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Contemporary insight into long-lasting endocrine and behavioral consequences of stress in adolescents and preventive potential of the drugs

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Abstract. The review presents literature data and the results of three-year experimental studies of the Department of Endocrinology of Reproduction and Adaptation of the State Institution «V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine» on the impact of chronic stress during puberty (pubertal stress) on the reproductive and hypothalamic-pituitary-adrenocortical (HPA) axis, as well as the preventive potential of pharmacological agents for its consequences. The relationship between the HPA and the hypothalamic-pituitary-gonadal (HPG) axes and the long-term consequences of pubertal stress are considered. Under the selected experimental conditions (immobilization of rats for 1 hour per day for 30-45 days after birth), chronic pubertal stress can lead to adverse long-term sex-specific effects on the reproductive and HPA axis of adult rats. In adult males who have undergone pubertal stress, while maintaining normal levels of testosterone in the blood plasma, the quantitative and qualitative indicators of the spermogram deteriorate, spermatogenesis is disrupted, and oxidative stress in the gonads increases. Chronic pubertal stress can cause a decrease in the basal level of corticosterone. In adult females, no negative long-term effects of chronic pubertal stress on the studied indicators of the HPA axis and the reproductive system were found, with the exception of an increase in the concentration of lipid peroxidation products in the ovaries, which indicates their lower vulnerability compared to males. Activation of the gamma-aminobutyric acid-ergic receptor with phenibut (amino-phenylbutyric acid hydrochloride) before stress sessions worsens the quantitative and qualitative indicators of the spermogram in adulthood, reduces the level of testosterone in the blood serum, and increases oxidative stress in the gonads of male rats compared to stressed animals. This indicates the risk of side effects when using phenibut in adolescents for the prevention of stress and anxiety-neurotic states. Oral administration of vitamin E before stress sessions in pubertal rats slightly improved the qualitative parameters of the spermogram of adult animals, reducing the percentage of pathological forms of spermatozoa. In addition, the level of corticosterone in the blood plasma after acute 1-hour stress was significantly higher than in those stressed only, although it did not reach the control level. In animals that were administered melatonin before stress sessions, the studied parameters did not differ from those that were exposed to pubertal stress only.

Keywords: stress, puberty, rats, gonad, testosterone, sexual behavior, oxidative stress, phenibut, vitamin E, melatonin.

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Introduction

The link between endocrine system disorders and stress has remained relevant for decades. This is fueled by ongoing wars, the accelerated pace of life, social tension, environmental pollution, everyday problems, unemployment, and other etiological factors. Moreover, the relevance of studying the effects of stress in Ukraine has increased during the COVID-19 pandemic and especially since the onset of Russian aggression in 2022. Numerous chemical toxicants – environmental pollution from combustion products, explosives, lubricants and fuels, heavy metals, etc. – are added to these stress-inducing factors.

One of the severe consequences of stress is post-traumatic stress disorder. Stress disorder researchers primarily focus on mental deviations such as obsessive-compulsive disorder, nightmares, depression, irritability, insomnia, and emotional detachment. However, stress also has psychosomatic complications in the form of hormonal, reproductive, and metabolic disorders, which have been studied to a much lesser extent [1]. The reproductive system is particularly vulnerable to stress [2-5].

Research into the effects of stress on adolescents is a key area of medical research. Puberty is associated with hormonal changes, internal experiences, and increased vulnerability to psychoemotional and other stressful factors. According to sociological studies, 25% of Ukrainian schoolchildren experience panic attacks during bombings and shelling, accompanied by feelings of fear and helplessness. About half of them experience nightmares and feelings of anger [6-8].

Even in times of peace, children are often subjected to psychological or physical abuse, which causes distress. Clinical and experimental data demonstrate mainly psychological and neurological consequences of stress during puberty: social maladjustment, aggressiveness, cognitive impairment, nervousness, anxiety, depression [9-14]. However, the long-term consequences of pubertal stress on the reproductive system and sexual behavior have been studied to a much lesser extent.

