišče. *Leta 1989 je International Standardisation Committee v Archives of Ophthalmology izdal Standard for Clinical Electroretinography, ki določa pet standardnih meritev, ki naj bi jih opravljali vsi laboratoriji za elektroretinografijo. Standardi določajo tudi vrste dražljajev, s katerimi izzovemo določene ERG aktivnosti, vrste elektrod, parametre ojačevanja signalov in druge parametre, ki določajo obliko ERG posnetkov.*

Metode. *Da bi prilagodili svoj merilni sistem za ERG novemu standardu, smo izboljšali predvsem stimulacijski del sistema. Izbrali smo kupolasti stimulator, kakršnega priporoča tudi standard, saj omogoča enakomerno osvetlitev mrežnice in je zato za draženje primernejši od navadnih bliskavic. Nastavljive ima tri jakosti dražljaja, ki določajo energijo ob sprostitvi bliska: 1 J, 10 J in 80 J. Pri vseh treh je trajanje bliska manjše od petih milisekund, kar ustreza zahtevi standarda, da mora biti dražljaj krajši od integracijskega časa najhitrejših fotoreceptorjev.*
Svetlost stimulatorja lahko spreminjamo tudi z nastavitvijo dveh svetlobnih filtrov na kupoli stimulatorja. Svetlost zmanjšujeta v različnih stopnjah, celotno slabljenje pa je produkt slabljenj obeh filtrov. S kombinacijo nastavitev lahko dosežemo tiste stopnje slabljenja, ki jih zahteva standard.
Poleg bliskov omogoča stimulator tudi časovno enakomerno svetlost ozadja. V skladu z zahtevami standarda jo lahko slabimo z barvnimi in brezbarvnimi filtri, in to glede na jakost bliskovnega dražljaja. Svetlost ozadja in integralno svetlost bliskovnega dražljaja smo merili z instrumentom UDT Model 81 RADIOMETER/PHOTOMETER in za rutinsko delo izbrali vrednosti parametrov, ki so v mejah standarda.
Poleg dražilnega dela ima sistem za ERG tudi komponente za zajem in procesiranje signalov in izhodne enote, kamor lahko rezultate meritev shranimo ali jih prikažemo v grafični in alfanumerični obliki. Sistem za zajem signalov je zasnovan na zmogljivem računalniku HP9000. Povezan je s programibilnim podsistemom Hewlett Packard "Multiprogramer HP98633A", ki vsebuje analogno-digitalne in digitalno-analogne pretvornike, časovni modul (timer), števec (counter) in še nekatere druge module. Omogoča največ šestnajstkanalne meritve, zato ga uporabljamo tudi za bolj zahtevne meritve EP. Računalniški program, ki povezuje vse dele merilnega sistema, je napisan doma. Pomemben del sistema je 16-kanalni ojačevalnik, ki je iz varnostnih razlogov profesionalna medicinska naprava. Vhodno stopnjo ima galvansko ločeno od napajalnega dela in drugih elektronskih delov ojačevalnika. Ojačevalniku lahko spreminjamo nastavitev parametrov (ojačenje, frekvenčne meje, strmine filtrov, vezave elektrod) bodisi ročno bodisi prek računalnika, priključenega na ojačevalnik.
Uporaba sistema je zelo preprosta. Ko iz menuja na zaslonu računalnika izberemo vrsto meritve, se vrednosti vseh potrebnih parametrov snemanja preberejo iz datotek na disku računalnika. Računalnik nato prek digitalnih povezav nastavi parametre na vseh napravah, ki so udeležene pri meritvi. Vse parametre lahko spremenimo tudi ročno z gumbi na aparaturah, vendar pa tega pri rutinskem delu ne uporabljamo, ker je pomembno, da snemamo vedno z enakimi parametri. To pa najbolje zagotavlja avtomatska nastavitev vseh parametrov z računalnikom.

