Review article/Pregledni članek

CELLULAR BASIS FOR ROD-CONE INTERACTIONS IN THE OUTER RETINA

CELIČNA PODLAGA MEDSEBOJNEGA VPLIVA MED PALIČNICAMI IN ČEPNICAMI V ZUNANJIH PLASTEH MREŽNICE

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Abstract – Background. *At least twice daily our retinas move between a light adapted, cone-dominated (photopic) state and a dark-adapted, color-blind and highly light-sensitive rod-dominated (scotopic) state. In between is a rather ill-defined transitional state called the mesopic state in which retinal circuits express both rod and cone signals. Consequently, in the mesopic state the retinal output to the brain contained in the firing patterns of the ganglion cells consists of information derived from both rod and cone signals. Morphology, physiology and psychophysics all contributed to an understanding that the two systems are not independent but interact extensively via both pooling and mutual inhibition. This review lays down a rationale for such rod-cone interactions in the vertebrate retinas. It suggests that the important functional roles of rod-cone interactions is in that they shorten the duration of the mesopic state. As a result, the retina is maintained in either in the (rod-dominated) high sensitivity photon counting mode or in the second mode which emphasizes temporal transients and spatial resolution (the cone-dominated photopic state).*

Conclusions. *Experimental evidence for pre- and postsynaptic mixing of rod and cone signals in the retina is shown together with the preeminent neuromodulatory role of both light and dopamine in controling inter-actions between rod and cone signals. Dopamine is shown to be both necessary and sufficient to mediate light adaptation in the retina.*

Ključne besede: *fotoreceptor; dopamin; horizontalne celice; adaptacijski proces*

Izvleček – Izhodišča. *Vsaj dvakrat na dan se naše mrežnice prilagajajo osvetlitvi in s tem spreminjajo stanje, pri katerem prevladujejo čepnice (cone-dominated), v tistega, kjer prevladujejo paličnice (rod dominated). Med tema stanjema je prehodno obdobje, ki je nekoliko ohlapno označeno kot mezopično stanje. V tem stanju se v mrežnici prepletajo tako signali paličnic in čepkov. Posledično se v mezopičnem stanju v električnem odvodu ganglijskih celic mrežnice nahajajo tako vzorci aktivacije ganglijskih celic po vzdraženju paličnic kot tudi čepnic. Morfologija, fiziologija in psihofizične metode vse prispevajo k razumevanju tega, da oba sistema nista neodvisna, ampak sodelujeta tako preko sočasnih spodbujevalnih kot tudi zaviralnih mehanizmov. Ta pregled prinaša oris soodvisnega delovanja paličnic in čepnic v mrežnicah vretenčarjev in predstavlja tezo, da je pomen interakcije med paličnicami in čepnicami v skrajšanju trajanja mezopičnega stanja na najmanjšo možno mero.*

Zaključki. *Predstavljeni so mehanizmi pred- in posinaptične regulacije signalov paličnic in čepnic in poudarjena nevromodulatorna vloga svetlobe, dopamina ter ostalih nevromodulatorjev v mrežnici pri regulaciji stanja adaptacije in metabolizmu retinalnega pigmentnega epitelija in posameznih vrst celic. Rezultati kažejo, da je dopamin nepogrešljiv in zadosten mediator svetlobne adaptacije v mrežnici.*

Introduction

From the very earliest work by Schultze and von Kries it has been known that rods and cones divide their working ranges: daylight vision originates in cones whereas the night vision is sustained by rods. Such a functional division of retinal signaling into rod-dominated and cone-dominated portions was supported by the classical experiments of Aguilar and Stiles (1) who showed a »break« between rod and cone increment threshold curves at backgrounds of around 6.10^4 quanta $(deg^2s)^{-1}$. At this intensity rods were therefore thought to desensitize and give way to the cone system (the »rod-cone break« or the »Purkinje shift«). According to the Aguilar and Stiles schema, the rod mechanism and the three cone mechanisms function over largely non-overlapping ranges of average environmental brightnesses and therefore behave as independent and parallel units. The cone system was assumed to take over from rods after these were saturated by photons; conversely, rods were thought to take over from cones when the visual stimulus became too dim for adequate photon capture by the cones.

Early on, three lines of evidence put to question the independence of the rod and cone systems. The first originated from the studies concerned with the adaptive effects of steady activation of one system upon the sensitivity of the other (2, 3). Psychophysical experiments showed that the rod-cone break occurred earlier with shortest wavelength stimuli, suggesting that cone-mediated signals may be under an inhibitory influence of the rod system. Now we know that when the rod system is light-adapted or bleached, the cone flicker threshold in the parafoveal retina can be lowered by as much as one log unit from its dark adapted value (4). Indeed, an extensive mixing of rod and cone signals has been recently demonstrated in both rabbit (5) and primate (6, 7) retinas. Secondly, Steinberg reported in 1969 (8) that the light response from mesopic cat horizontal cell (HC) bodies consists of both rod and cone signals. Since the cat HC body does not contact rods directly, a potential pathway for the rod signal entry into the HC was *via* the cone synapse through cones electrically coupled to rods. This hypothesis was substantiated a few years later when gap junctions were identified between rods and cones (9, 10). Finally, it was the realization that in duplex retinas rod and cone signals converge onto the same final common pathway – the ganglion cell – before exiting the eye (11, 12) that paved the way for a more comprehensive view of the mesopic state. The inevitable conclusion of the early work was that during the mesopic state, signals emanating from both rod and cone systems share the same retinal circuits. We now know that interactions between rod and cone signals occur in all species possessing duplex retinas (including amphibians, reptiles and mammals) at virtually every level of retinal signal processing (11, 13–23). Moreover, they occur within a significant range of behaviourally relevant environmental light intensities: many visual stimuli effective for rods can also activate cones (24), and *vice versa.* At the moment many of the mechanisms by which the signals from different photoreceptors interact are still unknown and the biological significance of the interactions is not completely understood. By observing and dissecting these mechanisms in the amphibian preparation we may have a usable tool to understand cellular mechanisms involved in such interactions. This review will illustrate some general mechanisms of rod-cone interactions that exist in the outer plexiform layer (OPL) at the first synapse in the retina. It will be shown that rod and cone signals mix both via electrical junctions between photoreceptors themselves as well as via 2nd messenger cascades in the postsynaptic cells. Many of these events are under neuromodulatory control with the catecholamine dopamine playing a central role.

