Slov Vet Res 2009; 46 (3): 85-91
UDC 57.085:577.175.6:612.6.052:612.823

Review Paper

IS MALE BRAIN DIFFERENT FROM FEMALE BRAIN?

Gregor Majdič

Center for Animal Genomics, Veterinary Faculty, University of Ljubljana, Gerbičeva 60, 1000 Ljubljana, Slovenia

E-mail: gregor.majdic @vf.uni-lj.si

Summary: In 1959, exactly 50 years ago, was published a paper by Phoenix, Goy, Gerall and Young entitled "Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig". Before the publication of this paper, it was widely accepted that hormones do act upon brain. However, the general thought was that hormones, especially sex steroid hormones, directly activate certain brain areas when needed, i.e. at the time of mating, parental care etc. In contrast to this thought, Phoenix and colleagues for the very first time proposed that hormone action in neonatal period could also permanently alter brain structure, and thus influence differences in behavior long after exposure to sex steroid hormones. The study of Phoenix and colleagues was therefore revolutionary, and as such, had many opponents at that time. Even the authors themselves were very cautious in their phrasing, never directly claiming that hormones could alter brain structure but rather even in the title used the words "tissues mediating mating behavior" instead of brain or central nervous system. Furthermore, as with many such revolutionary studies, study by Phoenix and colleagues left more questions unanswered than it did answer. The authors did not and could not know at that time exactly where and how do steroid hormones act in the brain, they did not know whether observed effects in their study arose from the direct action of testosterone or perhaps from some testosterone metabolite. In half the century since the publication of this seminal study, hundreds of papers have been published, confirming initial finding of Phoenix and colleagues, and these papers have provided answers to many questions raised by the authors. Today we know that at least in rodents, it is testosterone metabolite estradiol that masculinizes the brain. We know that brain structure could be altered by hormones in different periods including puberty and probably even in adult life. We know many locations in the brain where sex steroid hormones act to cause permanent structural changes. Nevertheless, the study of Phoenix, Goy, Gerall and Young still stands strong even after 50 years, confirming the revolutionary importance of their finding.

Key words: brain; sexual differentiation; steroid hormones; sex chromosomes

Introduction

Men and women differ and we all know that. Males are usually larger, have hoarser voice, facial hair and more muscular body while females have breasts, lack facial hair and have usually so called feminine body with narrow waist and broader hips and chest. Of course, males and females also differ in appearance of their external and internal sexual organs. But do the differences end here? According to many studies performed in the last decades, we can now confidently say no. There are many other differences beside differences connected with sexual reproduction. Studies in recent years and decades have demonstrated differences in such diverse biological phenomena as wound healing (1), drug detoxication in liver (2), and perhaps most importantly, differences in the brain, which are no longer considered to be a myth but are believed to be present and are thought to be important for explaining many physiological and patophysiological processes occurring in our bodies (3). From clinical point of view it is very important to bear in mind that many different diseases show different prevalence between sexes, and these disparities could not be explained only by differences in lifestyle (what was initially suggested for the incidence of lung cancer). Many psychiatric disorders also show sex bias. For example, , major depressive disorder, anxiety

Received: 14 July 2009
Accepted for publication: 1 September 2009

and eating disorders are much more prevalent in women, while schizophrenia, autism and attention deficit disorder are diagnosed more often in men (4). Because of these clinical implications, studies of sex differences are not only of academic interest, but have important implications for clinical practice, which will, undoubtedly, became even more important in future years with the development of pharmacogenomics.

Determination of sex in mammals

In mammals two sex chromosomes exist that determine the sex of the offspring. Females are homozygous for sex chromosomes with two X chromosomes and males are heterozygous with XY chromosomes. Sry, by far the smallest chromosome, poses an SRY gene, which is both sufficient and necessary for development of the male phenotype. SRY gene, first cloned in 1991 is small gene belonging to the group of high mobility group of proteins. Different studies have demonstrated that SRY alone is sufficient to trigger testis development (5, 6). Once testis is formed, hormones secreted from the testis govern subsequent development of male phenotype with antimullerian hormone (AMH/ MIS) being responsible for regression of female reproductive organs and steroid hormone testosterone being responsible for development of male secondary sexual organs. In females, ovaries remain relatively inactive until after birth and female secondary sexual organs develop in the absence of any hormonal exposure, what was clearly demonstrated by different clinical cases as well as in animal studies where even in complete absence of gonads (either ovary or testis) female secondary reproductive organs develop (7).