Zaključek. *Sistem, ki ga uporabljamo na Univerzitetnem inštitutu za klinično nevrofiziologijo, omogoča snemanje ERG, kot ga priporoča mednarodni standard. S tem smo zagotovili večjo mednarodno primerljivost svojih posnetkov.*

Ključne besede: *elektroretinografija; integralna svetlost; kupolasti stimulator; standardizacija*

Acknowledgement

The Organising Committee of the *9th Doctor Janez Faganel Memorial Lecture with the Symposium on Neurophysiological Evaluation of the Visual System* wishes to express its gratitude for the support with the organisation of the meeting and with the publication of the Proceedings first of all to the University Institute of Clinical Neurophysiology and Medical Centre Ljubljana, and to other sponsors and donors (alphabetically):

Zahvala

Organizacijski odbor *9. spominskega predavanja dr. Janez Faganel in Simpozija o nevrofiziološkem vrednotenju delovanja vidnega sistema* se zahvaljuje vsem, ki so pripomogli k organizaciji srečanja in k izdaji zbornika, predvsem Univerzitetnemu inštitutu za klinično nevrofiziologijo in Kliničnemu centru Ljubljana, ter vsem drugim sponzorjem in donatorjem (navajamo po abecedi):

Adriatic, Ljubljana
Art optika, Maribor
BIRING d.o.o., Trzin
DAIS d.o.o., davčno-finančno svetovanje, Ljubljana
Elektronika, Velenje
IBM Slovenija, Ljubljana
Kompas Hertz rent a car, Ljubljana
Krka, tovarna zdravil, Novo mesto
Lek, tovarna farmacevtskih in kemičnih izdelkov, Ljubljana
Loterija Slovenije
Margon Neva, Ljubljana
Medilog, Medical Electronics, Nieuwkoop, The Netherlands
MOBO International d.o.o., Ljubljana
Narodna demokratska stranka, OZ Ljubljana Bežigrad
Optika Cvern Marko, Radovljica
Optika Debeljak, Tržič
Optika Križnar Martin, Novo mesto
Optika M. Škofic, Domžale
Optika RIO, Izola
Optika Šimenc Tomaž, Ljubljana
Optika Weilguny Zvonko, Celje
Petrol trgovina, Ljubljana
Pharmakon AG, Zürich, Switzerland
Pivovarna Union, Ljubljana
Republic of Slovenia, Ministry of Science and Technology, Ljubljana
Rimc - Mehanooptika d.o.o., Krško
SALUS, Ljubljana
Sanolabor, Ljubljana
SKB banka d.d., Ljubljana
The British Council, Ljubljana
Vivian L. Smith Foundation for Restorative Neurology, Houston, Texas, U.S.A.
Založba VALKARTAS, Ljubljana
Zavarovalnica Triglav d. d., Ljubljana
Zavod za zdravstveno zavarovanje Slovenije, Ljubljana
Ze Te d.o.o., inženiring in konsulting, Ljubljana

NAVODILA SODELAVCEM ZDRAVNIŠKEGA VESTNIKA

Zdravniški vestnik (ZV) je glasilo Slovenskega zdravniškega društva. Naslov uredništva je Zdravniški vestnik, Komenskega 4, 61000 Ljubljana, tel. (061) 317-868.

Splošna načela

ZV objavlja le izvirna, še neobjavljena dela. Avtor je odgovoren za vse trditve, ki jih v prispevku navaja. Če ima članek več avtorjev, je treba navesti natančen naslov (s telefonsko številko) tistega avtorja, s katerim bo uredništvo kontaktiralo pri pripravi teksta za objavo, ter kateremu avtorju se pošiljajo zahteve za reprint.

Če prispevek obravnava raziskave na ljudeh, mora biti iz besedila razvidno, da so bile raziskave opravljene v skladu z načeli Kodeksa etike zdravstvenih delavcev SFRJ in Deklaracije iz Helsinkov/Tokia.

Če delo obravnava poizkuse na živalih, mora biti razvidno, da je bilo opravljeno v skladu z etičnimi načeli.

Prispevki bodo razvrščeni v eno od naslednjih rubrik: uvodnik, raziskovalni prispevek, strokovni prispevek, pregledni članek, pismo uredništvu in razgledi.

Raziskovalna poročila morajo biti napisana v angleščini. Dolga naj bodo do 8 tipkanih strani. Slovenski izvleček mora biti razširjen in naj bo dolg do tri tipkane strani. Angleški ne sme biti daljši od 250 besed.

Če besedilo zahteva aktivnejše posege angleškega lektorja, nosi stroške avtor.

Ostali prispevki za objavo morajo biti napisani v slovenščini jedrnato ter strokovno in slogovno neoporečno. Pri raziskovalnih in strokovnih prispevkih morajo biti naslov, izvleček, deskriptorji (ključne besede), tabele in podpisi k tabelam in slikam prevedeni v angleščino.

Članki so lahko dolgi največ 12 tipkanih strani (s tabelami, slikami in literaturo vred).