Response of the HPA and HPG axes to stressful stimuli

The classical paradigm of stress, proposed by G. Selye [15] as a universal stereotypical reaction of the body to any endogenous or exogenous psychoemotional or physical factors that disrupt homeostasis (general adaptation syndrome), has continuously evolved over the decades [16-17]. H. Selye identified the activation of corticosteroid secretion by the adrenal glands during stress as a central link in the formation of nonspecific resistance of the body. The trigger factor in this process is the activation of the sympathoadrenal system, the role of which in the body's response to life-threatening circumstances was substantiated by W. Cannon.

In the modern understanding of stress, the neuroendocrine system, or more specifically, the HPA axis, is given primary importance [18]. Over time, the term «stress» has come to denote not only the body's systemic response but also stereotypical changes at the cellular, subcellular (mitochondrial, endoplasmic reticulum stress), and molecular levels. At the molecular level, stress is manifested by the expression of *c-fos* and other immediate-action genes, heat shock proteins (chaperones), and interleukins. The concept of oxidative/nitrosative stress has emerged. It is impossible to imagine a stress response without changes in the activity of the nervous, immune, cardiovascular, endocrine, and other physiological systems.

Moderate chronic stress, known as eustress, trains the body's defenses, while extremely strong physical, psychoemotional, infectious, and other pathogenic stimuli induce distress. Distress progresses through stages, and the outcome is recovery or, in the case of irreversible pathological changes, death.

In mammals, chronic distress is accompanied by a limitation of reproductive potential, which is significant for survival of the species [19]. The HPG and HPA axes, and reactive oxygen species (oxidative stress) play a key role in disrupting reproductive functions during stress [20-22]. Decreased fertility in women is caused by disruptions in cyclic processes in the ovary, including anovulation, and is manifested by hypo- or amenorrhea. In men, libido weakens, sperm quality deteriorates, and testosterone secretion decreases. Experiments on rats showed that the cause of changes in testosterone secretion after acute immobilization stress is a change in the expression of genes for steroidogenesis in Leydig cells [23]. In female rats, chronic stress modulates estrous cycles, disrupts the maturation of oocytes and impairs their morphology [24].

The role of hypothalamic corticotropin-releasing hormone (CRH) and opioid peptides in stress-induced changes in reproductive functions

has been known for decades [25-27]. Over time, the flow of inducers and mediators to stress significantly expands, as well as the brain structures like limbic system – the amygdala and hippocampus.

The interaction of the HPA and HPG axes is ensured by a number of physiologically active substances – CRH of the paraventricular nuclei of the hypothalamus, norepinephrine, neuropeptide Y and serotonin, which are created in the brain stem, as well as glutamate in medial preoptic area, neuropeptide Y and opioids – in the arcuate and medial preoptic nuclei of the hypothalamus, vasopressin – in the supraoptic nuclei. Opioids, cannabinoids and gamma-aminobutyric acid stimulate in males and females the neurosecretory cells of the medial preoptic part of the hypothalamus, which synthesize luteinizing hormone-releasing hormone. In males, the secretion of luteinizing hormone (LH) changes, and in females, the pulsation of LH secretion becomes slower and its amplitude decreases. These reactions are subject to sex differences. For example, in males, the injection of neuropeptide Y into the third ventricle of the brain suppresses the secretion of pituitary LH [28], while in females stimulates it. The role of the kisspeptin family of arcuate nuclei in the interactions between the HPA and HPG axes axis is being actively studied [29, 30].

Induced by stressful stimuli, the release of norepinephrine from the synapses of neurons, which contacts the paraventricular nuclei of the hypothalamus, initiates the activation of CRH and vasopressin-synthesizing neurons, and thus activates the HPA axis. Therefore, due to the fact that their axons interact with LH releasing hormone-producing neurosecretory cells of the medial preoptic nuclei, the secretion of LH releasing hormone and pituitary LH is stimulated. This is joined by arginine vasopressin and opioids, in particular, beta-endorphin, which is separated from the proopiomelanocorticotropin molecule during the processing adrenocorticotropic hormone. After introducing arginine vasopressin into the third ventricle of the brain, a significant decrease in the secretion of testosterone at the background of an increase in the adrenocorticotropic hormone level and corticosterone in the blood plasma of males is observed [31].

