ESTROGENS AND DEVELOPING FEMALE BRAIN: TWO SIDES OF THE COIN

LITERATURE REVIEW

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INTRODUCTION

The history of estrogens began 125 years ago when Austrian scientist E. Knauer ovariectomized rabbits and discovered preventive effect of re-implanted ovarian tissue on uterine atrophy [1]. In 1929, the American biochemist Doisy extracted from the urine of pregnant women and obtained in a crystalline form the estrogenic hormone theelin [2]. With an interval of one month, a similar work was done by the German biochemist Butenandt, who called this preparation "proginone" [3]. This hormone was later named "estrone". Ten years later Doisy and co-workers reported purification of dihydrotheelin [4], which is estradiol-17β (E2), the most powerful natural estrogen.

Estrogens, along with progesterone, play a key role in the functioning of the female reproductive system in mammals. In humans, they are responsible for many reproductive disorders and tumor growth in adolescence, reproductive age and menopause. For instance, estrogens are known to contribute to endometrial and breast cancer development [5, 6]. As for breast cancer is concerned, estrogens play dualistic role in pathogenesis and treatment of this disease. Endogenic E2 can stimulate breast cancer growth in E2-positive cases, which are successfully cured with the antiestrogenic drugs. On the other hand, due to its capability of stimulating apoptosis of breast cancer cells, a high dose synthetic estrogens can prevent and treat metastatic breast cancer in postmenopausal hysterectomized women that are resistant to long-term estrogen deprivation [7, 8].

Likewise, estrogens can exert a dualistic effect on the processes of steroid-dependent development of neuroendocrine system and behavioral structures of the brain. This work summarizes the research results by the author and his collaborators, as well as literature data on that issue.

MODIFYING EFFECT OF THE NATURAL ESTROGENS ON DEVELOPING FEMALE NEUROENDOCRINE SYSTEM AND BEHAVIOR

Hormones and growth factors play a crucial role in morphogenesis of embryo. In the fetal period of development and early postnatal life, they continue to participate in the formation and maturation of the functions of physiological systems. One of the directions of this process is hormonal control of the development of the neuroendocrine system and associated neural networks that regulate various forms of instinctive behavior such as eating, reproductive, grooming and others.

In accordance with the concept of fetal origin of adult health and diseases [9–11], an early-life events can create the risks of diseases in the late periods of life [12–15]. Insufficiency or excess of nutritional factors during pregnancy can cause epigenomic changes in the developing fetus [16]. In some cases, E2 can prevent pathological changes. Experiments on rats have shown that metabolic disorders in female offspring caused by the high-fat diet of mothers during pregnancy and early postnatal life can be prevented by E2. In this case, E2 reversed the diet-induced increase in proopiomelanocortin matrix RNA in the brain, which indicates its ability to modify the programming of the feeding system in the critical period of its development. [17].

The central nervous, endocrine and reproductive systems of humans and animals has distinct functional, anatomical and microarchitectural signs of sexual dimorphism. They are formed in the process of intrauterine and somatosexual development and are determined primarily by the genetic program. The contribution of genetic factors to the formation of sexual orientation and gender identity has been proven: homozygous twins are more likely to have the same orientation than heterozygous ones [18]. In both sexes, an immature brain is potentially capable of developing along the female type. In adulthood, it manifests as female sexual behavior and ability for pre-ovulation estrogen-induced surge of pituitary luteinizing hormone (LH), which is required for ovulation. Due to the plasticity of the brain, the implementation of the developmental program can be modified irreversibly under the influence of the hormonal, neurotransmitter and cytokine microenvironment.

In recent decades, numerous experimental and clinical studies have demonstrated the important role of steroid hormones in the epigenetic programming of reproductive functions and the hypothalamic-pituitary-adrenocortical system (HPA axis) [19–21]. Sexual differentiation of the brain (SDB) is a classic example.

There are several ways of epigenetic modification of gene expression by hormonal and other microenvironmental factors. The main ones are DNA hypermethylation (decreases gene activity)

or DNA demethylation (increases gene activity), histone acetylation (increases gene activity) and messenger RNA interference with microRNAs (20–30 nucleotides).

Even now, specialists in the field of drug toxicology at the stage of preclinical studies of potential drugs focus on detecting anatomical signs of teratogenicity of newborns, ignoring the risks of the remote in time functional disorders. Instead, many of drugs have concomitant hormonal activities, the ability to affect the synthesis, metabolism and reception of neurotransmitters, modulate membrane ion channels, and so on. Some of them are able to disrupt the process of programming physiological functions, in particular, neuroendocrine regulation of reproduction and stress reactivity. Progestin drug, which is characterized by concomitant weak androgenic activity, in pregnant women caused defeminization of behavior in the female offspring [22].