V besedilu se lahko uporabljajo le enote SI in tiste, ki jih dovoljuje Zakon o merskih enotah in merilih (Uradni list SFRJ št. 13/76).

Spremni dopis

Spremno pismo mora vsebovati: 1. izjavo, da poslano besedilo ali katerikoli del besedila (razen abstrakta) ni bilo poslano v objavo nikomur drugemu; 2. da so vsi soavtorji besedilo prebrali in se strinjajo z njegovo vsebino in navedbami; 3. kdaj je raziskavo odobrila »Etična komisija«; 4. da so preiskovanci dali pisno soglasje k sodelovanju pri raziskavi; 5. pisno dovoljenje za objavo slik, na katerih bi se ev. lahko prepoznala identiteta pacienta; 6. pisno dovoljenje založbe, ki ima avtorske pravice, za ponatis slik, shem ali tabel.

Tipkopis

Prispevki morajo biti poslani v trojniku, tipkani na eni strani boljšega belega pisarniškega papirja formata A4. Med vrsticami mora biti dvojni razmik (po 27 vrstic na stran), na vseh straneh pa mora biti rob širok najmanj 30 mm. Avtorji, ki pišejo besedila s pomočjo PC kompatibilnega računalnika, jih lahko pošljejo uredništvu na 5 1/4 inčnih disketah, formatiranih na 360 Kb ali 1,2 Mb, kar bo pospešilo uredniški postopek. Ko bo le-ta končan, uredništvo diskete vrne. Besedila naj bodo napisana s programom Wordstar ali z drugim besedilnikom, ki hrani zapise v ASCII kodi. V besedilu so dovoljene kratice, ki pa jih je treba pri prvi navedbi razložiti. Že uveljavljenih okrajšav ni treba razlagati (npr. l za liter, mg za miligram itd.).

Naslovna stran članka naj vsebuje slovenski naslov dela, angleški naslov dela, ime in priimek avtorja z natančnim strokovnim in akademskim naslovom, popoln naslov ustanove, kjer je bilo delo opravljeno (če je delo skupinsko, naj bodo navedeni ustrezni podatki za soavtorje). Naslov dela naj jedrnato zajame bistvo vsebine članka. Če je naslov z avtorjevim priimkom in imenom daljši od 90 znakov, je treba navesti še skrajšano verzijo naslova za tekoči naslov. Na naslovni strani naj bo navedenih tudi po pet ključnih besed (uporabljene naj bodo besede, ki natančneje opredeljujejo vsebino prispevka in ne nastopajo v naslovu; v slovenščini in angleščini) ter eventualni financerji raziskave (s številko pogodbe).

Druga stran naj vsebuje slovenski izvleček, ki mora biti strukturiran in naj vsebuje naslednje razdelke in podatke:

Izhodišča (Background): Navesti je treba glavni problem in namen raziskave in glavno hipotezo, ki se preverja.

Metode (Methods): Opisati je treba glavne značilnosti izvedbe raziskave (npr. trajanje), opisati vzorec, ki se ga proučuje (npr. randomizacija, dvojno slepi poizkus, navzkrižno testiranje, testiranje s placebom itd.), standardne vrednosti za teste, časovni odnos (prospektivna, retrospektivna študija).

Navesti je treba način izbora preiskovancev, kriterije vključitve, kriterije izključitve, število preiskovancev, vključenih v raziskavo in koliko jih je vključenih v analizo. Opisati je treba posege, metode, trajanje jemanja posameznega zdravila, kateri preparati se med seboj primerjajo (navesti je treba generično ime preparata in ne tovarniško) itd.

Rezultati (Results): Opisati je treba glavne rezultate študije. Pomembne meritve, ki niso vključene v rezultate študije, je treba omeniti. Pri navedbi rezultatov je treba vedno navesti interval zaupanja in natančno raven statistične značilnosti. Pri primerjalnih študijah se mora interval zaupanja nanašati na razlike med skupinami. Navedene morajo biti absolutne številke.

Zaključki (Conclusions): Navesti je treba le tiste zaključke, ki izhajajo iz podatkov, dobljenih pri raziskavi; treba je navesti ev. klinično uporabnost ugotovitkov. Navesti je treba, kakšne dodatne študije so še potrebne, preden bi se zaključki raziskave klinično uporabili. Enakovredno je treba navesti tako pozitivne kot negativne ugotovitve.

Ker nekateri prispevki (npr. pregledni članki) nimajo niti običajne strukture članka, naj bo pri teh strukturiranost izvlečka ustrezno prilagojena. Dolg naj bo od 50 do 200 besed; na tretji strani naj bodo: angleški naslov članka, ključne besede v angleščini in angleški prevod izvlečka.