The relationship between the HPA and HPG axes is two-sided. According to our data, androgenization of female rats by subcutaneous implantation of silastic capsules with testosterone resulted in a weakening of the HPA axis response to one-hour immobilization stress or the introduction of norepinephrine bitartrate into the third ventricle of the brain [32]. Androgen antagonism in relation to the stress reactivity of the HPA axis is also confirmed by other researchers [33]. Estrogens affect the neurosecretory cells of the hypothalamus that secrete CRH. In the promoter zone of the CRH gene, estrogen response elements are present, which directly stimulate the synthesis of CRH. The direct stimulating effect of estradiol on the adrenal cortex, in particular, its sensitivity to adrenocorticotropic hormone, has been shown [34]. Apparently, the higher level of estrogen in the blood of females in comparison to that of males the main reason for the greater intensity of the HPA axis in response to stress [35].

Another pathway of interaction between the HPA and HPG axes is realized by the influence of estrogens and androgens on the synthesis of arginine vasopressin in the supraoptic nuclei of the hypothalamus with subsequent stimulation of adrenocorticotropic hormone secretion by this neuropeptide.

HPA and HPG axes responses to stressful stimuli in adolescence

One of the manifestations of hormonal changes during puberty in humans and animals is increased emotional lability, sensitivity of the endocrine and nervous systems to a large number of stressful stimuli, especially to psychoemotional stimuli. An increased response of the HPA axis to stress, compared to adults, was first shown by L. Goldman et al. [36] and then confirmed by other researchers [37-40]. An indicator of HPA axis hyperreactivity is an increase in the level of glucocorticoids in the blood (cortisol in humans, guinea pigs, dogs, corticosterone in rats, rabbits and other rodents). For example, after restraint stress in 30-day-old rats, the amplitude of the increase in blood corticosterone levels is higher, and the period of return to basal levels is longer than in adults [41].

The aforementioned changes in HPG axis function in response to stress in adult males and females are even more pronounced during puberty. This includes inhibition of gonadotropic hormone and sex steroid secretion, a reduction in LH pulsation, and prolactin hypersecretion. The trigger for these changes is a stress-induced increase in CRH secretion.

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Consequences of stress in adolescence

Disturbances in the hormonal balance during stress and after the end of stress can negatively impact the reproductive system [20]. Particularly dangerous are the critical periods of formation of reproductive functions, first of all, neuroendocrine regulation of reproduction and sexual behavior. Activation of the HPA axis during critical periods of development may have long-term or irreversible effects on the reproductive function of an adult organism [42].

Adolescence is the second and final critical period for the development of the HPA and HPG axes, following the prenatal period. It is known that stress during puberty affects sexual maturation differently in boys and girls: accelerates in girls and delays in boys. However, in girls, severe chronic distress not only does not lead to early menarche, but, on the contrary, can cause anovulation and primary amenorrhea of hypothalamic origin [43,44], which causes infertility and is accompanied by polycystic ovary syndrome in almost 60% of cases [45].

The pathogenesis of reproductive disorders has been studied primarily in laboratory animals. Various stress methods and hormonal administration have been used. Administration of corticosterone, an effector of the HPA axis, via drinking water to rats from postnatal days 30 to 58, which corresponds to puberty, induced neuroendocrine and somatic changes, including changes in sex hormone levels, expression of neuropeptide Y receptor genes in the ventromedial nuclei of the hypothalamus, associated with appetite and hunger, and decreased reproductive organs weights [46]. These changes were significantly more pronounced in males. In females, two-week intravenous administration of CRH, starting on postnatal day 28, delayed puberty [47].