An outline of rod-cone interactions

Rod and cone signals mix at virtually every level of retinal organization.
1) presynaptically via electrical contacts which connect rod and cone inner segments and/or synaptic terminals,
2) postsynaptically via mutual shunting,
3) postsynaptically through intracellular modulation by 2nd messengers,
(4) transynaptically via release of neuromodulatory chemicals such as dopamine, melatonin or somatostatin.

Rod and cone signals mix presynaptically

Intracellular recording from vertebrate photoreceptors under mesopic conditions shows that rods express a significant amount of cone input which shapes their spectral sensitivity as well as responses in the time domain (25, 26). Cone inputs in green-sensitive rods are best evoked with long wave stimuli which excite both rods and red-sensitive cones (e. g., 13). The reverse situation also holds: rod signals can be recorded from mesopic cones (10). The primary conduit for the presynaptic mixing of rod and cone signals are gap junctions which exist between photoreceptors in virtually all vertebrate species (23, 27, 28). Although the identity of the connexins forming these electrical synapses is as yet unknown, the junctions themselves have been well characterized morphologically. In *Xenopus,* the gap junctions between rods and cones are formed directly between the respective inner segments. Their area is approximately 0.016 μm^2, consisting on average of 70 connexons, which is about 3 times less than junctions between rods alone (29).
Not all rods are connected equally well to cones. A wide range of spectral sensitivities and fusion frequencies is seen in mesopic rods recorded under identical conditions, suggesting

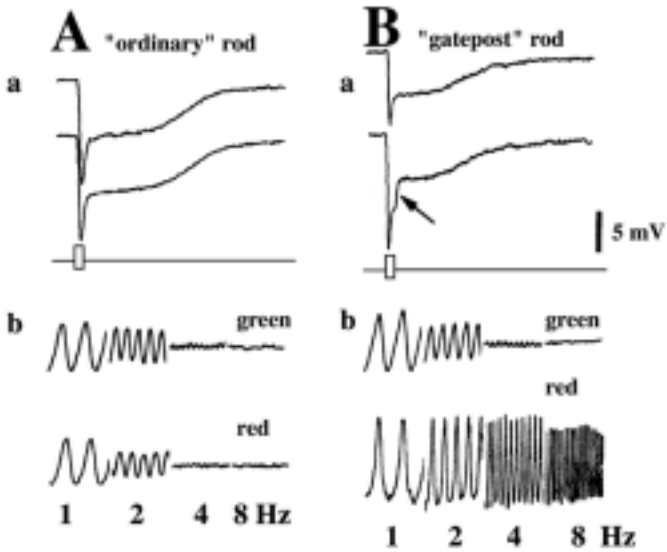


Fig. 1. *Intracellular recording from rod photoreceptors.* ***Aa*** *»Ordinary« rod responses to green (567 nm) and red (667 nm) steps of light matched for equal absorbance by the rods. Stimulus marker is 300 msec.* ***Ab*** *Responses to sinusoidally modulated green (567 nm; 11.56 log quanta cm^{-2} s^{-1}) and red (660 nm; 13.63 log quanta cm^{-2} s^{-1}). Cells were exposed to a flicker ramp with frequencies from 1 to 8 Hz. Note that the fusion frequency for this cell is below 4 Hz for both red and green stimuli.* ***Ba*** *»Gatepost« rod responses to green and red steps of light. Note that the red, but not the green, flash evokes a transient response in the rod strongly resembling the cone light response (arrow). Stimulus marker is 200 msec.* ***Bb*** *Flicker responses of the gatepost rod peter out before 4 Hz whereas responses to red flicker are maintained even at 8 Hz.*

Sl. 1. *Intracelularni posnetki iz paličnic.* ***Aa*** *»Običajni« odzivi paličnic na zeleno (567 nm) in rdečo (667 nm) svetlobo, ki je uglašena z enakim absorpcijskim spektrom posameznih paličnic. Stimulus marker meri 300 msec.* ***Ab*** *Odzivi na sinusno modulirano zeleno (567 nm; 11.56 log quanta cm^{-2} s^{-1}) in rdečo (660 nm; 13,63 log quanta cm^{-2} s^{-1}) svetlobo. Celice so bile izpostavljene seriji hitrih svetlobnih dražljajev s frekvencami med 1 do 8 Hz. Vidno je, da je frekvenca, pri kateri se posamezni odzivi zlijejo v enega, pri tej celici nižja od 4 Hz, tako za rdeče kot tudi zelene dražljaje.* ***Ba.*** *»Gatepost« odzivi paličnic na zelene in rdeče dražljaje. Razvidno je, da rdeči, ne pa tudi zeleni dražljaji izvabijo prehodne odzive v paličnicah, ki močno spominjajo na odzive čepnic (puščica). Stimulus marker meri 200 msec.* ***Bb*** *Odzivi na draženje paličnic izginejo že pod 4 Hz, medtem ko so odzivi na rdeče utripanje ohranjeni tudi še pri 8 Hz.*

that some rods receive more cone input than others. When these rods are labeled with neurobiotin and examined under the electron microscope, their morphology turns out to be virtually identical to the »normal« green-sensitive rods (29); hence it is possible that they are distinguished from the majority rods simply by a higher connexon density. These »gatepost« rods redistribute the cone signal into the rod network (29, 30). While the function of the gatepost rods (which may comprise about 10% of rod population) is not known, it is possible that they help increase temporal resolution of the retinal network by feeding the rod signal into the cone network.