Hyperandrogenism is the most common endocrine pathology in women of fertile age [23]. In a latent or manifest form, it occurs in 10–20% of the female population and in 1.5–3.0% of all gynecological patients. Hyperandrogenism of ovarian or adrenal origin is the leading pathogenetic factor of polycystic ovary syndrome, which occurs in 6–15% of women of fertile age [24]. Hyperandrogenic condition of a pregnant woman can be the cause of polycystic ovary disease, menstrual irregularities, infertility, and sexual orientation aberration in the direction of masculinization in the female offspring. An excess of androgens in an intrauterine female fetus with a classic form of congenital hyperplasia of the adrenal cortex (deficiency of steroid 21-hydroxylase) can lead to homo- or bisexual orientation in adulthood [25, 26]. It has been shown recently that testosterone administration to pregnant rats causes not only irregular ovulation or anovulation, but also affects ovary lipid metabolism and ovarian steroidogenesis in adult female offspring [27].

The critical period of SDB, when the brain is sensitive to the programming by androgens, occurs in humans in the middle trimester of pregnancy. In rabbits, guinea pigs, sheep and other animals, it also ends before birth. However, in rodents (rats, mice, hamsters) the critical period covers the last week before birth (in rats, pregnancy lasts 21–22 days) and the first 10–12 days after it. Therefore, studies of epigenetic modification of developing neuroendocrine system are performed mainly on rodents.

While studying the mechanisms of androgen-induced anovulation, it was unexpectedly found out that the masculinization of the developing neuroendocrine system is realized not by testosterone itself, but by E2, which is derived in situ from testosterone. The high level of maternal estrogens produced by the placenta and other tissues, unlike synthetic estrogens, does not cause masculinization of the brain of the female fetus, probably due to estrogen-binding alpha-fetoprotein (AFP), a glycoprotein which is produced in high quantities by the fetal liver, and present in the fetal blood circulation. It was postulated that only natural estrogens, which are formed locally in the nervous tissue, interfere with SDB. On the other hand, clinicians are aware of cases of reversal of sexual orientation of women whose mothers took the synthetic estrogen diethylstilbestrol during pregnancy [28]. This is probably due to the low affinity of synthetic steroids for AFP and testosterone-estradiol-binding globulin, which form complexes with natural estrogens and thus deprives them of hormonal activity.

Long-standing controversy over the possible role of AFP as a protector against the masculinizing or defeminizing effect of maternal estrogens on the sexual differentiation of the developing female brain has been resolved positively in experiments on AFP-knocked mice [29]. The brain and behavior of AFP-knocked female mice were masculinized and defeminized. This pathology was prevented by embryonic treatment with the aromatase inhibitor.

Studying the long-term effects of a high dose of prenatal E2 on the female offspring we observed a disruption of estrus cycle and a decline in plasma E2 levels which were accompanied by quasi-copulative male-typical behavior. Probably, AFP is not able to bind a large amount of E2, and part of it enters the fetal brain.

The most common experimental model for studying the long-term consequences of SDB disorders is the neonatal androgenization of female rats. A single injection of a microdose of testosterone to a female in one of the first days after birth is enough for her to develop in her future life anovulatory state, infertility, alteration of estrus cycle and behavioral features of masculinization of the brain as a result of a violation of SDB. The neonatal androgen programs male-typical sexual behavior and the refractoriness of the neuroendocrine centers of the brain of a mature female to the stimulating effect of estrogens on the secretion of gonadotropins, that is, the preovulatory surge of LH.

Using an experimental model of neonatally androgenized female rats, we have studied the pathogenesis of SDB disorders. Upon reaching puberty the females developed irregular ovulation or anovulation and persistent estrus dependently of testosterone dose and timing of the hormone injections. In females 3–4 months of age, blood plasma levels of LH and progesterone decreased, E2 level decreased with a mild form of polycystic ovary and increased with a severe form. The uptake of tritiated E2 by the tissues of the hypothalamus, pituitary gland, and uterus was significantly reduced, which explains their reduced sensitivity to E2. In the hypothalamus, the content of neurotransmitters changed, in particular, a low concentration of noradrenaline and dopamine was found. Male-typical sexual behavior in neonatally androgenized females was characterized by the appearance of mounting on a receptive female. At the same time, the lordosis index, which characterizes female-typical behavior in the presence of an active male, decreased tenfold [21].

Together with our research team, we have studied the sequence of metabolic transformations of testosterone in the neuroendocrine structures of the newborn brain, and substantiated the neurochemical concept based on the key role of hypothalamic estrogens, their metabolites and noradrenaline in SDB [20, 21, 30, 31].

The first step is testosterone conversion to E2. This reaction is catalyzed by aromatase (CYP19A1, estrogen synthetase; EC 1.14.14.1. enzyme of cytochrome P450 family) [32]. Within brain, aromatase is present in the highest concentration in the hypothalamus, in particular, in the medial preoptic region of the rodent brain, which in females is identified as a neuroendocrine center for the regulation of ovarian and estrous cycles, and in males as a center for the regulation of male sexual behavior. The idea of necessity of conversion of androgens to estrogens for masculinization of the developing neuroendocrine system was proposed by B. McEwen et al. [33] and F. Naftolin [34]. It was sup-

ported by the data that only the aromatizable androgens, testosterone and androstenedione, when implanted intracerebrally or systemically to newborn female rats, are capable of causing anovulation at puberty. In our experiments, SDB disorders could be prevented by the simultaneous administration of testosterone to newborn females with aromatase inhibitors.