Immobilization of male rats for 6 hours per day for 15 days, starting from late puberty (40 days), during sexual behavior testing in 45-day-old rats, prolonged the latency period of the first mounting, but increased copulatory activity. This was associated with a delay in testicular maturation, an increase in basal levels of corticosterone, prolactin, and testosterone, and a decrease in plasma LH levels. Stress for 60 days led to impaired spermatogenesis [48-50]. Solitary housing in a cage (emotional stress) for 25-50 days of postnatal life was associated with increased copulatory activity in 90-day-old males [51]. Social isolation of female mice from day 25 to day 60 weakened receptive behavior, which was not restored upon return to the social group [52]. Changes in dopamine levels in the brain likely play a role in the pathogenesis of reproductive disorders induced by pubertal stress [53].

The Department of Endocrinology of Reproduction and Adaptation of the SI «V.P. Komisarenko Institute of Endocrinology and Metabolism of the NAMS of Ukraine» studied the long-term impact of pubertal stress on the reproductive system of rats and the possibilities of pharmacological prevention of disorders in case of their detection [42, 54-60]. The main results of this study are presented below.

The experiments were conducted on rats of local breeding with a fixed date of birth. As a stress model, restriction in plastic containers for 1 hour per day from 30 to 45 days after birth was used. The onset of puberty was recorded by the descent of the testicles into the scrotum or the vaginal opening.

Pubertal stress did not affect the timing of puberty in males. Instead, it delayed female sexual maturation by more than 3 days, which is consistent with studies in another stress model [61] and experiments with the administration of CRH [47]. Male golden hamsters have responded to pubertal stress by delaying puberty [62]. Thus, in rodents, the effect of stress on the timing of puberty is the opposite of that in humans.

The weight of the body, testes, ovaries and accessory sexual glands did not differ in 6-month-old animals of both sexes of the control and experimental groups, as did the level of testosterone in the serum of males. With the exception of slight vacuolization of spermatogenic epithelial cells, no significant morphological changes were detected in the testes. However, a decrease in the relative number of late spermatids was observed in stressed animals. Similar, but more pronounced changes in the number of mature spermatids occurred in a study on another model of pubertal stress [49]. According to C.T. Ribeiro et al. [63], pubertal stress causes a redistribution of the density of the tubular and intertubular compartments in the testes.

Adult stressed males differed from controls in 30% decrease in the number of spermatozoa in the epididymis and a 2.4-fold slowdown in gamete respiration (redox processes). But sperm motility remained at the level of control animals. The number of sperm with increased body tortuosity (the so-called «soft» forms) increased by a third. The detected signs of pathospermia may be the cause of reduced fertility of stressed males.

One of the possible causes of pathospermia may be a shift in the pro-antioxidant balance in the testicles. Therefore, in the gonads of adult males who underwent pubertal stress, the content of lipid peroxidation products was determined. The content of malondialdehyde in the testicles exceeded the control values by an average of one and a half times, and diene conjugates by almost twice, which indicates oxidative stress. But in another experiment, these data were not confirmed, which is the basis for further research.

Female rats in our experiments turned out to be less vulnerable to the pathogenic effect of pubertal stress. They preserved the phase structure and periodicity of the estrous cycle. No morphological changes and the number of follicles in the ovaries were detected. But the content of malondialdehyde in the ovaries of experimental animals increased almost twice. Signs of oxidative stress were detected in the serum of two-month-old female rats as a result of pubertal stress [64].

Testing of sexual behavior in male rats stressed during adolescence revealed a significant increase in motivational and copulatory behavior compared to non-stressed animals. The median latency period to first mount on a receptive female was reduced by an average of eight and a half times, and the latency period for intromission was also reduced. These changes occurred against the background of unchanged serum testosterone levels and the preservation of a normal response of the HPG axis to androgen receptor blockade with flutamide. This does not indicate hormonal nature of changed behavior, but rather is a consequence of a violation of the formation of sexual behavior at the level of neuroendocrine structures of the brain.