The flicker data and comparison of small amplitude responses to green and red stimuli suggest that even in the dark adapted state the cone input to rods may be significant and that therefore the principle of univariance does not hold even under these conditions (23, 29, 31). The rod-cone coupling is modulated by background light – when the intensity of the background light is increased, coupling becomes stronger (26). Recent work in *Xenopus* has revealed that this effect is likely caused by the neuromodulator dopamine (29). Dopamine binds to D2/D4 receptors located in inner, and possibly outer, segments of rods and cones of many species, including *Xenopus* (32, 33). Subsequently, dopamine initiates a signaling cascade which ultimately results in opening of junctions between rods and cones. In addition to modulating gap junctions, dopamine controls a variety of other signaling pathways in photoreceptors, including the non-selective I_h cation channel, high voltage-activated Ca^{2+} channels and various cytosolic enzymes. This action of dopamine is likely via the heterotrimeric G proteins such as G_i and G_o which in turn modulate photoreceptor $[cAMP]_i$ (34) and/or $[Ca^{2+}]i$ (35–38). Another, if less explored, D2-dopaminergic action may be modulation of release of the synaptic transmitter via regulation of $[Ca^{2+}]i$, [cAMP]i or [IP3]i.

Although the emphasis in this paragraph is on electrical aspect of the interaction between rods and cones, it is important to emphasize that there may be other presynaptic venues of communication between these two photoreceptor classes. For example, in addition to redistributing the electrical signal, gap junctions may also gate the spread of 2nd messengers between the inner segments and synaptic terminals of rods and cones. The diffusional lengths for cAMP and IP3 are large (220 μM and 17 μM, respectively (39), making interaction via diffusible factors quite likely (see, for example, 40, for some early suggestive evidence). Moreover, a direct rod-to cone chemical ribbon synapse in the salamander retina was described as early as 1974 by Mariani and Lasansky. Is it possible, that the mGluR1 and mGluR8 metabotropic receptors recently described in synaptic terminals of rods in several species, including rat (41) and cat (42) are the postsynaptic elements at such interphotoreceptor synapses?

Finally, coupling between rods and cones may have important implications for understanding of how the retinal clock synhronizes its rhythmicity. Both rods and cones exhibit circadian behaviour. A clock must be controlling both these photoreceptor classes in order to insure that all cells exhibit the necessary entrainment. Recent evidence suggests that an important element in entraining the clock is an interaction between dopamine D2 and melatonin receptors (43).

In conclusion, photoreceptors are the first site in the retina which shows a dynamic regulation by neuromodulation. In the mesopic state, when all rods collect and temporally sum more than one quantum per integration time – that is, when illumination may be too dim for cones and too strong for rods, the rod-cone junctions open, allowing the cone signal with its high temporal resolution the use of the rod network which has a higher gain and channeling the robust rod signal into the cone pathway. An additional advantage of coupling is an increase in signal to noise ratio. Coupling could smooth a signal over the coupled path by up to 80% before spatial acuity was compromised. On the other hand, in the dark adapted state when it is important for 2nd order cells to detect dim signals, weak coupling between rods and cones prevents the shunting of the rod signal into the cones and thus gives the synapse greater sensitivity to light. Therefore, the gain between rods and postsynaptic cells is high under these conditions (22). Neither light nor dopamine modulates junctions between rods (26, 29), indicating that the modulation of electrical synapses between rods and cones is specifically related to light adaptation.

Rod and cone signals mix postsynaptically

Amphibian (i. e., *Xenopus, Rana, Ambystoma, Necturus*) luminosity horizontal cells (L-HCs) and bipolar cells (BCs) receive converging synaptic inputs from both rods and cones. Rod and cone systems activated during the mesopic state can be distinguished by their respective spectral sensitivities and kinetics of light responses measured from the optic nerve, the ERG or individual cells. The contribution from the two respective photoreceptor classes is, for example, clearly seen in the

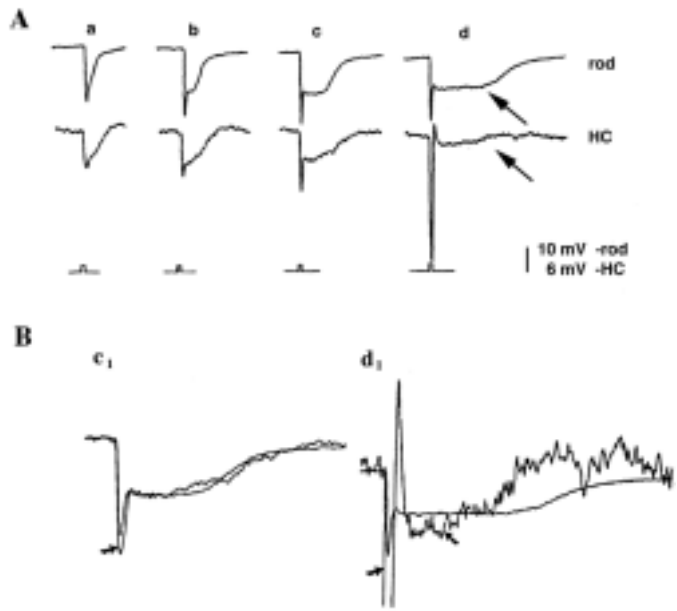


Fig. 2. *Aa-d. Simultaneous recording from a rod and an L-HC in the mesopic state (9.88; 10.72; 11.55; 12.38 logQ). Stimulus markers are 200 msec. Note that the strongest flash induces a suppression of the rod tail in the HC but not in the rod itself (arrow). B. Scaled and superimposed responses from panels c and d. Whereas the responses of the rod and HC in c are remarkably similar – note in particular the kinetics of the onset and the offset of the cells' light responses, both their amplitude and kinetics are dramatically changed with a stronger flash in d.*

Sl. 2. *Aa-d. Sočasno snemanje s paličnic in L-HC v mezopičnih pogojih (9,88; 10,72; 11,55; 12,38 logQ). Enota dolžine dražljaja je 200 msec. Razvidno je, da najmočnejši svetlobni bliski povzročijo supresijo odziva paličnic v HC, ne pa tudi v samih paličnicah (puščica). B.Umerjeni in superponirani odzivi iz segmentov c in d. Čeprav so si odzivi paličnic in HC v segmentu c izjemno podobni – glej predvsem kinetiko začetka in konca svetlobnega odziva obeh vrst celic – se tako amplituda kot tudi kinetika odzivov dramatično spremeni pri draženju z močnejšimi bliski (d).*