Already in the first days after the administration of testosterone to newborn females, in the medial preoplptic region, the disappearance or weakening of the sexual dimorphism of aromatase activity, the content of sex-specific proteins and biogenic monoamines is found. These changes indicate an epigenetic reprogramming of the developing female brain towards masculinization.

It was found that neonatal introduction of testosterone leads to an increase in the concentration of noradrenaline in the hypothalamus of newborn female rats, and this effect is prevented by the concomitant use of steroid aromatase inhibitors [35, 36]. Testosterone-induced increase in the hypothalamic concentration of noradrenaline is mediated by catecholestrogens, hydroxylated derivatives of estrogens originated from testosterone. The newly formed 2α- and 4α-hydroxylated estrogens compete with noradrenaline for the use of the enzyme catechol-O-methyltransferase in the methylation reaction and thus slow down the metabolism of noradrenaline i.e. contribute to the growth of its content in the hypothalamus. This effect of catecholestrogens is confirmed by an increase in the concentration of noradrenaline in the tissues of the hypothalamus of newborn female rats treated with catecholestrogens. On the other hand, inhibition of catecholamine synthesis in the hypothalamus by α-methyl-p-tyrosine produces an effect similar to that of aromatase inhibitors, preventing the masculinizing effect of exogenous testosterone on the developing brain.

Exploring the ability of a number of catecholestrogens administered to newborn females intracerebrally or systemically, to disrupt SDB we found that only 4α-E2 is capable of causing defeminization of the neuroendocrine system in the form of anovulatory syndrome. It is noteworthy that an increase in the concentration of noradrenaline in the hypothalamus of newborn females caused by the administration of tropolone, catechol-O-methyltransferase inhibitor, not accompanied by the administration of testosterone or estrogens, does not lead to the development of anovulatory state [37].

Thus, estrogens/catecholestrogens (4α-E2) and noradrenaline are the major neurochemical determinants of testosterone-induced programming of neuroendocrine control of ovulation in the females, and they co-operate with each other. At this stage of individualistic development, the synaptic system has not yet been formed. Therefore, in the case of SDB, noradrenaline acts not as a neurotransmitter, but as an inducer of differentiation of immature neurocytes (Figure). This diagram also reflects the mechanisms of dysfunction of the HPA axis of female rats as a result of early androgenization. It is expressed in changes in sex-specific characteristics of corticosteroid secretion and adrenocortical response to an acute stress.

As for the aforementioned ability of diethylstilbestrol and, possibly, other xenoestrogens to modify sexual differentiation of behavior, it is possible that it does not require the participation of natural catechol estrogens.
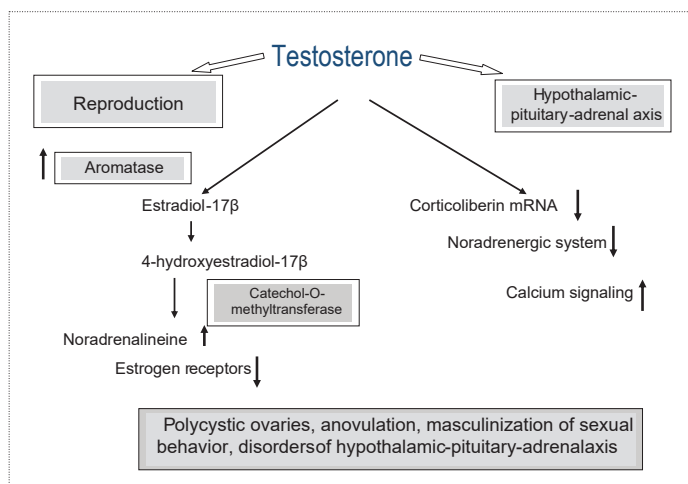

Figure. Neurochemical mechanisms of neuroendocrine disorders resulting from early-life androgenization of female rat

EARLY-LIFE EFFECTS OF THE XENOESTROGENS ON DEVELOPING FEMALE BRAIN

Xenoestrogens are non-steroidal substances of anthropogenic or natural origin, which have a weakly expressed estrogenic activity. These include bisphenol A, parabens, some pesticides, and others. Phytoestrogens, that is, xenoestrogens of plant origin, represent a specific group. Among them, the most pronounced estrogenic activity is shown by coumestrol, daidzein, genistein.

Feeding to mothers of female pups with xenoestrogen-rich soy supplements during 3–21 postnatal days (100 mg/kg body weight at genistein equivalent) led to disorders of neurondecrine regulation of reproductive system: disruption of estrous cycles with concomitant changes in hormonal profile, egg pathology, deterioration of the egg implanting and reducing offspring number [38]. Neonatal xenoestrogens interfere with SDB. Application of genisteine or coumestrol in the early postnatal life of rats and mice caused disruption of the estrus cycle, ovulation, implantation and development of the embryo [39, 40]. But neither gametes nor embryos were injured, which is confirmed by the normal development of early embryos after transferring to normal females.