Na naslednjih straneh naj sledi besedilo članka, ki naj bo smiselno razdeljeno v poglavja in podpoglavja, kar naj bo razvidno iz načina podčrtavanja naslova oz. podnaslova, morebitna zahvala in literatura. Odstavki morajo biti označeni s spuščeno vrstico. Tabele, podpisi k slikam, prevedeni tudi v angleščino in razlaga v tekstu uporabljenih kratic morajo biti napisani na posebnih listih.

Tabele

Natipkane naj bodo na posebnih listih in zaporedno oštevilčene. Imeti morajo najmanj dva stolpca. Vsebovati morajo: naslov (biti mora dovolj poveden, da razloži, kaj tabela prikazuje, ne da bi bilo treba brati članek; če so v tabeli podatki v odstotkih, je treba v naslovu navesti bazo za računanje odstotka; treba je navesti, od kod so podatki iz tabele, ev. mere, če veljajo za celotno tabelo, razložiti podrobnosti glede vsebine v glavi ali čelu tabele), čelo, glavo, morebitni zbirni stolpec in zbirno vrstico ter opombe ali pa legendo uporabljenih kratic v tabeli. Vsa polja morajo biti izpolnjena in mora biti jasno označeno, če ev. manjkajo podatki.

V besedilu prispevka je treba označiti, kam spada posamična tabela.

Slike

Risbe morajo biti risane s črnim tušem na bel trd papir. Pri velikosti je treba upoštevati, da bodo v ZV pomanjšane na širino stolpca (88 mm) ali kvečjemu na dva stolpca (180 mm). Morebitno besedilo na sliki mora biti izpisano z letraset črkami Helvetica Medium. Treba je upoštevati, da pri pomanjšanju slike za tisk velikost črke ne sme biti manjša od 2 mm. Grafikoni, diagrami in sheme naj bodo uokvirjeni.

Na hrbtni strani vsake slike naj bo s svinčnikom napisano ime in priimek avtorja, naslov članka in zaporedna številka slike. Če je treba, naj bo označeno, kaj je zgoraj in kaj spodaj.

V besedilu prispevka je treba označiti, kam spada posamična slika.

Literatura

Vsako trditev, dognanje ali misel drugih je treba potrditi z referenco. Neobjavljeni podatki ali pa osebno sporočilo ne spada v seznam literature. Navedke v besedilu je treba oštevilčiti po vrstnem redu, v katerem se prvič pojavijo, z arabskimi številkami v oklepaju. Če se pozneje v besedilu znova sklicujemo na že uporabljeni navedek, navedemo številko, ki jo je navedek dobil pri prvi omembi. Navedki, uporabljeni v tabelah in slikah, naj bodo oštevilčeni po vrstnem redu, kakor sodijo tabele ali slike v besedilo. Pri citiranju več del istega avtorja dobi vsak navedek svojo številko, starejša dela je treba navesti prej. Vsi navedki iz besedila morajo biti v seznamu literature.

Literatura naj bo zbrana na koncu članka po zaporednih številkah navedkov. Če je citiran članek napisalo 6 avtorjev ali manj, jih je treba navesti vse; pri 7 ali več je treba navesti prve tri in dodati et al. Če pisec prispevka ni znan, se namesto imena napiše Anon. Naslove revij, iz katerih je navedek, je treba krajšati, kot to določa Index Medicus.

Primeri citiranja

– primer za knjigo:

1. Bohinjec J. Temelji klinične hematologije. Ljubljana: Dopisna delavska univerza Univerzum, 1983: 182–3.

– primer za poglavje iz knjige:

2. Garnick MB, Brenner BM. Tumors of the urinary tract. In: Braunwald E, Isselbacher KJ, Petersdorf RG, Wilson JD, Martin JB, Fauci AS eds. Harrison's principles of internal medicine. 11th ed. Vol 2. New York: McGraw Hill, 1987: 1218–21.

– primer za članek v reviji:

3. Šmid L, Žargi M. Konikotomija – zakaj ne. Med Razgl 1989; 28: 255–61.

– primer za članek iz revije, kjer avtor ni znan:

4. Anon. An enlarging neck mass in a 71-year-old woman. AM J Med 1989; 86: 459–64.

– primer za članek iz revije, kjer je avtor organizacija:

5. American College of Physicians. Clinical ecology. Ann Int Med 1989; 111: 168–78.

– primer za članek iz suplementa revije:

6. Miller GJ. Antithrombotic therapy in the primary prevention of acute myocardial infarction. Am J Cardiol 1989; 64: Suppl 4: 29B–32B.