HC light response. Fig. 2 shows a simultaneous intracellular recording from a mesopic rod and a HC pair:
While the rod component dominates the HC responses to dim 527 nm flashes (as seen by the similarity of their respective waveforms, Fig. 3Aa-c), a bright flash (Fig. 2Ad) evokes a strong cone component in the HC. When the flash responses in c and d are scaled and matched for the »tail components« contributed by the rod signal, two elements are noteworthy:
1. in the time course of the HC repolarization in **d** is markedly different from the time course of the rod,
2. the rod component in the light responses to the brighter flash **(d)** is smaller from the response to dimmer flashes **(c).**
The suppression of the rod signal by the cone signal is shown in more detail in the Fig. 2B. In response to a dimmer flash, the light responses of the rod and the response of the HC are very similar (Fig. 2B panels c). In fact, were it not for the cone-mediated »nose« (see arrow), the HC light response would be very similar to the rod light response. This suggests that a large range of the presynaptic rod voltage change is transmitted quasi-linearly to the HC – certainly more than the few mV proposed by Attwell et al. (44). The rod-HC response match changes when the preparation is exposed to a higher intensity flash. Now, as shown in the Fig. 3B panel d, *the cone »nose« is increased* whereas, simultaneously, the *rod signal in the HC is dramatically depressed without the response of the rod itself being appreciably altered.* Not only is the magnitude of the rod component in the HC decreased but note that the kinetics of the HC light response also changes with an increase in the cone input. This suggests that the reduction and eventual complete disappearance (with bright flashes) of the rod signal in HCs cannot be explained by a simple saturation of the rod system or a shunt of the rod signal in the postsynaptic cell. Rather, it is likely that cone-activated intracellular mechanisms within the HC actively suppress the rod signal in the period during which the release of glutamate from rods is still suppressed. In the mesopic state, therefore, **a postsynaptic intracellular inhibitory signal activated by the cone pathway acts to reduce the gain of the rod-HC synapse.** The section below provides evidence that the cAMP pathway, activated by the dopamine D1 receptor, participates in the creation of such inhibition.

Dopamine controls transition from rod dominated to cone dominated vision

Retinal dopamine is synthesized by the dopaminergic amacrine cell – a relatively sparse, uniquely identifiable type of tyrosine hydroxylase-positive cell whose processes ramify in the sublayers 1, 3 and 5 of the IPL (45). In *Xenopus,* some processes emanating from this cell do reach the OPL but do not branch there, and it is likely that most of the released dopamine reaches its targets by diffusion from the IPL (46, 47). In light adapted eyes the retinal concentration of dopamine reaches > 0.5 μM, which is enough to dramatically alter the balance between rod and cone signals (31, 46, 48). We now know that **dopamine is both necessary and sufficient to light adapt the scotopic retina** (31) and conversely, by adding D1 and D2 dopamine receptor blockers to a light adapted retina it is possible to show that retinal cells within minutes adopt a phenotype typical of the dark adapted state (19, 31, 49). The action of dopamine is both presynaptic *via* the D2/D4 dopamine receptor and postsynaptic *via* the D1 dopamine receptor (29, 31, 50). What is the physiological stimulus for dopamine release? One important insight provided by the work of Witkovsky and Shi (20) is that the weak, rod-effective light at dawn is already enough to turn on dopamine release. Now we know that light stimulates dopamine synthesis (by upregulating both the TH enzyme and its gene) as well as its release. The finding by Witkovsky and Shi thus allows us visualize an elegant circuit: at dawn rods activate ON bipolar cells which in turn trigger release of dopamine from the TH-positive amacrine cells. Dopamine subsequently diffuses to the OPL, where it activates the cone circuits.
A fundamental rule that holds for all duplex retinas examined so far is that **only cells that are in contact with cones respond to dopamine.** This rule has been confirmed both by immunohistochemistry and through biochemical and physiological experiments. This is true for amphibian HCs which receive inputs from cones and rods (19) as well as for teleost HCs which are connected to cones only (51). Thus teleost cone-HCs possess D1 dopamine receptors and respond to dopamine (52) whereas rod-HCs do not respond to DA neither do they contain dopamine receptor of any class (53). Similar results were observed in the mammalian retina (54).
Activation of D1 receptors causes the HC to display all the signs characteristic of photopic state: spectral sensitivity that corresponds to red cone pigment (19) and flicker response that mimicks flicker responsiveness of cones, but not rods.
Xenopus HCs contact both rods and cones via ionotropic KA/AMPA receptors (55). The same is true for the *Xenopus* OFF BCs (55). Since both inputs are of the same (excitatory) sign how can the apparently contradictory postsynaptic action of dopamine on the cone signal (potentiated) and the rod signal (suppressed) be explained? One possibility is that the dendritic tips contacting cone pedicles and rod spherules contain different subunits of GluRs. Another, not mutually exclusive explanation is that only the HC (and BC) dendrites contacting cone pedicles, but not rod spherules, possess D1 dopamine receptors. As a consequence, dopaminergic potentiation of the cone input could shunt the comparatively smaller non-potentiated rod signal (49). The great variability between the relative rod/cone input between different L-HCs recorded under the same adaptational condition (D. Križaj, unpublished observation) may be therefore due to different densities of D1 receptors or D1R-associated proteins.
Although the shunt hypothesis may explain a dopamine-mediated change in the amplitude, it cannot account for the large difference in the kinetics between the mesopic and scotopic rod signals measured in the HCs. One alternative explanation which takes into account the kinetics changes rests on the neuromodulatory nature of dopaminergic action. The D1 mechanism is known to be coupled to adenylate cyclase and/or the phospholipase C and thus may exert its action by either an increase in [cAMP] and/or IP3/DAG (37, 56). It is suggested here that the kinetic changes in the HC light responses are caused by the D1-dopamine receptor mediated activation of intracellular signaling mechanisms (see below). In classical experiments during the early 80-ies, Dowling's group showed that dopamine elevates [cAMP]i in the teleost HC, which in turn activates the protein kinase A (PKA; 52). This work suggested that the biochemical signature in HCs exposed to dopamine is dramatically changed compared to naïve cells. Is it possible that the effect of the D1 agonist on the rod-cone balance in the HC occurs via cAMP cascade? Following exposure to dopamine, levels of cAMP in horizontal cells are increased (57) which may influence several adaptation-related mechanisms, including receptor desensitization and regulation of glutamate receptor-gated channels (58). We addressed this question by injecting cAMP in one of two simultaneously recorded dark adapted HCs. When two HCs are recorded simultaneously, the injection of cAMP into one cell radically changes its kinetics. The injected cell is less sensitive to dim flicker (Fig. 3A), whereas its responsiveness to bright flicker is enormously potentiated (Fig. 3B), suggesting that it is dominated by cone inputs rather than rod inputs. Note also that exposure to the bright light saturates the control HC (as evidenced by the half-wave rectification typical for saturated HC flicker re-