The results of a number of studies support the postulate of functional teratology, according to which the most vulnerable developing physiological system with regard to endocrine disruptors is neuroendocrine regulation of reproduction, behavior, and HPA axis [21, 41]. Such changes may be based on modifications of the brain microstructure and hormone receptors in the hypothalamus, amygdala and other neuroendocrine areas of the brain.

One of the most common xenoestrogens is bisphenol A, which is present in many plastic products. This endocrine disruptor binds to E2 receptor and initiates hormonal signaling. Bisphenol A even at low expositional dose is capable of transferring across the human placenta in active unconjugated form [42].

In female rats born to mothers who received oral bisphenol A at daily doses of 2.5 µg/kg or 25.0 µg/kg on gestation days 6–21, the expression of estrogen receptors ERα and ERβ in the mediobasal hypothalamus and amygdala changed. Due to perinatal administration of low doses of bisphenol A to female rats, the expression of estrogen receptor in the sex-dimorphic

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medial-preoptic nuclei and periventricular nuclei of the hypothalamus reduced [43–45]. However, it should be noted that in the question of the early effect of bisphenol A on the microstructure of sex-dimorphic areas of the developing brain, there is no generally accepted point of view, which encourages further research.

Arcuate nucleus of the brain is involved in neuroendocrine control of hormonal homeostasis. Noteworthy are a decrease in the expression of muscarinic receptor-3 and adiponectin receptor-1, as well as changes in the expression of serotonin and cholecystokinin receptors, in this nucleus in female rats exposed to bisphenol A for the last 4 days before birth and in the first week of postnatal life [46].

Neuroendocrine and behavioral effects of perinatal exposure to low doses of bisphenol A include disturbance of estrous cyclicity and decreased response of the LH to oophorectomy in adult female rats [47, 48], alteration of maternal behavior in mice [49] and rats [50], anxiety and spatial memory in female mice [51].

Even extremely small doses of bisphenol A, lower than those allowed for humans, used perinatally in rats, disrupted SDB. Female rat offspring exposed to bisphenol A at daily dose of 25 µg/kg body weight from gestation day 7 to postnatal day 22 showed altered spatial learning in a water maze test indicating masculinization of developing brain [52]. In the absence of anatomical evidence of teratogenic effects, bisphenol A caused an inversion of the size of the blue spot of the rat brain, which is normally larger in females, and behavior in the open field [53]. The perinatal effect of low doses of bisphenol A on mice was also manifested in the attenuation of sex-specific of behavior in the open field, and in addition, in the disappearance of sexual differences in the number of tyrosine hydroxylase-positive neurons in the preoptic area of the brain by reducing it in females [54].

According to our recent research, administration of low dose of bisphenol A to rats during the last week of pregnancy leads to lowering of blood E2 levels and masculinization of sexual behavior in adult female offspring, which, however, is not accompanied by its defeminization.

HPA axis dysfunction is known to be associated with some age-related psychiatric, cognitive, and neurodegenerative disorders [55]. Therefore, the state of HPA system in prenatally exposed to bisphenol A individuals is of some interest. A study of long-term effects of perinatal exposure to low dose of bisphenol A on female offspring demonstrated an increase in basal corticosterone levels in the blood and a decrease in glucocorticoid receptor expression in the hypothalamus. The rats demonstrated impaired spatial memory, anxious behavior, and a weakened corticosterone response to stress (swimming), and a lack of reduction in glucocorticoid receptor expression, which usually occurs under stress.

There are also medical and psychological data on changes in behavior in girls due to prenatal exposure to bisphenol A [56, 57], which may be caused by modification of HPA axis. High concentrations of bisphenol A r in the urine of pregnant women correlated with increased levels of cortisol in the saliva of three-month-old girls. Instead, the stress-reactivity of HPA axis in girls was weakened, which indicates disruption of sex-dimorphic peculiarities of HPA axis function [58].

POSSIBLE ROLE OF ESTRADIOL IN THE FEMALE BRAIN DEVELOPMENT IN PUBERTY

It is assumed that, regardless of gender, brain development is programmed in a female pattern. So far, no convincing experimental and clinical evidence has been presented that during the intrauterine development of the female fetus or in the early postnatal period, estrogens are involved in the programming of neuroendocrine regulation and female behavior. Nevertheless, the high content of AFP in the blood of the fetus and early postnatal life does not exclude the possibility of the participation of estrogens in the feminization of the female brain during puberty, when the amount of protein decreases sharply down to trace levels. The article by Bakker J, Baum MJ [59] mentions research results from Steward and Cygan about enhancement of female-typical behavior of gonadectomized male and female rats treated with E2 during puberty (postnatal days 30–40). Besides, E2 induces the female pattern of progesterone receptor in developing hypothalamus. It is proposed that the feminizing action of estradiol normally occurs in genetic females between birth and the age of puberty [59].