Longer-term stressing of males during puberty, moreover, in a different stress model, revealed a weakening of the motivational component of male sexual behavior in male rats, but an increase in copulatory activity [51], which is consistent with our data.

Female-type sexual behavior was studied in castrated males, which were previously injected with estradiol diacetate and progesterone, in the presence of a normal male. Lordosis reactions were absent in stressed males, which indicates the refractoriness of the brain to the stimulating effect of female sex hormones, i.e., the preservation of the masculine type of sexual differentiation of the brain.

Pubertal stress reduced the level of corticosterone in the blood plasma of adult males by 45%, but not in females. The response of HPA axis to one-hour immobilization remained normal. E.P. Harris et al. [11] also did not find the effect of pubertal stress on HPA axis reactivity in rats of both sexes in the swimming test.

A decrease in basal corticosterone levels in males stressed during puberty was also found by Mancini GF et al. [65]. This phenomenon was not observed in other studies [66-68]. However, these studies used different stress models.

Trying to cope with adolescent stress

A logical continuation of the study of the delayed negative effects of pubertal stress was the attempt to prevent them with pharmacological agents with different mechanisms of action. Initially, the gamma-aminobutyric acid receptor agonist phenibut (amino-phenylbutyric acid hydrochloride) was chosen for this purpose, because of its anxiolytic activity and the ability to mitigate the body's response to stressful events. In adult rats that at puberty received phenibut intragastrically at a dose of 100 mg/kg bw before stress sessions, the number of sperm in the epididymis decreased by 21% compared to stressed rats. Compared to the control group, these animals had a tendency to increase the number of immobile sperm and a significant decrease in the number of their normal forms. At the same time, the level of testosterone in the blood serum decreased by 46% compared to control males and more than twice compared to stressed ones. This was accompanied by the development of oxidative stress, as evidenced by the activation of lipid peroxidation in the testes. Thus, the use of phenibut resulted in an effect opposite to that expected. The data obtained on the side effects of phenibut indicate the risk of their long-term manifestations when using phenibut in adolescents for the prevention of stress and anxiety-neurotic states. On the other hand, phenibut caused a moderate mitigating effect on changes in some indicators of sexual behavior.

It is appropriate to note here that a single intense combined stress on the 40th day after birth with restress a week later causes morphological disorders in the testicles in two-month-old male rats, and the use of a serotonin reuptake inhibitor - fluoxetine for three weeks after restress only worsens these disorders [69].

It is known that changes in sexual behavior and testicular morphology induced by chronic stress are

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associated with the pathogenic effect of oxidative stress [21, 70]. Therefore, it was considered appropriate to use antioxidant agents, namely, vitamin E and melatonin, to prevent these effects in pubertal male rats. An oil solution of vitamin E was administered intragastrically at a dose of 50 mg/kg bw before stress sessions. The use of vitamin E caused a significant decrease in the percentage of pathological forms of sperm in adult males compared with both stressed during puberty and control animals. Therefore, vitamin E exerted a moderate protective effect on sperm quality. The level of testosterone in the blood serum remained normal. The level of corticosterone after 1-hour immobilization was significantly elevated in comparison with stressed animals.

In animals that were administered melatonin before stress sessions, the studied indicators did not differ from those that were exposed to puberty stress alone.