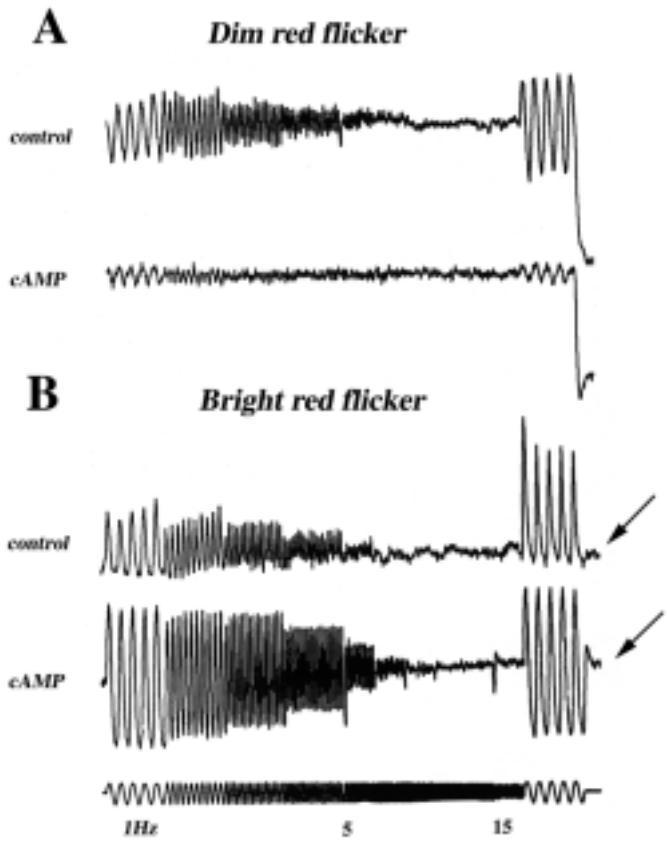


Fig. 3. *Simultaneously recorded HC pair. Stimulation with a sinusoidal 650 nm 1–15 Hz flicker ramp at two intensities differing by 1.8 log units. The control cell responded well to the dim red flicker and became saturated with the bright red flicker. On the contrary, the cAMP-injected cell was relatively insensitive to the dim flicker, responding vigorously to the bright flicker. Note that the injected cell, unlike the control cell, responded from the middle of its dynamic range.*

Sl. 3. *Sočasno snemanje para horizontalnih celic. Draženje s sinusoidnim dražljajem valovne dolžine 650 nm, ki utripa s frekvenco 1–15 Hz pri dveh intenzitetah dražljaja, ki se razlikujeta za 1,8 logaritmične enote. Kontrolna celica se dobro odzove na šibke svetlobne bliske in postane nasičena ob draženju s svetlimi rdečimi dražljaji. Nasprotno je cAMP-injicirana celica relativno neobčutljiva na šibke bliske, a zelo močno odzivna na svetle dražljaje. Pozornost pritegne dejstvo, da se injicirana celica, za razliko od kontrolne celice, začne odzivati šele od sredine svojega dinamičnega razpona.*

sponses) whereas the cAMP-injected cell oscillates around a mean membrane potential. Taken *in toto,* the effect of injecting cAMP is identical to that obtained by the application of the D1 receptor agonist (see Fig. 4) or by adapting the retina with strong background light.

This experiment strongly suggests that **DA acts as a postsynaptic switch modulating the balance between the rod and cone pathways** and that intracellular 2nd messengers can play an important role in regulating the relative weight of rod and cone information in retinal cells. Indeed, an elevation of [cAMP] in the HC is sufficient to light adapt its response phenotype.

Both dopamine, and D1 dopamine agonists also depolarize the HCs, consistent with increasing the amplitude of the glutamate-gated current (the reversal of which is at 0 mV) (50). This effect of dopamine is probably achieved through the dopamine-mediated facilitation of the glutamate-induced current flow through **AMPA receptor-gated channels.** The phenomenon was first described in teleost HCs by Knap and Dowling (58) and later observed also in *Xenopus* (50) as well as in tiger salamander cells.

In conclusion, dopamine has two complementary effects on HCs: it (1) **decreases** the amplitude of rod signals and it (2) **increases** the amplitude of the cone signals. Part of dopamine's action includes a potentiation of the excitatory currents flowing through the postsynaptic AMPA receptors located at cone: HC synapses. Additional effects of dopamine may include modulation of gap junctions, calcium channels, intracellular calcium stores and GABA receptors (56). Dopamine controls the balance of rod and cone signals in HCs at least partly through [cAMP], which apparently acts as an intracellular »switch« between scotopic and photopic cytosolic milieus.

Network adaptation as a dynamic balance between retinal dopamine and melatonin concentrations in normal and dystrophic retina

Retinal dopamine concentration is influenced by a variety of neuromodulators. Dopamine release, for example, is enhanced by 5-HT and cholinergic agonists on one hand, and suppressed by GABA and opiates on the other (56). A particularly potent modulator of dopamine release is melatonin, which was found to be effective at picomolar concentrations (59). Melatonin tells the retina that darkness has arrived by inducing several dark-adaptive changes in retinal cells (43). The action of melatonin is suppressed by dopamine. The mesopic state could therefore be alternatively defined as a balance between dopaminergic and melatonergic mechanisms, vying for the control over cone and rod pahways, respectively. This balance may be disturbed in retinal pathologies. Hawlina and coworkers (60) found, for example, that melatonin level is increased in dystrophic RCS rats prior to retinal degeneration. Further to that finding, Hankins and Ikeda (61) have shown that exogenous application of comparable concentrations of melatonin as found in RCS rats to normal rats can mimic the situation found in dystrophic RCS rats – blockage of release of dopamine on HC (Fig. 4). Melatonin increase may therefore cause dopamine capture in DA-amacrine and IPL cells and affect important metabolic processes such as renewal of photoreceptor cells (disc-shedding) light adaptation and melanin granules migration (60–62).

