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STUDY OF NEUROTROPIC EFFECTS OF SEX STEROIDS ON AN EXPERIMENTAL MODEL OF ACUTE STRESS

© Mikhail S. Nekrasov[1], Sarng S. Pyurveev[1, 2], Albina S. Nekrasova[1], Irina I. Mogileva[1], Yulia A. Konstantinova[1], Elena Yu. Bok[1], Vera A. Kuzina[1], Michael M. Zabezhinsky[1], Aleftina A. Kravtsova[1], Ksenia V. Morozova[1], Ruslan I. Glushakov[1]

[1] Saint Petersburg State Pediatric Medical University. 2 Lithuania, Saint Petersburg 194100 Russian Federation
[2] Institute of Experimental Medicine. 12 Academician Pavlov str., Saint Petersburg 197022 Russian Federation

Contact information: Sarng S. Pyurveev — Assistant Professor of the Department of Pathological Physiology with a course in Immunopathology. E-mail: dr.purveev@gmail.com ORCID: https://orcid.org/0000-0002-4467-2269 SPIN: 5915-9767

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Abstract. ***Introduction.*** Mental disorders associated with the consequences of stressors represent a serious healthcare problem. Neurosteroids, including progesterone and its metabolite allopregnanolone, play an important role in regulating emotions and stress responses. This suggests their therapeutic potential in correcting post-stress anxiety and depressive disorders. ***The aim*** of this study was to investigate the stress-protective effects of progesterone in an animal model of post-traumatic stress disorder (PTSD) induced by predator exposure. ***Materials and methods.*** Forty male rats were randomly divided into four groups: control, predator stress, predator stress + progesterone, and predator stress + sulpiride (an antipsychotic). The animals' behavior was tested using a battery of behavioral tests including the elevated plus maze, the open field test, and the forced swim test. ***Results.*** The results demonstrated that the administration of progesterone significantly reduced anxiety and depressive-like behavior compared to the group exposed to predator stress. Rats treated with progesterone showed increased locomotor and exploratory activity in the open field test, spent more time in the open arms of the elevated plus maze, and exhibited decreased immobility time in the forced swim test. These effects were comparable to those observed with sulpiride, highlighting the anxiolytic and antidepressant properties of progesterone. ***Conclusion.*** The results confirm the potential use of progesterone as a therapeutic agent in the treatment of stress-related disorders and emphasize its modulatory influence on the brain's GABAergic system. Further research is necessary to elucidate the underlying mechanisms and to optimize treatment protocols.

Keywords: post-traumatic stress disorder, progesterone, neurosteroids

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ИЗУЧЕНИЕ НЕЙРОТРОПНЫХ ЭФФЕКТОВ ПОЛОВЫХ СТЕРОИДОВ НА ЭКСПЕРИМЕНТАЛЬНОЙ МОДЕЛИ ОСТРОГО СТРЕССА

© Михаил Сергеевич Некрасов[1], Сарнг Саналович Пюрвеев[1, 2], Альбина Сергеевна Некрасова[1], Ирина Ивановна Могилева[1], Юлия Абрамовна Константинова[1], Елена Юрьевна Бок[1], Вера Александровна Кузина[1], Михаил Маркович Забежинский[1], Алефтина Алексеевна Кравцова[1], Ксения Владимировна Морозова[1], Руслан Иванович Глушаков[1]

[1] Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, д. 2, Российская Федерация
[2] Институт экспериментальной медицины. 197022, г. Санкт-Петербург, ул. Академика Павлова, д. 12, Российская Федерация

Контактная информация: Сарнг Саналович Пюрвеев — ассистент кафедры патологической физиологии с курсом иммунопатологии. E-mail: dr.purveev@gmail.com ORCID: https://orcid.org/0000-0002-4467-2269 SPIN: 5915-9767