Reproductive development could be divided into two phases. Initial phase occurs during development in utero and comprises of gonadal differentiation and development of secondary sexual organs (penis, scrotum, accessory glands in males and clitoris, vagina, uterus and oviduct in females). This phase is followed by quiescent period during childhood. During puberty, second phase of sexual development occurs with hormones secreted from gonads (this time both from ovaries and testes) triggering sexual maturation and appearance of secondary sexual characteristics such as breasts and wide hips in females, facial hair, muscular body and hoarse voice in males. In addition, several recent studies have also shown that sexual hormones also influence brain development and that several changes occur in the brain during puberty due to exposure to large amount of sex steroid hormones (8).

Development of sex differences in the brain

Brain control and govern all processes in the living organism, including reproduction. Therefore, it is not surprisingly or unexpectedly to know that sex differences exist also in the mammalian brain. This has been known for many decades with most differences being described in parts of limbic system, mostly in the hypothalamus and preoptic area, two areas closely connected with the function of the reproductive system (9). The classical view of brain sexual differentiation is built around the dogma that hormones secreted by gonads are solely responsible for differences in the brain between sexes. This hypothesis originated in 1959 when Phoenix, Goy, Gerall and Young published now classical study showing that prenatal administration of testosterone to female guinea pigs induced masculinized behavior in adult female guinea pigs (10). The importance of sex steroid hormones for differences in sexual behavior was acknowledged prior to this publication, although before 1959 it was believed that all actions of sex steroids are activational effects and not organizational. Study by Phoenix et al. (10) therefore for the first time showed that prenatal exposure to sex steroid testosterone could permanently alter brain function. Female guinea pigs that were given testosterone prenatally displayed masculinized behavior as adults, long after testosterone treatment, what could only resulted from permanent effect of testosterone on developing brain. Study by Phoenix et al. of course did not provide all important answers such as which hormone at what time and in what part of the brain is responsible for the sexual differentiation of the brain. Nevertheless, this study was of outmost importance as the first study showing that hormones could permanently alter brain structure and function. In the fifty years after this discovery, many questions about organizational effects of sex steroid hormones have been answered. We now know that at least in rodent brains, estradiol and not testosterone is responsible for the masculinization of the brain. Testosterone, secreted from the testes in male fetuses is transported into the brain, where it is converted into estradiol by cytochrome P450 aromatase, locally expressed in different parts of the brain (11, 12). While female fetuses are not exposed to testosterone from their gonads, they are still exposed to estradiol from their mothers. To prevent

masculinization of the female brain, large amounts of alpha-fetoprotein are present in the blood of female fetuses, which could bind estradiol and thus preventing it from entering into the brain (13). Studies in last decades have also indentified many areas of the brain that are altered during development due to exposure to sex steroids, not only areas closely connected with reproduction, but also in the areas important for emotional responses such as amygdala and even other areas such as hippocampus and cerebellum (14-17). One of the best known and studied examples is sexually dimorphic nucleus in the preoptic area (SDN), first identified by Gorski et colleagues in the late seventies (18). This nucleus is larger in males than in females and is believed to be important for male sexual behavior although its precise role is not yet known. SDN has been identified in different species such as sheep (19), macaque (20) and even humans (21, 22). Two other areas in the mammalian brain that are sexually dimorphic are ventromedial hypothalamic nucleus and bed nucleus of stria terminals (23-25). Both areas are involved in the regulation of sexual behavior and it is thus not surprisingly that these two areas are different in males and females. Perhaps more interesting are reports about sex differences in cerebellum and hippocampus (15-17). These two areas are not involved in the regulation of reproductive behavior, nevertheless, several studies have shown that sexual dimorphism exist also in hippocampus and cerebellum. Considering the function of these two areas, it is less surprisingly to find sex differences in morphology and gene expression. Hippocampus is considered to be involved in memory and spatial orientation, and spatial orientation in humans is now considered to be one of the important sexually dimorphic traits (26). As for cerebellum, several different human diseases such as autism and attention deficit disorder that show strong sexual dimorphism are thought to originate from the dysfunction of cerebellum (15). Therefore, it is not surprisingly to find sex differences also in these two areas.