These questions were addressed by Hawlina and Ikeda using chronic intraperitoneal application of D2 receptor agonist bromocriptine in dystrophic RCS rats and normal heterozygous RCS rats (62). It was shown by electroretinography and histology, that bromocriptine retards degeneration in dystrophic RCS rats (Fig. 4), presumably by restoring extracellular action of dopamine. Interestingly, ERG responses in normal rats treated with bromocriptine had linearly lower amplitudes than vehicle-treated animals at all levels of stimulus intensity, showing the effect of neutral density filter (Fig. 5). This implies, that exogenous dopamine D2-agonists may cause long-term light-adaptive mechanisms such as melanin granules shielding around the photoreceptors outer segments, in addition to short term adaptation processes described above.

Why is there a need for inhibitory rod-cone interactions?

One problem inherent in the structure of the retina is that retinal circuits did not evolve separate rod-dedicated and

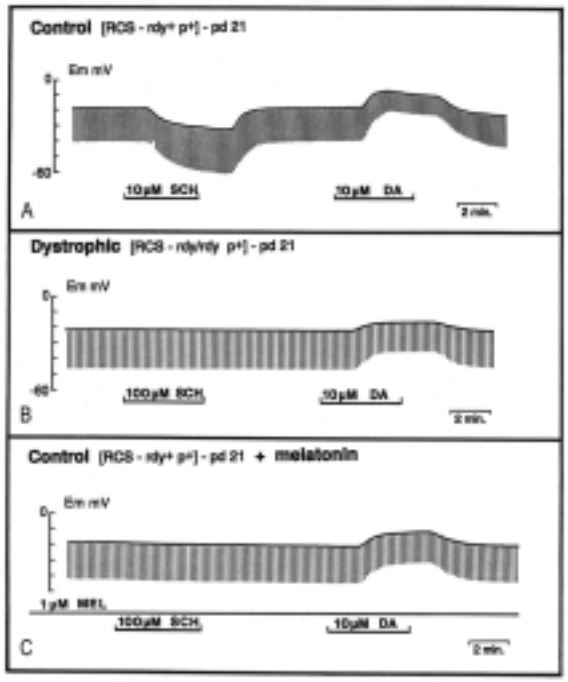


Fig 4. *The effects of SCH 23390 (D1 receptor antagonist) and dopamine (DA) on the responses of horizontal cells recorded from control and dystrophic RCS rat retinae. (A): The responses of a horizontal cell from a control RCS rat aged 21 days. (B): The responses from a dystrophic RCS rat aged 21 days. (C): Similar responses from a control RCS horizontal cell recorded in the presence of melatonin. Note that, whilst exogenous dopamine depolarized horizontal cells in all three cases, SCH 23390 hyperpolarized only the control RCS cell and not the dystrophic RCS cell, or the control cell recorded in the presence of 200–400 nM of melatonin. Thus the pharmacological abnormality of the dystrophic RCS cells can be mimicked in control cells by the addition of exogenous melatonin (61).*

Sl. 4. *Učinek SCH 23390 (D1 receptorski antagonist) in dopamina (DA) na odzive horizontalnih celic posnetih iz kontrolnih in distrofičnih mrežnic podgan tipa RCS. (A): Odzivi s horizontalnih celic kontrolne podgane pri starosti 21 dni. (B): Odzivi s horizontalnih celic distrofične podgane v starosti 21 dni. (C): Podobni odzivi kot pri distrofični podgani s horizontalnih celic normalne kontrolne podgane v prisotnosti melatonina. Opazno je, da je eksogeni dopamin depolariziral horizontalne celice v vseh treh primerih, medtem ko je SCH 23390 (ki kaže na funkcijo endogenega dopamina) hiperpolariziral le kontrolno celico, ne pa tudi distrofične ali normalnih celic v prisotnosti 200–400 nM melatonina. To pomeni, da je farmakološko abnormnost pri distrofični podgani možno simulirati z dodatkom melatonina (61).*

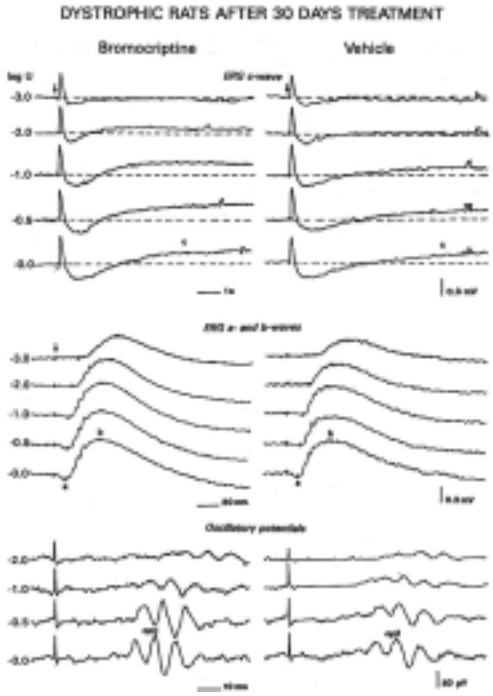


Fig. 5. *Typical components of the ERG in the dystrophic RCS rats at 40–43 days of age with a 30-day treatment with the bromocriptine (left side), or the vehicle (right side). Note that all the ERG responses are better preserved in the bromocriptine-treated group which implies that D2-agonists retard development of this type of retinal degeneration.*