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Резюме. ***Введение.*** Психические расстройства, связанные с последствиями стрессоров, представляют собой серьезную проблему для здравоохранения. Нейростероиды, в том числе прогестерон и его метаболит аллопрегнанолон, играют важную роль в регуляции эмоций и стрессовых реакций, что позволяет предположить их терапевтический потенциал в коррекции постстрессовых тревожных и депрессивных расстройств. ***Целью*** данного исследования было изучение стресс-протекторного действия прогестерона в животной модели посттравматического стрессового расстройства (ПТСР), вызванного воздействием хищника. ***Материалы и методы.*** Сорок крыс-самцов были случайным образом разделены на четыре группы: контроль, стресс от хищника, стресс от хищника + прогестерон и стресс от хищника + сульпирид (антипсихотик). Поведение животных тестировалось в батарее поведенческих тестов с использованием «приподнятого крестообразного лабиринта», теста «открытое поле» и теста на принудительное плавание. ***Результаты*** показали, что введение прогестерона значительно снижало тревожность и депрессивно-подобное поведение по сравнению с группой переживших стресс предъявления хищника. Животные, получавшие прогестерон, демонстрировали повышенную локомоцию и исследовательское поведение в тесте «открытое поле», большее время нахождения в открытых руках в «приподнятом крестообразном лабиринте» и уменьшение времени неподвижности в тесте на принудительное плавание. Эти эффекты были сопоставимы с теми, что наблюдались при использовании сульпирида, что подчеркивает анксиолитические и антидепрессивные свойства прогестерона. ***Заключение.*** Полученные результаты подтверждают возможность использования прогестерона в качестве терапевтического средства для лечения расстройств, связанных со стрессом, и подчеркивают его модулирующее воздействие на ГАМК-эргическую систему мозга. Необходимы дальнейшие исследования для выяснения основных механизмов и оптимизации протоколов лечения.

Ключевые слова: посттравматическое стрессовое расстройство, прогестерон, нейростероиды

INTRODUCTION

Psychogenic disorders, widespread in modern society, prove to become a significant burden on healthcare system, especially if people are present in dangerous zones of war action, local conflicts, natural and manmade disasters [1]. Meanwhile health conditions associated with psychological trauma, stress and anxiety are included in the number of the most prevalent mental disorders which result in a significant economic burden for the system of healthcare. WHO-sponsored studies have demonstrated that the spread of mood disorders has dramatically increased over the past decade: patients diagnosed with depression and anxiety account for 4.4% and 3.6% of the adult population [2]. Modern therapeutic approaches, including medication, are effective in relieving the symptoms of anxiety disorders and manifestations of post-traumatic stress disorder (PTSD) in a large proportion of patients [2]. However, the main problem of modern pharmacological correction of these disorders, alongside a significant number of side effects, is a marked reduce of the severity of special individual symptoms and of the clinical picture of a disease in general, but not the elimination of the cause of the disease [3]. With the awareness of the multidimensional and comorbid nature of mental illness it becomes evident that anxiety-phobic spectrum disorders are phenomena that exceed modern diagnostic potential and known pathophysiological mechanisms [4].

Sex steroid hormones play a basic role not only in reproductive biology, but also participate in maintaining the homeostasis of the nervous system, while many steroid hormones are also synthesized de novo in the central and peripheral nervous system out of cholesterol molecules by means of neuronal cells [5]. In the central nervous system, neurosteroids perform various functions: regulation and metabolism of GABA, glutamate and other mediators, certain stages of neurogenesis such as neuronal growth, formation and growth of dendrites, myelination, synapse formation and neurones survival. Thus, sex steroids are involved not only in the coordination of reproductive health, but also in the regulation of emotions, mood and social behavior [6].

Progesterone and its neuroactive metabolite allopregnanolone ((3α,5α)-3-hydroxypregnan-20-one or 3α,5α-THP) play a key role in the response to stress action [7]. Several studies have demonstrated that depressive and anxious behavior is associated with changes in progesterone and/or allopregnanolone levels, with stated normalization of these neurosteroid levels when treated with anxiolytics or antidepressants [8]. The data obtained serve as the pathogenetic basis for the use of progesterone and its metabolites in the treatment of anxiety spectrum disorders. For example, brexanolone, being an analogue of endogenous allopregnanolone, was approved by the FDA in 2019 as a medication for the treatment of severe post-partum depression. However, it is suggested that the use of progesterone and its neuroactive metabolites has therapeutic potential and may be effective in the treatment of other mental disorders, regardless of gender [9].

THE AIM OF THE STUDY

To analyze the stress-protective properties of progesterone in an animal model of post-traumatic stress disorder.

MATERIALS AND METHODS

General experimental design

An experimental investigation was conducted to study the stress-protective effect of progesterone. To simulate a traumatic event, the classical method of imaging a predator was implemented. In our study, the tiger python (*Python molurus*) was used as a predator (stressor). Based on behavioral tests, a pronounced change in behavioral patterns was recorded in rats of each group: freezing, huddling, prolonged and altered grooming.