CONCLUSION

Thus, in early life, estrogens play a dualistic role in programming the neuroendocrine system and behavior, depending on the sex of the individualistic and the period of individualistic development.

Conflict of interest

The author of this review declares no conflict of interest regarding commercial or financial relations with organizations and/or individuals.

REFERENCES/ЛІТЕРАТУРА

1. The estrogen elixer: A History of hormone replacement in America. Baltimore: The Johns Hopkins Press. 2007
2. Veler, C.D., Thayer, S., Doisy, E.A. "The preparation of the crystallinefollicular ovarian hormone: theelin." J Biol Chem 87 (1930): 357–71.
3. Butenandt, A. "Uber progynon ein krytalisiertes exualhormon." Die Naturwissenschaften 17 (1929): 879.
4. Huffman, M.N., Thayer, S.A., Doisy, E.A. "The isolation of a-dihydrotheelin from human placenta." J Biol Chem 133 (1940): 567–71.
5. Reznikov, A. "Hormonal impact on tumor growth and progression." Exp Oncol 37.3 (2015): 162–72.
6. Gibson, D.A., Simitsidellis, I., Collins, F., Saunders, P.T.K. "Androgens, oestrogens and endometrium: a fine balance between perfection and pathology." J Endocrinol 246.3 (2020): R75-R93.
7. Haddow, A., Watkinson, J.M., Paterson, E., Koller, P.C. "Influence of synthetic oestrogens on advanced malignant disease." Br Med J 2.4368 (1944): 393–8.
8. Jordan, V.G. "The new biology of estrogen-induced apoptosis applied to treat and prevent breast cancer." Endocr Relat Cancer 22.1 (2015): R1–31.
9. Barker, D.J. "The developmental origins of chronic adult disease." Acta Paediatr Suppl 93 (2004): 26–33.
10. Bakker, J., De Mees, C., Douhard, Q., et al. "Alpha-fetoprotein protects the developing female mouse brain from masculinization and defeminization by estrogens." Nat Neurosci 9.2 (2006): 220–6.
11. De Boo, H.A., Harding, J.E. "The developmental origins of adult disease (Barker) hypothesis." Aust NZ J Obstet Gynaecol 46 (2006): 4–14.
12. Барабой, В.А. Фізіологія, біохімія і психологія стресу / В.А. Барабой, О.Г. Резніков. – К: Інтерсервіс, 2013.
Baraboy, V.A., Reznikov, O.G. Physiology, biochemistry and psychology of Stress. Kyiv. Interservice (2013).
13. Perets, O.V., Sergienko, L.Y., Seliukova, N.Y., et al. "Potentiating effect of excessive consumption of fructose on obesity development in offspring of mothers stressed during pregnancy." Problemy Endokrynnoi Patologii 4 (2016): 83–90.
14. Vaiserman, A.M. "Epigenetic programming by early-life stress: evidence from human populations." Dev Dyn 244.3 (2015): 254–65.
15. Wang, Y., Wu, H., Sun, Z.S. "The biological basis of sexual orientation: How hormonal, genetic, and environmental factors influence to whom we are sexually attracted." Front Neuroendocrinol 55 (2019): 100798.
16. Goyal, D., Limesand, S.W., Goyal, R. "Epigenetic responses and the developmental origins of health and disease." J Endocrinol 242.1 (2019): T105–T119.
17. Carrillo, B., Collado, P., Díaz, F., et al. "Physiological and brain alterations produced by high-fat diet in male and female rats can be modulated by increased levels of estradiol during critical periods of development." Nutr Neurosci 22.1 (2019): 29–39.
18. Ganna, A., Verweij, K.J.H., Nivard, M.I.G., et al. "Large-scale GWAS reveals insights into the genetic architecture of same-sex sexual behavior." Science 365.6456 (2019): eaat7693.
19. Dorner, G. Hormones and brain differentiation. Amsterdam. Elsevier Sci (1976).
20. Резников, А.Г. Половые гормоны и дифференциация мозга / А.Г. Резников. – К.: Наукова думка, 1982.
Reznikov, A.G. Sex hormones and the brain differentiation. Kyiv. Naukova dumka (1982).
21. Резніков, О.Г. Перинатальне програмування розладів ендокринних функцій та поведінки / О.Г. Резніков. – К.: Наукова думка, 2019.
Reznikov, O.G. "Perinatal programming of disorders of endocrine functions and behavior." Kyiv. Naukova dumka (2019).

22. Reinisch, J.M., Sanders, S.A. "Prenatal gonadal steroidal influences on gender-related behavior." Progr Brain Res 61 (1984): 407–16.

23. Nordenström, A., Falhammar, H. "Management of endocrine disease: Diagnosis and management of the patient with non-classic CAH due to 21-hydroxylase deficiency." Eur J Endocrinol 180.3 (2019): R127–R145.