Sl. 5. *Tipični ERG valovi pri distrofičnih podganah tipa RCS pri starosti 40–43 dni po 30-dnevnem dajanju bromokriptina (levi stolpec), oz. nosilne raztopine (desni stolpec). Opazno je, da so vse amplitude ERG odzivov višje v skupini, ki je prejemala bromokriptin, kar kaže, da dopaminski D2 agonisti zavirajo napredovanje te oblike distrofije mrežnice.*

cone-dedicated pathways. This is particularly evident in lower vertebrates, where bipolar and horizontal cells receive direct rod and cone inputs – but is a fact of life for mammalian retinas too, especially in the light of recent evidence (5–7, 63, 64). Thus, when the retina is in a transition from a cone-dominated to a rod-dominated state of adaptation, most retinal channels are simultaneously filled with both rod and cone signals. This presents a timing problem: if both rods and cones respond to the same visual stimulus, then the retinal output would represent the same object twice: first with a fast, cone-mediated signal followed by a slower, rod mediated signal (this integration might be performed by the retinal ganglion cells, which simultaneously process »fast« signals through AMPA receptors and »slow« signals through the NMDA receptors [65]). It is probably disadvantageous for an animal to receive double-latency information concerning the same even/object. This might, for example, result in an ambiguity of target's location and movement across the retina. Alternatively, an interference between the signals might lead to an artificial enhancement/destruction of the signal at certain temporal frequencies (see, for example, the destructive interference between rod and cone flicker recorded from *Xenopus* rods in 29). The mutual antagonism between the rod and cone signals decreases the magnitude of this problem as whichever system is more strongly activated will exert a powerful suppressive influence upon the other. This would preserve the integrity of timing. Such interaction between rod and cone signals was indeed demonstrated in cat, where rod and cone system may inhibit each other by at least 30% (66) and in mesopic *Xenopus* HCs, where a suppression of the cone-HC synapse disinhibits the rod-HC synaptic signal (50). With respect to adaptation, such a **tug of war between the two types of signals serves to shorten the mesopic range:** even though the weaker system is neither subthreshold nor saturated it is not expressed because it is inhibited by the stronger signal. The mechanism of the inhibition involves, at least in part, the neuromodulator dopamine which potentiates the cone signal and suppresses rod signals in a variety of retinal cells, including horizontal cells, bipolar cells and ganglion cells (55). Hence, although they are still active in responding to light, rods are prevented

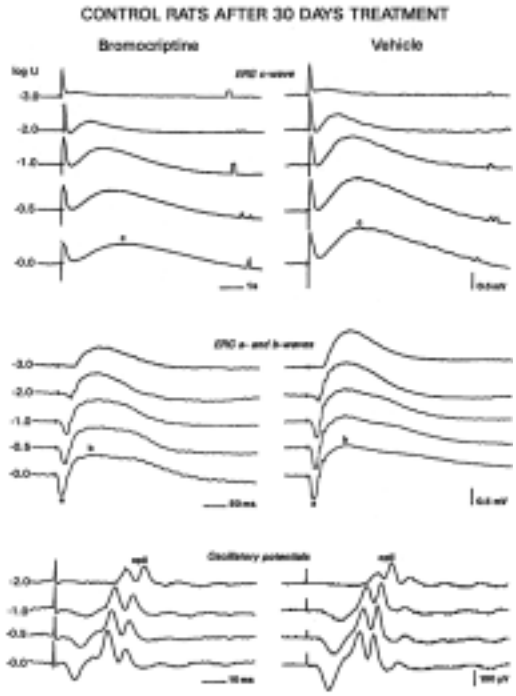


Fig. 6. *Typical components of the ERG in the normal heterozygous RCS rats at 40–43 days of age with a 30-day treatment with the bromocriptine (left side), or the vehicle (right side). Note that, conversely to the dystrophic rats, all the ERG responses are lower in the bromocriptine-treated animals over all tested stimulus intensities (–0.0 do –3.0 log U). This shows the effect of neutral-density filter, implying long-term light adaptive mechanisms in the D2 agonist-treated retinas.*

Sl. 6. *Tipični primer ERG valov pri normalnih heterozigotnih RCS podganah v starosti 40–43 dni po 30-dnevnem dajanju bromokriptina (levi stolpec), ali nosilne raztopine (desni stolpec).Opazno je, da so, v nasprotju z distrofičnimi podganami, vse amplitude pri tretirani kontrolni skupini nižje pri vseh intenzitetah stimulusa (–0,0 do –3,0 log E), kar kaže na efekt filtra nevtralne gostote. To kaže, da D2-dopaminski agonisti povzročijo aktivacijo dolgotrajnejših mehanizmov adaptacije na svetlobo.*

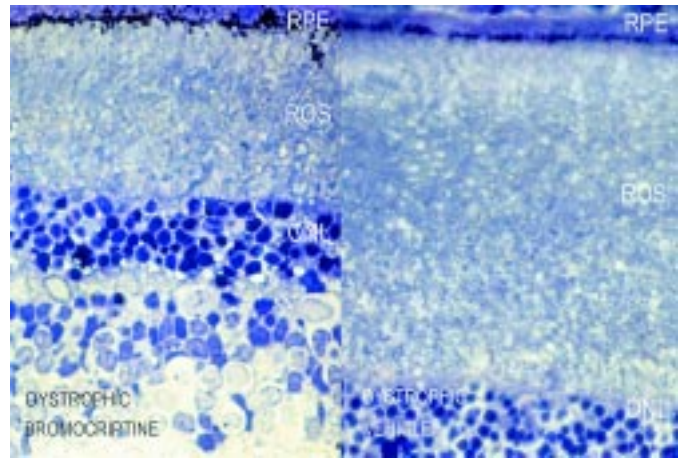
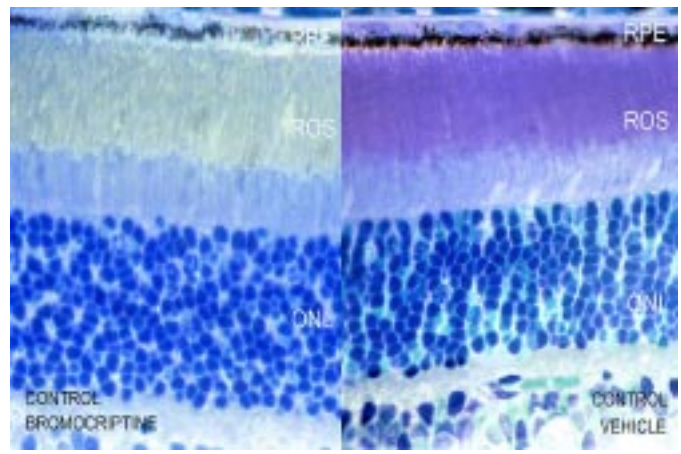