Conclusions

Under the selected experimental conditions, chronic pubertal stress can lead to adverse long-term sex-specific effects on the reproductive system and hypothalamic-pituitary-adrenocortical axis of adult rats. In adult males who have undergone pubertal stress, while maintaining normal testosterone levels in the blood plasma, quantitative and qualitative (reduction in the respiratory index and an increase in the number of «soft» forms of sperm) spermogram parameters may deteriorate, spermatogenesis may be disrupted, and oxidative stress in the gonads may increase. Chronic pubertal stress may cause a decrease in basal corticosterone levels. In adult females, no negative long-term effects of chronic pubertal stress on the studied indicators of the hypothalamic-pituitary-adrenocortical axis and reproductive system were detected, with the exception of an increase in the concentration of products of lipid peroxidation in the ovaries, which indicates their lower vulnerability compared to males. Activation of the gamma-aminobutyric acid-ergic system with phenibut before stress sessions worsens the quantitative and qualitative indicators of spermatogram in adulthood, reduces the level of testosterone in serum and increases oxidative stress in the gonads of male rats compared to stressed animals. Administration of vitamin E before stress sessions slightly improved the qualitative indicators of spermatogram in adult animals. In adult animals that received vitamin E combined with adolescent stress, the blood plasma level of corticosterone after acute 1-hour stress was significantly higher than in those stressed alone. In animals that were administered melatonin before stress sessions, the studied indicators did not differ from those that were exposed to puberty stress alone.

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Abbreviations

CRH – corticotropin-releasing hormone
HPA – hypothalamic-pituitary-adrenocortical
HPG – hypothalamic-pituitary-gonadal
LH – luteinizing hormone

СУЧАСНИЙ ПОГЛЯД НА ТРИВАЛІ ЕНДОКРИННІ ТА ПОВЕДІНКОВІ НАСЛІДКИ ПУБЕРТАТНОГО СТРЕСУ ТА ПРЕВЕНТИВНИЙ ПОТЕНЦІАЛ ЛІКАРСЬКИХ ЗАСОБІВ

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Резюме. В огляді наведено дані літератури та результати трьохрічних експериментальних досліджень відділу ендокринології репродукції та адаптації стосовно впливу хронічного стресу під час статевого дозрівання (пубертатний стрес) на репродуктивну та гіпоталамо-гіпофізарно-адренокортикальну системи (ГГАС), а також превентивного потенціалу фармакологічних засобів щодо його наслідків. Розглянуто взаємовідносини між ГГАС і гіпоталамо-гіпофізарно-гонадною системою (ГГГС) та довготривалі наслідки пубертатного стресу. За обраних експериментальних умов (іммобілізація щурів по 1 год на день протягом 30-45 днів після народження), хронічний пубертатний стрес може призводити до несприятливих довгострокових статево-специфічних впливів на репродуктивну та ГГАС системи дорослих щурів. У дорослих самців, що зазнали пубертатного стресу, на тлі збереження нормального вмісту тестостерону в плазмі крові, погіршуються кількісні та якісні показники спермограми, порушується сперматогенез і посилюється оксидативний стрес у статевих залозах. Хронічний пубертатний стрес може спричиняти зниження базального вмісту кортикостерону. У дорослих самиць не виявлено негативних віддалених ефектів хронічного пубертатного стресу на досліджувані показники стану ГГАС та репродуктивної системи, за винятком збільшення концентрації продуктів перекисного окислювання ліпідів у яєчниках, що вказує на їхню меншу вразливість порівняно з самцями. Активація ГАМК-ергічної системи фенібутом (гідрохлорид амінофенілмасляної кислоти) перед сеансами стресування погіршує кількісні та якісні показники спермограми в дорослому віці, зменшує рівень тестостерону в сироватці крові та посилює оксидативний стрес у гонадах самців щурів порівняно зі стресованими тваринами. Це вказує на ризик побічних ефектів при застосуванні фенібуту в підлітків із метою профілактики стресових і тривожно-невротичних станів. Введення вітаміну Е в шлунок перед сеансами стресування щурів пубертатного віку дещо покращувало якісні показники спермограми дорослих тварин, зменшуючи відсоток патологічних форм сперматозоїдів. Крім того, рівень кортикостерону в плазмі крові після гострого 1-годинного стресу був у них вірогідно вищим, ніж у лише стресованих, хоча і не досягав рівня контролю. У тварин, яким перед сеансами стре-

сування вводили мелатонін, досліджувані показники не відрізнялись від тих, які зазнали лише пубертатного стресу.

Ключові слова: стрес, пубертація, щури, гонади, тестостерон, статева поведінка, оксидативний стрес, фенібут, вітамін Е, мелатонін.

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