Is there a role for sex chromosomes in brain sexual differentiation?

Many studies in the last 50 years since the publication of the paper by Phoenix et al. (10) have shown the importance of sex steroid hormones for brain sexual differentiation. It is now clearly established that sex steroids have important role in brain development in different periods, not only prenatally but also postnatally, during puberty and in the adult life in both animals and humans. However, there was always a question lurking in the dark whether all sex differences in the brain could be explained by one unifying theory about organizational effects of sex steroids. The idea that sex chromosomes could also play a role in brain sexual differentiation was for sometime sidelined because some studies have shown that normal XX females could be completely masculinized (for some phenotypes) if treated with testosterone at appropriate time periods, and likewise, normal XY males could be completely feminized for some phenotypes if fetal testosterone production or action is blocked (27, 28). However, in the early nineties, several studies suggested that sex steroid hormones might not be the whole answer to sexual differentiation (29-32). In the last decade, several studies indeed provided evidence for hormone independent brain sexual differentiation.

Several approaches have been used to study sex differences in the brain that develop in the absence of hormone exposure. One approach is to study fetal brain development early during development, before gonads develop and start to produce sex steroid hormones. This approach was used in several studies and has provided evidence that some sex differences do occur very early during development, before fetuses are exposed to endogenous sex steroid hormones. Study by Kolbinger et al. (30) demonstrated sex differences in dopaminergic neurons in rat fetuses already on day 14.5 p.c. while genomic study by Dewing et al. (33) identified over 50 genes whose expression differed between male and female mouse brain on day 10.5 p.c., well before gonads start to produce sex steroids. However, of real importance would be studies that would demonstrate hormone independent sex differences in adult animals, either in brain morphology or behavior. To achieve these goals, two different models, each with advantages and disadvantages, have been developed.

A very useful model for studying genetic differences between sexes is so called four core genotype (FCG) mouse model. In these mice, *sry* gene has been manipulated (translocated or mutated) to produce normal XY males, normal XX females, XX males (*sry* gene translocated to autosome) and XY females (*sry* gene mutated) (34). In XY females and XX males genetic sex does not correspond with phenotypic sex and therefore, relative contribution of sex chromosomes and sex hormones could be studied. This is the most studied model for hormone independent brain sexual differentiation so far, and

several studies have shown some differences that could not be attributed to sex hormones but must arise due to differences in sex chromosomes. Initial studies with FCG mice did not reveal any differences that could be attributed to the effect of sex chromosomes for different parameters such as male sexual behavior, cell numbers in hypothalamic anteroventral periventricular nucleus (AVPV), the size of the spinal nucleus of the blubocavernosus (SNB), cortical thickness and progesterone receptor expression in preoptic area (POA) (35, 36). These studies therefore confirmed classical organizational-activational-hypothesis of brain sexual differentiation. However, arginin vasopressin (AVP) immunoexpression in lateral septum (LS), which is also known to be sexually dimorphic, differed between XY and XX mice of the same phenotypic sex suggesting that this difference is partially dependent on sex chromosomes (34, 37). Further studies revealed even stronger evidence that sex chromosomes do account for some sex differences between male and female mice. When mesencephalic cells were dissociated from 14.5 days old mouse embryos and cultured, more dopamine producing cells (I.E. tyrosine hydroxlase expressing cells) developed in cultures from XY embryos than in those from XX embryos (38), what confirmed the results from previous studies (30, 31). Adult FCG mice were also tested for male to male aggressive behavior (after testosterone treatment of adult gonadectomized mice) and XY females were more aggressive than XX females while there was no difference between XY and XX males (37). Furthermore, there were differences in nociception, parental behavior and habit formation that could not be attributed to sex hormones but have to be consequences of sex chromosomes (39-42). Perhaps most interestingly, FCG mouse model was also applied to studies of incidence and progression of autoimmune diseases, a very important issues as most autoimmune diseases in humans including multiple sclerosis and systemic lupus erhytematosus have a strong sex difference in prevalence. XX mice showed much stronger autoimmune responses than XY mice and although organizational/activational effect of sex steroid hormones do account to some extent for observed sex differences, a study by Smith-Bouvier et al. (43) strongly suggest that sex chromosomes also play an important role in development of the differences between sexes in incidence and progression of autoimmune diseases.