Fig. 7. *Histological picture of the photoreceptor layer of dystrophic RCS rat at 43 days of age treated with bromocriptine (left) and vehicle (right). Magnification 400×. Note better preserved photoreceptor layer with still discernible structure in bromocriptine-treated animal whilst in vehicle-treated animal virtually no photoreceptor structure is seen and the debris is much thicker (equal magnification!). It appears possible that addition of exogenous dopamine agonist has restored the process of phagocytosis of the outer segments by the retinal pigment epithelium which is blocked in RCS rats, presumably caused by excess of melatonin. RPE – retinal pigment epithelium, ROS – rod outer segments, ONL – outer nuclear layer.*

Sl. 7. *Histološki posnetek plasti fotoreceptorskih celic distrofične RCS podgane v starosti 43 dni. Levo je posnetek mrežnice pri podgani tretirani z bromokriptinom, desno pa z nosilno raztopino. Povečava 400-krat. Vidna je bolje ohranjena struktura fotoreceptorjev na levem posnetku, medtem, ko je na desnem posnetku težko ločiti kakršnokoli strukturo fotoreceptorjev, sloj debrisa pa je mnogo debelejši (enaka povečava!). Videti je, da je dodatek dopaminskega agonista delno obnovil proces fagocitoze fotoreceptorjev v retinalnem pigmentnem epiteliju, ki je sicer pri distrofičnih RCS podganah zavrt, morda zaradi prevelike količine melatonina. RPE – retinal pigment epithelium, ROS – rod outer segments, ONL – outer nuclear layer.*

Fig. 8. *Histological picture of the photoreceptor cell layer in control RCS rats at 39 days of age treated with bromocriptine (left) and vehicle (right). Magnification 400×. Note grayish coloration of the photoreceptor outer segments of the treated retina, showing dispersion of melanin granules in light adaptation state. RPE – retinal pigment epithelium, ROS – rod outer segments, ONL – outer nuclear layer.*

Sl. 8. *Histološki posnetek plasti fotoreceptorskih celic kontrolne RCS podgane v starosti 39 dni. Levo je posnetek mrežnice pri podgani tretirani z bromokriptinom, desno pa z nosilno raztopino. Povečava 400-krat. Vidna je sivkasta obarvanost zunanjih segmentov fotoreceptorjev, kar kaže prisotnost zaščitnega sloja melaninskih granul med fotoreceptorji v stanju adaptacije na svetlobo. RPE – retinal pigment epithelium, ROS – rod outer segments, ONL – outer nuclear layer.*



from sending a signal down the optic nerve. Thus the end result of the dopaminergic suppression of the rod signal is that the retina is pushed still further into the photopic state.
A similar phenomenon with an opposite sign – that of rods suppressing the cone system (14) acts to shut the cones off the dark adapted state. The mechanism that underlies this rod-mediated suppression of cone signals is still completely unknown. Perhaps not surprisingly, this effect is diminished by dopamine (18).
What, if any, role do rod-cone interactions have in determining the behaviour of the organism is presently not known. However, the fact that the sensitivities of individual rod and cone receptors measured physiologically are far closer to one another than are the rod-mediated and cone-mediated behavioural thresholds is strongly suggestive of the possibility that postreceptoral interactions between the two signaling pathways contribute to behaviourally relevant perception. In addition to the classical notion of synaptic adaptation at the photoreceptor synapse, the role of which is to prevent saturation and thus maintain coding in the region of the highest sensitivity (67), we may now add suppression of the weaker pathway resulting in a shortening of the mesopic state as another mechanism which contributes to maintaining the retina in an optimal functional state.

Conclusions

The action of dopamine and the action of light in the amphibian retina (19, 31) are nearly identical suggesting that dopamine acts as a switch to turn on the photopic state and shorten the duration of the mesopic state. Under dark adapted conditions, retinal dopamine concentration is low (e. g.150 nM) and the retina is dominated by rod signals. An increase in ambient light has several consequences: 1. it light-adapts rods proportionately more than cones resulting in a larger proportion of glutamate released from cones; 2. it stimulates dopamine release from TH-positive amacrine cells. Subsequently, dopamine acts at several sites in the retina to potentiate the cone signal and suppress the rod signal. One action of dopamine is to facilitate electrical coupling between rods and cones. Another is the potentiation of the excitatory transmission at the cone-HC synapse through both an enhancement of the current flow through the cone transmitter-gated channels and a suppression of the rod signal via an unspecified intracellular 2nd messenger cascade. The suppression is initiated by the D1 dopamine receptor and may, at least in part, involve a rise in [cAMP]i. It is interesting to note that dopamine plays an opposite yet complementary role in intracellular signaling of photoreceptors and HCs: the binding of dopamine to the D1 receptor in HCs **increases** $[cAMP]_{HC}$ resulting in a **closure of the gap junctions between neigbouring HCs.** On the other hand, activation of the D2 receptor in the photoreceptors by dopamine **decreases the [cAMP]photoreceptor and opens the gap junctions between rods and cones.** Thus dopamine may **increase the temporal resolution by opening gap junctions between rods and cones and the spatial resolution by closing the gap junctions between coupled HCs and amacrine cells.** Similar parallel modulation of junctional coupling by D1 and D2-like mechanisms may also occur in other areas of the CNS, such as the nucleus accumbens (68).
The overall conclusion is that synaptic transmission at the photoreceptor output synapse is fixed neither presynaptically nor postsynaptically. Rather, a highly complex and dynamic pattern of extracellular modulators, receptor proteins and intracellular signaling cascades results in an adaptable and ever shifting functional state which is optimized for the behavioural action and dysfunction of which may result in retinal disease.

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