Maintenance of animals, formation of experimental groups and randomization

40 white mongrel male rats weighing 240–250 grams, from the Rappolovo laboratory animal nursery (Leningrad Region) were taken for the study. The animals were kept under standard

Table 1

Description of experimental groups

Group name	Group Description	Number of laboratory animals, n	Study drug/placebo
Con	Group of animals receiving intraperitoneal injection of solvent	10	0.9% NaCl
PS	Group of animals exposed to vital stress	10	0.9% NaCl
PS+P	Group of animals exposed to vital stress receiving progesterone	10	progesterone
PS+S	Group of animals exposed to vital stress receiving an antipsychotic drug	10	sulpiride

Table 2

Pharmacological agents used in the study

INN	Trade name, dosage form (manufacturer, country)	Method of administration, dose	
Progesterone	Prolutex, oil solution (Angelini, Switzerland)	Subcutaneously, 8 mg/kg	Within 10 days before the day of stress exposure
Sulpiride	Egnonyl, solution for injection (Sanofi-Aventis, France)	Intraperitoneal, 10 mg/kg	Once every 30 minutes. before stress

Table 3

Behavior of animals in the "Open field" test after exposure to vital stress

Index		Con	PS	PS+P	PS+S
Locomotion	n	20.5±3.5	16.40±4.2 *	21.2±3.2#	12.5±1.3 #
Sniffing	n	2.4±1.67	6.9±0.59*	3.3±0.9#	2.1±0.9
Movement in place	n	4.8±1.2	2.20±0.6*	3.4±1.2	2.6±1.2*
Grooming	n	2.9±1.5	5.5±1.9*	6.43±2.8*	1.9±0.9*#
Vertical racks	n	1.51±0.77	1.71±0.87	1.8±0.8	0.5±0.1*#
Racks With emphasis	n	7.00±0.7	6.2±1.87	8.1±1.5#	4.4±1.2*#
Mink research	n	7.60±1.45	16.40±1.3*	15.2±2.1*#	2.3±1.5 * #

Note. * p ≤0.05 — significant differences compared to the control group; # p ≤0.05 — significant differences compared to animals that experienced a traumatic event; n — number of acts, M±m.

vivarium conditions, 5 animals were placed in plastic cages with free access to water and granulated food. After a 14-day quarantine, the experimental animals were divided using a random number generator into 4 equal experimental equal groups (Table 1, 2):

Model of vital stress

Modeling of the stress effect was carried out by placing a group of rodents (n=10) into a transparent plastic container with a perforated cover this container was placed opposite the terrarium in which a food object (rat) was placed next to the tiger python; the process of the attack and consumption of the food object was observed by rats from the plastic container [1].

Behavioral tests

To record changes in emotional-motor patterns of the control and experimental groups, a battery of behavioral tests was used.

The "Elevated Crucified Maze" installation is designed to study the behavior of rodents under the conditions of variable stress (with a free choice of comfortable conditions) and allows to assess the level of anxiety of the animal (by preference for darkness/light, fear of highness, severity and dynamics of "peeking out" behavior).

Open field test. The technique makes it possible to record a whole range of behavioral components: the motor activity of rodents, level of anxiety, the degree of expression of indicative and exploratory behavior.

Forced swimming (behavioural despair, Porsolt test) is a universally recognized test for assessing depressive behavior in rodents. Mice or rats are used as experimental animals. Each animal, one at a time, is placed in a cylinder with water, with a diameter of 18 to 38 cm, 40 cm high, i.e. large enough for rats or mice to swim freely in it. The water temperature is maintained within 22–23 °C. The time during which the animal hangs motionless in the water, i.e., demonstrates symptoms of depression, the duration of the first episode of active swimming, the total swimming time, and the number of dives are recorded. The longer time of immobility, the shorter the total swimming time and the duration of the first episode of active swimming, the higher the level of depression, and vice versa. Testing time is 6 minutes.

Ethical rules and regulations

The work was carried out in accordance with the ethical principles established by the Basel Declaration (signed in Basel on November 30, 2010), the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (adopted in Strasbourg on March 18, 1986 and confirmed in Strasbourg on June 15, 2006), and approved by the Local ethical committee.