Steroidogenic factor 1 (SF-1) was initially discovered as a transcription factor regulating expression of different steroidogenic enzymes (44). Further studies, however, revealed it's much wider role in development and function of endocrine system as SF-1 knockout mice are born without gonads and adrenal glands, have disorganized ventromedial hypothalamic nucleus and unfunctional gonadotrope cells in the pituitary (45, 46). In SF-1 knockout mouse embryos, genital ridges form normally on day 10.5 p.c. (46). However, almost immediately after formation of genital ridges, cells became apoptotic and by day 12.5 p.c., genital ridges disappear. As steroidogenesis in fetal mouse testis starts only after day 12.5 p.c., these mice are never exposed to any endogenous sex steroid hormones. SF-1 knockout mice are born completely sex reversed; both XX and XY pups show female phenotype. Since SF-1 knockout mice are never exposed to any sex steroid hormones, they are another very useful model to study hormone independent development of sex differences in the brain. SF-1 knockout model differ from FCG model in one very important way: FCG mice develop gonads independently from chromosomal sex and are thus exposed to sex steroid hormones during neonatal and pubertal development. Sex steroid hormones could influence brain development and could perhaps even mask or overcome some sex differences that would develop in complete absence of hormones. SF-1 knockout mice are, in contrast to FCG mice, never exposed to any endogenous sex steroid hormones and thus provide a unique model allowing searching for sex differences that develop in true hormone-less environment. Initial studies with SF-1 knockout mice, like studies with FCG mice, did not reveal any major differences between sexes. As expected, sexually dimorphic nucleus was not present in either XX or XY SF-1 knockout mice, conforming that prenatal exposure to testosterone is necessary for the development of this nucleus. However, immunocytochemical studies did reveal some sex differences present in both WT and SF-1 knockout mice such as number of calbindin immunopositive cells in the ventromedial hypothalamus and neural nitric oxide synthase in the AVPV (47). However, sex difference in AVP expression in LS was not confirmed, suggesting that other factors and not just sex chromosomes influence expression of AVP in LS. Recent studies with SF-1 knockout mice revealed very interesting observation in female sex behavior. Unlike in rats, WT mice of both sexes are capable of showing female sexual behavior when treated with estradiol and progesterone. In our studies we found that although mice from all four

(WT male, WT female, SF-1 knockout male, SF-1 knockout female) groups did show lordosis, there was a large difference in lordosis quotient between WT male and female mice, with, as expected, female mice showing much stronger lordotic response when stimulated by a WT stud male. SF-1 knockout mice of both sexes also showed lordosis, although it was not as strong as in WT females, suggesting that developmental exposure to sex steroids is important also for proper development of lordotic behavior in adult mice. However, most interestingly, there was a significant sex difference in lordosis quotient between XX and XY SF-1 knockout mice suggesting that this behavioral trait is at least partially influenced by sex chromosomes. Similarly to FCG mice, small sex differences were also found in parental and some social behaviors between XX and XY SF-1 knockout mice, suggesting the effect of sex chromosomes.

Conclusions

Many decades of studies have convincingly shown that differences between male and female brain exist. Undoubtedly, many studies have demonstrated morphological differences between male and female brains in animals, and some studies have provided evidence that such differences most likely exist also in humans. We do not understand all the processes that govern sexually dimorphic brain development and several recent studies suggested that sex chromosomes, not only sex hormones, could influence sex specific development. More difficult are questions how to correlate morphological differences in the brain with certain sex specific behaviors, although even there we saw a big progress in recent years. Several studies have provided evidence that sex differences in hippocampus might be connected with sex differences in spatial orientation, and sex differences in amygdala might be connected with differences in emotional responses. Since the seminal paper by Phoenix and colleagues in 1959, we have made large strides ahead and we now have answers to many questions, asked by Phoenix and colleagues. Nevertheless, many questions still remain unanswered and are waiting for new studies to shed the light.