24. Татарчук, Т.Ф. Оптимізація функції яєчників та метаболічного статусу при синдромі полікістозних яєчників / Т.Ф. Татарчук, Н.В. Косей, Т.М. Тутченко, М.І. Гламазда // Репродуктивна ендокринологія. – 2020. – №2 (52). – С. 18–22.
Tatarchuk, T.F., Kosei, N.V., Tutchenko, T.M., Hlamazda, M.I. "Optimization of ovarian function and metabolic status in syndrome of polycystic ovaries." Reprod Endocr 2.52 (2020): 18–22.

25. Dittmann, R.W., Kappes, M.E., Kappes, M.H. "Sexual behavior in adolescent and adult females with congenital adrenal hyperplasia." Psychoneuroendocrinol 17 (1992): 153–70.

26. Meyer-Bahlburg, H.F., Dolezal, C., Baker, S.W., New, M.I. "Sexual orientation in women with classical or non-classical congenital adrenal hyperplasia as a function of degree of prenatal androgen excess." Arch Sex Behav 37.1 (2008): 85–99.

27. Abruzzese, G.A., Heber, M.F., Ferreira, S.R., et al. "Prenatal androgen exposure affects ovarian lipid metabolism and steroid biosynthesis in rats." J Endocrinol 247.3 (2020): 239–50.

28. Ehrhardt, A.A., Meyer-Bahlburg, F.L., Rosen, L.R. "Sexual orientation after prenatal exposure to exogenous estrogen." Arch Sex Behav 14 (1985): 57–77.

29. Bakker, J., De Mees, C., Douhard, Q., et al. "Alpha-fetoprotein protects the developing female mouse brain from masculinization and defeminization by estrogens." Nat Neurosci 9.2 (2006): 220–6.

30. Nosenko, N.D., Reznikov, A.G. "Sexual differentiation of the brain as a manifestation of its plasticity." Neurophysiology 33.2 (2001): 125–34.

31. Reznikov, A.G. Hormone-neurotransmitter imprinting in the neuroendocrine control of reproduction. New York. Harwood Academic Publishers (1994).

32. Simpson, E., Santen, R.J. "Celebrating 75 years of oestradiol." J Mol Endocr 55.3 (2015): T1–T20.

33. McEwen, B., Coirini, H., Westlund-Danielsson, A., et al. "Steroid hormones as mediators of neural plasticity." J Steroid Biochem Mol Biol 39 (1991): 223–32.

34. Naftolin, F. "Brain aromatization of androgens." J Reprod Med 39.4 (1994): 257–61.

35. Reznikov, A.G., Nosenko, N.D. "It is possible that noradrenaline is the biogenic monoamine responsible for androgen-dependent sexual brain differentiation." Exp Clin Endocrinol 81.1 (1983): 91–3.

36. Reznikov, A.G., Nosenko, N.D., Tarasenko, L.V. "Prevention of the anovulatory syndrome and testosterone-induced rise in catecholamine level in the hypothalamus of newborn rats with steroid aromatase inhibitors." Exp Clin Endocrinol 90.2 (1987): 185–9.

37. Reznikov, A.G., Nosenko, N.D., Tarasenko, L.V. "Augmentation of the sterilizing effect of neonatal androgenization with tropolone, a catechol-O-methyltransferase inhibitor, in female rats." Neuroendocrinology 52.5 (1990): 455–9.

38. Чистякова, Е.Е. Гормональний стан та плідність самок щурів, які в неонатальний період отримували фітоестрогени / Е.Е. Чистякова, О.В. Сомова, Н.О. Карпенко // Вісник проблем біології і медицини. – 2011. – №1 (83). – С. 122–124.
Chistyakova, E.Y., Somova, O.V., Karpenko, N.O. "The hormonal state and fertility of female rats phitoestrogenized during suckling." Visnyk Problem Biologii i Medytsyny 1.87 (2011): 122–4.

39. Whitten, P.L., Lewis, C., Naftolin, F. "A phytoestrogen diet induces the premature anovulatory syndrome in lactationally exposed female rats." Biol Reprod 49 (1993): 1117–21.

40. Jefferson, W.N., Padilla-Banks, E., Goulding, E.H., et al. "Neonatal exposure to genistein disrupts ability of female mouse reproductive tract to support embryo development and implantation." Biol Reprod 80 (2009): 425–31.

41. Резніков, О.Г. Довгостроковий вплив внутрішньоутробного опромінення самців щурів дибутилфталатом на різні частини репродуктивної системи / О.Г. Резніков, О.В. Сачинська, Л.І. Полякова [та ін.] // Фізіологічний журнал. – 2019. – №65 Т. 3 (Додаток). – С. 100–101.
Reznikov, O.G., Sachynska, O.V., Polyakova, L.I., et al. "Long-term effects of prenatal exposure of male rats to dibutylphthalate on various parts of the reproductive system." Fiziologichnyi Zhurnal 65.3 Suppl. (2019): 100–1.

42. Balakrishnan, B., Henare, K., Thorstensen, E.B., et al. "Transfer of bisphenol A across the human placenta." Am J Obstet Gynecol 202.4 (2010): 393.e1–7.