– primer za članek iz zbornika referatov:

7. Schneider W. Platelet metabolism and membrane function. In: Ulutin ON, Vinazzer H eds. Proceedings of 4th international meeting of Danubian league against thrombosis and haemorrhagic diseases. Istanbul: Goezlem Printing and Publishing Co, 1985: 11–5.

Sodelovanje avtorjev z uredništvom

Prispevke oddajte ali pošljite le na naslov: Uredništvo Zdravniškega vestnika, Komenskega 4, 61000 Ljubljana. Za prejete prispevke izda uredništvo potrdilo. V primeru nejasnosti so uredniki na voljo za posvet, najbolje po poprejšnjem telefonskem dogovoru [tel. (061) 317-868].

Vsak članek daje uredništvo v strokovno recenzijo in jezikovno lekturo. Po končanem redakcijskem postopku, strokovni recenziji in lektoriranju vrnemo prispevek avtorju, da popravke odobri, jih upošteva in oskrbi čistopis, ki ga vrne s popravljenim prvotnim izvirnikom. Med redakcijskim postopkom je zagotovljena tajnost vsebine članka.

Avtor dobi v korekturo prvi krtačni odtis s prošnjo, da na njem označi vse tiskovne pomote. Spreminjanja besedila ob tej priliki uredništvo ne bo upoštevalo. Korekture je treba vrniti v treh dneh, sicer uredništvo meni, da avtor nima pripomb.

Rokopisov in slikovnega materiala uredništvo ne vrača.

Dovoljenje za ponatis slik, objavljenih v ZV, je treba zaprositi od Uredništva Zdravniškega vestnika, Komenskega 4, 61000 Ljubljana.

Navodila za delo recenzentov

Če zaprošeni recenzent prispevka ne more sprejeti v oceno, naj rokopis vrne. Hvaležni bomo, če v tem primeru predlaga drugega primernega recenzenta. Če meni, da poleg njega prosimo za oceno prispevka še enega recenzenta (multidisciplinarna ali mejna tema), naj to navede v svoji oceni in predlaga ustreznega strokovnjaka.

Recenzentovo delo je zelo odgovorno in zahtevno, ker njegovo mnenje največkrat vodi odločitev uredništva o usodi prispevka. S svojimi ocenami in sugestijami recenzenti prispevajo k izboljšanju kakovosti našega časopisa. Po ustaljeni praksi ostane recenzent avtorju neznan in obratno.

Če recenzent meni, da delo ni vredno objave v ZV, prosimo, da navede vse razloge, zaradi katerih delo zasluži negativno oceno. Negativno ocenjen članek po ustaljenem postopku skupaj z recenzijo (seveda anonimno) uredništvo pošlje še enemu recenzentu, kar se ne sme razumeti kot izraz nezaupanja prvemu recenzentu.

Prispevke pošiljajo tudi mladi avtorji, ki žele svoja zapažanja in izdelke prvič objaviti v ZV ter jim je treba pomagati z nasveti, če prispevek le formalno ne ustreza, vsebuje pa pomembna zapažanja in sporočila.

Od recenzenta uredništvo pričakuje, da bo odgovoril na vprašanja na obrazcu ter da bo ugotovil, če je avtor upošteval navodila sodelavcem, ki so objavljena v vsaki številki ZV, in da bo preveril, če so podane trditve in misli verodostojne. Recenzent mora oceniti metodologijo in dokumentacijo ter opozoriti uredništvo na ev. pomanjkljivosti, posebej še v rezultatih.

Ni treba, da se recenzent ukvarja z lektoriranjem in korigiranjem, čeprav ni napak, če opozori na take pomanjkljivosti. Posebej prosimo, da je pozoren na to, ali je naslov dela jasen in koncizen in ali ustreza vsebini; ali izvleček povzema bistvene podatke članka; ali avtor cit isti številki kot ocenjevano delo.

Recenzij ne plačujemo.

Zdravniški vestnik

GLASILO SLOVENSKEGA ZDRAVNIŠKEGA DRUŠTVA ZDRAV VESTN, LETNIK 62, SEPTEMBER 1993, Stran 1-109, SUPPL. I

NEVROFIZIOLOŠKI VIDIKI VIDNEGA SISTEMA

VSEBINA