References

1. Gilliver SC, Ruckshanthi JP, Hardman MJ, Nakayama T, Ashcroft GS. Sex dimorphism in wound healing: the roles of sex steroids and macrophage migration inhibitory factor. Endocrinology 2008; 149(11): 5747-57.

2. Clodfelter KH, Holloway MG, Hodor P, Park SH, Ray WJ, Waxman DJ. Sex-dependent liver gene expression is extensive and largely dependent upon signal transducer and activator of transcription 5b (STAT5b): STAT5b-dependent activation of male genes and repression of female genes revealed by microarray analysis. Mol Endocrinol 2006; 20(6): 1333-51.

3. Diamond M. Clinical implications of the organizational and activational effects of hormones. Horm Behav 2009; 55(5): 621-32.

4. Davies W, Wilkinson LS. It is not all hormones: alternative explanations for sexual differentiation of the brain. Brain Res 2006; 1126(1): 36-45.

5. Berta P, Hawkins JR, Sinclair AH, et al. Genetic evidence equating SRY and the testis-determining factor. Nature 1990; 348: 448-450.

6. Koopman P, Gubbay J, Vivian N, Goodfellow PN, Lovell-Badge R. Male development of chromosomally female mice transgenic for Sry. Nature 1991; 351: 117-21.

7. Gilbert SF. Developmental biology. Sunderland, Massachusetts: Sinauer Associates, 1994.

8. Schulz KM, Molenda - Figueira HA, Sisk CL. Back to the future: the organizational-activational hypothesis adapted to puberty and adolescence. Horm Behav 2009; 55(5): 597-604.

9. Becker JB, Berkley KJ, Geary N, Hampson E, Herman JP, Young E. Sex differences in the brain: from Genes to Behavior. Oxford, New York: Oxford University Press, 2007.

10. Phoenix CH, Goy RW, Gerall AA, Young WC. Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. Endocrinology 1959; 65: 369-82.

11. Lephart ED. A review of brain aromatase cytochrome P450. Brain Res Brain Res Rev 1996; 22(1): 1-26.

12. Harada N. [Estrogen synthetase (P-450. aromatase) as a regulatory factor concerning sexual differentiation of brain and sexual behavior--physiological functions and regulation of gene expression of aromatase]. Seikagaku 1993; 65(2): 67-85.

13. Bakker J, De Mees C, Douhard Q, Balthazart J, Gabant P, Szpirer J, Szpirer C. Alpha-fetoprotein protects the developing female mouse brain from masculinization and defeminization by estrogens. Nat Neurosci 2006; 9(2): 220-6.

14. Cooke BM, Stokas MR, Woolley CS. Morphological sex differences and laterality in the prepubertal medial amygdala. J Comp Neurol 2007; 501(6): 904-15.

15. Dean SL, McCarthy MM. Steroids, sex and the cerebellar cortex: implications for human disease. Cerebellum 2008; 7(1): 38-47.

16. Galea LA, Spritzer MD, Barker JM, Pawluski JL. Gonadal hormone modulation of hippocampal neurogenesis in the adult. Hippocampus 2006; 16(3): 225-32.

17. McCarthy MM, Konkle AT. When is a sex difference not a sex difference? Front Neuroendocrinol 2005; 26(2): 85-102.

18. Gorski RA, Harlan RE, Jacobson CD, Shryne JE, Southam AM. Evidence for the existence of a sexually dimorphic nucleus in the preoptic area of the rat. J Comp Neurol 1980; 193(2): 529-39.

19. Roselli CE, Larkin K, Resko JA, Stellflug JN, and Stormshak F. The volume of a sexually dimorphic nucleus in the ovine medial preoptic area/anterior hypothalamus varies with sexual partner preference. Endocrinology 2004; 145(2): 478-83.

20. Vasey PL, Pfaus JG. A sexually dimorphic hypothalamic nucleus in a macaque species with frequent female-female mounting and same-sex sexual partner preference. Behav Brain Res 2005; 157(2): 265-72.

21. Swaab DF, Gooren LJ, Hofman MA. The human hypothalamus in relation to gender and sexual orientation. Prog Brain Res 1992; 93: 205-17.