43. Cao, J., Rebuli, M.E., Rogers, J., et al. "Prenatal bisphenol A exposure alters sex-specific estrogen receptor expression in the neonatal rat hypothalamus and amygdala." Toxicol Sci 133.1 (2013): 157–73.

44. Rebuli, M.E., Cao, J., Sluzas, E., et al. "Investigation of the effects of subchronic low dose oral exposure to bisphenol A (BPA) and ethinyl estradiol (EE) on estrogen receptor expression in the juvenile and adult female rat hypothalamus." Toxicol Sci 140.1 (2014): 190–203.

45. Arambula, S.E., Belcher, S.M., Planchart, A., et al. "Impact of low dose oral exposure to bisphenol A (BPA) on the neonatal rat hypothalamic and hippocampal transcriptome: A CLARITY-BPA Consortium Study." Endocrinology 157.10 (2016): 3856–72.

46. Roepke, T.A., Yang, J.A., Yasrebi, A., et al. "Regulation of arcuate genes by developmental exposures to endocrine-disrupting compounds in female rats." Reprod Toxicol 62 (2016): 18–26.

47. Talsness, C., Fialkowski, O., Gericke, C., et al. "The effects of low and high doses of bisphenol A on the reproductive system of female and male rat offspring." Congen Anomal 40 (2000): S94–S107.

48. Rubin, B.S., Murray, M.K., Bamassa, D.A., et al. "Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels." Environ Health Perspect 109.7 (2001): 675–80.

49. Palanza, P., Howdeshell, K.L., Parmigiani, S., vom Saal, F.S. "Exposure to a low dose of bisphenol A during fetal life or in adulthood alters maternal behavior in mice." Environ Health Perspect 110 Suppl. 3 (2002): 415–22.

50. Della Seta, D., Minder, I., Dessi-Fulgheri, F., Farabollini, F. "Bisphenol-A exposure during pregnancy and lactation affects maternal behavior in rats." Brain Res Bull 65.3 (2005): 255–60.

51. Ryan, B.C., Vandenbergh, J.G. "Developmental exposure to environmental estrogens alters anxiety and spatial memory in female mice." Horm Behav 50.1 (2006): 85–93.

52. Hass, U., Christiansen, S., Boberg, J., et al. "Low-dose effect of developmental bisphenol A exposure on sperm count and behaviour in rat." Andrology 4.4 (2016): 594–607.

53. Kubo, K., Arai, O., Omura, M., et al. "Low dose effects of bisphenol A on sexual differentiation of the brain and behavior in rats." Neurosci Res 45 (2003): 345–56.

54. Rubin, B.S., Lenkowski, J.R., Schaeberle, C.M., et al. "Evidence of altered brain sexual differentiation in mice exposed perinatally to low, environmentally relevant levels of bisphenol A." Endocrinology 147.8 (2006): 3681–91.

55. De Kloet, E.R., Joëls, M., Holsboer, F. "Stress and the brain: from adaptation to disease." Nature Rev Neuroscience 6 (2005): 463–75.

56. Harley, K.G., Gunier, R.B., Kogut, K., et al. "Prenatal and early childhood bisphenol A concentrations and behavior in school-aged children." Environ Res 126 (2013): 43–50.

57. Rochester, J.R., Bolden, A.L., Kwiatkowski, C.F. "Prenatal exposure to bisphenol A and hyperactivity in children: a systematic review and meta-analysis." Environ Intern 114 (2018): 343–56.

58. Giesbrecht, G.F., Ejaredar, M., Liu, J., et al. "Prenatal bisphenol A exposure and dysregulation of infant hypothalamic-pituitary-adrenal axis function: findings from the APrON cohort study." Environ Health 16.1 (2017): 47.

59. Bakker, J., Baum, M.J. "Role for estradiol in female-typical brain and behavioral sexual differentiation." Front Neuroendocrinol 29.1 (2008): 1–16.

ESTROGENS AND FEMALE DEVELOPING BRAIN: TWO SIDES OF THE COIN

Literature review

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The review highlights current views and hypotheses on the pathogenetic role of natural and xenoestrogens in the disorders of programming of neuroendocrine regulation of reproduction, alaptation, and various forms of instinctive behavior (reproductive, eating, parental, etc.) in the perinatal period of development of the female brain. Catecholestrogens, which are formed in the brain as a result of sequential metabolic conversions of testosterone, are involved in exogenous or endogenous androgen-induced defeminization of hypothalamic control of ovulation in early female ontogenesis. In the research on female animals with a knocked out gene of alpha-fetoprotein, the protective role of this protein against the possible pathogenic effect of placental estrogens on the developing brain of female fetuses was proved. The damaging effect of phytoestrogens (genistein, coumestrol) in the early postnatal period on the formation of ovulatory cycles has been shown. Evidence from studies in rodents and other animal species, supported by clinical observations, indicate the potential damaging effect of exposure to low levels of environmental xenoestrogens on the developing brain, in particular on its sexual differentiation and the hypothalamic-pituitary-adrenal axis. The potential hazard of the perinatal exposure to low doses of bisphenol A for the formation of estrogen receptors in the hypothalamus and amygdala of the female brain, sexual behavior and ovulation is discussed. Special attention is paid to the possible physiological role of natural estrogens in the formation of the female neuroendocrine system during puberty. It was concluded that in the early stages of female life, estrogens play a different role in the programming of the neuroendocrine system and behavior, depending on the period of individual development.

Keywords: estrogens, xenoestrogens, bisphenol A, alpha-fetoprotein, hyperandrogenism, sex differentiation, brain development, reproduction, female, rat.

ЕСТРОГЕНИ ТА ЖІНОЧИЙ МОЗОК, ЩО РОЗВИВАЄТЬСЯ: ДВІ СТОРОНИ МЕДАЛІ

Огляд літератури

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Огляд висвітлює сучасні погляди та гіпотези щодо патогенетичної ролі природних та ксеноестрогенів у порушеннях програмування нейроендокринної регуляції репродукції, адаптації та різних форм інстинктивної поведінки (репродуктивна, харчова, батьківська та ін.) у перинатальний період розвитку жіночого мозку. Катехолестрогени, які утворюються в головному мозку в результаті послідовних метаболічних перетворень тестостерону, беруть участь в індукованій екзогенними або ендогенними андрогенами дефемінізації гіпоталамічного контролю овуляції в ранньому жіночому онтогенезі. У дослідженнях на самках тварин із нокаутованим геном альфа-фетопротеїну була доведена захисна роль цього білка від можливого патогенного впливу плацентарних естрогенів на мозок плодів самок. Показано патогенну дію фітоестрогенів (геністеїн, куместрол) у ранній постнатальний період на формування овуляторних циклів. Дані досліджень на гризунах та інших видах тварин, підкріплені клінічними спостереженнями, вказують на потенційний пошкоджуючий ефект низьких рівнів ксеноестрогенів навколишнього середовища на мозок, що розвивається, зокрема на його статеву диференціацію та систему «гіпоталамус-гіпофіз-надниркові залози». Обговорюється потенційна небезпека перинатального впливу низьких доз бісфенолу А для формування рецепторів естрогенів у гіпоталамусі та мигдалинах жіночого мозку, сексуальної поведінки та овуляції. Особлива увага приділяється можливій фізіологічній ролі природних естрогенів у формуванні жіночої нейроендокринної системи в період статевого дозрівання. Зроблено висновок, що на ранніх стадіях жіночого життя естрогени відіграють різну роль у програмуванні нейроендокринної системи та поведінки залежно від періоду індивідуального розвитку.

Ключові слова: естрогени, ксеноестрогени, бісфенол А, альфа-фетопротеїн, гіперандрогенізм, статева диференціація, розвиток мозку, репродукція, самка, щур.

ЭСТРОГЕНЫ И РАЗВИВАЮЩИЙСЯ ЖЕНСКИЙ МОЗГ: ДВЕ СТОРОНЫ МЕДАЛИ

Обзор литературы

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Обзор освещает современные взгляды и гипотезы относительно патогенетической роли природных и ксеноэстрогенов в нарушениях программирования нейроэндокринной регуляции репродукции, адаптации и различных форм инстинктивного поведения (репродуктивного, пищевого, родительского и др.) в перинатальном периоде развития женского мозга. Катехолэстрогены, которые образуются в головном мозге в результате последовательных метаболических превращений тестостерона, участвуют в индуцированной экзогенными или эндогенными андрогенами дефеминизации гипоталамического контроля овуляции в раннем женском онтогенезе. В исследованиях на самках животных с нокаутированным геном альфа-фетопротеина была доказана защитная роль этого белка от возможного патогенного воздействия плацентарных эстрогенов на мозг плодов самок. Показано патогенное действие фитоэстрогенов (генистеин, куместрол) в раннем постнатальном периоде на формирование овуляторных циклов. Данные исследований на грызунах и других видах животных, подкрепленные клиническими наблюдениями, указывают на потенциальный повреждающий эффект низких уровней ксеноэстрогенов окружающей среды на развивающийся мозг, в частности на его половую дифференциацию и систему «гипоталамус-гипофиз-надпочечники». Обсуждается возможная опасность перинатального воздействия низких доз бисфенола А для формирования рецепторов эстрогенов в гипоталамусе и миндалинах женского мозга, полового поведения и овуляции. Особое внимание уделяется возможной физиологической роли природных эстрогенов в формировании женской нейроэндокринной системы в период полового созревания. Сделан вывод, что на ранних стадиях жизни женского организма эстрогены играют разную роль в программировании нейроэндокринной системы и поведения в зависимости от периода индивидуального развития.

Ключевые слова: эстрогены, ксеноэстрогены, бисфенол А, альфа-фетопротеин, гиперандрогенизм, половая дифференциация, развитие мозга, размножение, самка, крыса.