22. Swaab DF, Gooren LJ, Hofman MA. Brain research, gender and sexual orientation. J Homosex 1995; 28(3-4): 283-301.

23. al-Shamma HA , De Vries GJ. Neurogenesis of the sexually dimorphic vasopressin cells of the bed nucleus of the stria terminalis and amygdala of rats. J Neurobiol 1996; 29(1): 91-8.

24. Dugger BN, Morris JA, Jordan CL, Breedlove SM. Androgen receptors are required for full masculinization of the ventromedial hypothalamus (VMH) in rats. Horm Behav 2007; 51(2): 195-201.

25. Matsumoto A , Arai Y. Sex difference in volume of the ventromedial nucleus of the hypothalamus in the rat. Endocrinol Jpn 1983; 30(3): 277-80.

26. Manson JE. Prenatal exposure to sex steroid hormones and behavioral/cognitive outcomes. Metabolism 2008; 57 (Suppl 2): S16-21.

27. Dohler KD, Coquelin A, Davis F, Hines M, Shryne JE, Gorski RA. Pre- and postnatal influence of testosterone propionate and diethylstilbestrol on differentiation of the sexually dimorphic nucleus of the preoptic area in male and female rats. Brain Res 1984; 302(2): 291-5.

28. Nordeen EJ, Nordeen KW, Sengelaub DR, Arnold AP. Androgens prevent normally occurring cell death in a sexually dimorphic spinal nucleus. Science 1985; 229(4714): 671-3.

29. Beyer C, Eusterschulte B, Pilgrim C, Reisert I. Sex steroids do not alter sex differences in tyrosine hydroxylase activity of dopaminergic neurons in vitro. Cell Tissue Res 1992; 270(3): 547-52.

30. Kolbinger W, Trepel M, Beyer C, Pilgrim C, Reisert I. The influence of genetic sex on sexual differentiation of diencephalic dopaminergic neurons in vitro and in vivo. Brain Res 1991; 544(2): 349-52.

31. Reisert I, Engele J, Pilgrim C. Early sexual differentiation of diencephalic dopaminergic neurons of the rat in vitro. Cell Tissue Res 1989; 255(2): 411-7.

32. Reisert I, Pilgrim C. Sexual differentiation of monoaminergic neurons--genetic or epigenetic? Trends Neurosci 1991; 14(10): 468-73.

33. Dewing P, Shi T, Horvath S, Vilain E. Sexually dimorphic gene expression in mouse brain precedes gonadal differentiation. Brain Res Mol Brain Res 2003; 118(1-2): 82-90.

34. De Vries GJ, Rissman EF, Simerly RB, et al. A model system for study of sex chromosome effects on sexually dimorphic neural and behavioral traits. J Neurosci 2002; 22(20): 9005-14.

35. Markham JA, Jurgens HA, Auger CJ, De Vries GJ, Arnold AP, Juraska JM. Sex differences in mouse cortical thickness are independent of the complement of sex chromosomes. Neuroscience 2003; 116(1): 71-5.

36. Wagner CK, Xu J, Pfau JL, Quadros PS, De Vries GJ, Arnold AP. Neonatal mice possessing an Sry transgene show a masculinized pattern of progesterone receptor expression in the brain independent of sex chromosome status. Endocrinology 2004; 145(3): 1046-9.

37. Gatewood JD, Wills A, Shetty S, et al. Sex chromosome complement and gonadal sex influence aggressive and parental behaviors in mice. J Neurosci 2006; 26(8): 2335-42.

38. Carruth LL, Reisert I, Arnold AP. Sex chromosome genes directly affect brain sexual differentiation. Nat Neurosci 2002; 5(10): 933-4.

39. Gioiosa L, Chen X, Watkins R, et al. Sex chromosome complement affects nociception in tests of acute and chronic exposure to morphine in mice. Horm Behav 2008; 53(1): 124-30.

40. Gioiosa L, Chen X, Watkins R, Umeda EA, Arnold AP. Sex chromosome complement affects nociception and analgesia in newborn mice. J Pain 2008; 9(10): 962-9.

41. McPhie-Lalmansingh AA, Tejada LD, Weaver JL, Rissman EF. Sex chromosome complement affects social interactions in mice. Horm Behav 2008; 54(4): 565-70.

42. Quinn JJ, Hitchcott PK, Umeda EA, Arnold AP, Taylor JR. Sex chromosome complement regulates habit formation. Nat Neurosci 2007; 10(11): 1398-400.

43. Smith-Bouvier DL, Divekar AA, Sasidhar M, et al. A role for sex chromosome complement in the female bias in autoimmune disease. J Exp Med 2008; 205(5): 1099-108.

44. Parker KL, Schimmer BP. Steroidogenic factor 1: a key determinant of endocrine development and function. Endocr Rev 1997; 18(3): 361-77.

45. Ikeda Y, Luo X, Abbud R, Nilson JH, Parker KL. The nuclear receptor steroidogenic factor 1 is essential for the formation of the ventromedial hypothalamic nucleus. Mol Endocrinol 1995; 9(4): 478-86.

46. Luo X, Ikeda Y, Parker KL. A cell-specific nuclear receptor is essential for adrenal and gonadal development and sexual differentiation. Cell 1994; 77: 481-90.

47. Budefeld T, Grgurevic N, Tobet SA, Majdic G. Sex differences in brain developing in the presence or absence of gonads. Dev Neurobiol 2008; 68(7): 981-95.

SE MOŠKI MOŽGANI RAZLIKUJEJO OD ŽENSKIH?

G. Majdič

Povzetek: Leta 1959, natančno pred petdesetimi leti, je bil objavljen članek z naslovom "Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig" (Organizacijski vpliv testosterona pred rojstvom na tkiva, ki urejajo spolno obnašanje pri samicah morskih prašičkov) avtorjev Phoenixa, Goya, Geralla in Younga. Pred objavo tega članka je splošno veljalo, da spolni hormoni lahko vplivajo na delovanje možganov, a obstajalo je prepričanje, da hormoni lahko vplivajo na možgane samo trenutno, tako da sprožijo določene procese kot je na primer spolno obnašanje. V nasprotju s tem prepričanjem so Phenix in sodelavci prvič pokazali dokaze, da spolni hormoni lahko dolgoročno spremenijo strukturo možganov in tako povzročijo razlike v obnašanju, ki se pokažejo šele dolgo časa po dejanskem delovanju spolnih hormonov. Raziskava Phoenixa in sodelavcev je bila zato revolucionarna, saj je postavila popolnoma novo dogmo, in zato je pričakovano imela tudi veliko nasprotnikov. Tudi sami avtorji so bili previdni, saj niso imeli odgovorov na številna vprašanja. Zato nikjer niso neposredno trdili, da hormoni zares lahko vplivajo na strukturo možganov ali centralnega živčnega sistema, temveč so raje uporabljali izraz "tkiva, ki sodelujejo pri urejanju spolnega obnašanja". Seveda je tudi ta raziskava, kot mnoga druga revolucionarna odkritja, pustila več vprašanj kot pa podala odgovorov. Avtorji te raziskave niso mogli vedeti, kdaj in kje natančno spolni hormoni vplivajo na razvoj možganov. Prav tako niso vedeli, ali na možgane vpliva neposredno testosteron ali kakšen njegov presnovni produkt. V petdesetih letih od objave članka Phoenixa in sodelavcev je bilo objavljenih na desetine ali celo stotine raziskav, ki so potrdile osnovna opažanja avtorjev in odgovorile na mnoga vprašanja. Danes tako vemo, da je vsaj pri glodavcih ženski spolni hormon estradiol (ki nastane iz testosterona lokalno v možganih) tisti, ki zares sproži razvoj moških možganov. Vemo tudi, da se lahko možgani spreminjajo pod vplivom spolnih hormonov v različnih obdobjih, pred rojstvom in po njem, v času pubertete in najverejtneje do neke mere tudi v odraslem življenju. Vseeno pa je raziskava Phoenixa, Goya, Geralla in Younga tudi po petdesetih letih še vedno aktualna in veljavna, kar potrjuje revolucionarnost njihovega odkritja.

Ključne besede: možgani; spolne razlike; steroidni hormoni; spolni kromosomi