Statistical data processing

Descriptive statistics methods for quantitative characteristics included estimation of the mean (x), standard error of the mean (SE) and root mean square error (m), median

Table 4

Behavior of animals in the elevated plus maze test and the Porsolt test after exposure to vital stress

Index		Experimental group			
		Con	PS	PS+P	PS+S
Behavior of animals in the elevated plus maze test after exposure to vital stress					
Time is up your sleeve	t	87.86±3.12	10.14±0.93*	26.57±0.71 #	22.57±1.28 #
Time on your sleeve	t	202.3±3.04	286.7±0.86 *	268.4±0.71 #	273.6±1.67 #
Behavior of animals in the Porsolt test after exposure to vital stress					
Active swimming	t	242.8±6.21	201.3±9.39*	251.5±5.93 #	190.8±6.70
Passive swimming	t	72.33±0.98	91.83±1.74*	76.17±2.78 #	64.17±1.40 #
Immobilization	t	44.33±5.64	67.00±8.72*	36.67±5.36 #	105.0±6.39 #

Note. * p ≤0.05 — significant differences compared to the control group; # p ≤0.05 — significant differences compared to animals that experienced a traumatic event; t — time of act (seconds); M±m.

(Me), and confidence interval boundaries. Data are presented as arithmetic mean ± standard error of the mean or median with confidence interval boundaries. The distribution of the trait in the group was performed based on Monte Carlo methods. To compare the control and experimental groups with a regular distribution, the student's test was used. The statistical significance of differences was assessed using the GraphPad Prism 8.0 software package. Of the nonparametric tests, the Kruskal–Wallis's test was also used to compare the groups. The critical level of significance of the null statistical hypothesis (about the absence of significant differences or factor influences) was taken equal to 0.05.

RESULTS

Our study was carried out in two stages: at the first stage, changes in emotional and exploratory behavior were recorded between intact control (n=10) and animals that were exposed to vital stress; at the second stage, the influence of pharmacological agents on emotional — exploratory behavior and on animals that had experienced the effects of vital stress was analysed.

After exposure to vital stress, a number of patterns of emotional, exploratory and motor behavior was recorded in the Open Field test. The behavior of the studied animals was characterized by a significant (p ≤0.05) decrease in the number of sniffs in animals that had experienced vital stress, which is assessed as a manifestation of exploratory behavior and a decrease in the negative emotionality of the "novelty" of the open field (Table 3). In animals of the experimental group, the "Open Field" test recorded a significant decrease in locomotion time (p ≤0.05) relative to the control group of animals, which was assessed as a decrease in locomotor behavior. However, in animals that survived the effect of a vital stress, a significant increase of acts of grooming and exploration of minks, which characterizes an increase of exploratory behavior was observed.

Important data were obtained after administering progesterone and sulpiride to animals that had survived a traumatic event. Intraperitoneal administration of sulpiride significantly reduced the following behavioral acts: locomotion and movement on a place, as well as the number of acts of grooming and exploration of minks, both in the control group and in the group of animals that survived exposure to vital stress (p ≤0.05). Changes in behavioral patterns were also observed after intraperitoneal administration of progesterone to animals that had experienced a traumatic event. A positive effect on the "emotionality" zone was characterized by a significant increase in sniffing (p ≤0.05), an increase in locomotor activity was also observed (p ≤0.05). Also attracts attention that a simultaneous increase in the reaction of exploration of minks, both relative to the control and relative to animals that experienced a traumatic event, and a decrease in acts of grooming, may indicate the controversial effect of intraperitoneal administration of progesterone on the areas of "exploratory" behavior.

When analyzing the influence of a traumatic event in the "Elevated Cruciform Maze" test, experimental animals showed a significant increase (p ≤0.05) in the time spent in the closed arm of the device, which indicates an increase in the level of anxiety in comparison with the control group of animals.

Intraperitoneal administration of the studied pharmacological agents demonstrated the tranquilizing (anxiolytic) effect of both the oil solution of progesterone and the reference drug, sulpiride. The tranquilizing effect consisted of reducing the time the experimental animals spent in the closed arm of the installation and, accordingly, increasing the time the animals spent in the open arm, which may indicate a decrease in the level of anxiety (Table 4).

When analyzing the influence of a traumatic event by the Porsolt test, experimental animals showed increased depres-

sion compared to animals in the control group. In animals that survived an encounter with a predator, there was a statistically significant increase in the time of immobilization ($p \leq 0.05$) compared to the control group.

THE DISCUSSION OF THE RESULTS

The antidepressant effect of progesterone is to normalize the time of behavioral patterns in animals that have experienced stressors, while the use of the drug compared has shown its more pronounced tranquilizing effect, since the time of immobilization, i.e., immobility of animals increased 2 times relative to intact control and 1.5 times relative to animals that experienced stress ($p \leq 0.05$). The introduction of progesterone had a milder effect (Table 4).

Progesterone and its metabolites act on target cells through 2 signaling pathways: classical (canonical, genomic pathway) and non-classical (non-canonical, non-genomic pathway). In the classical signaling pathway, both progesterone and 5α-dihydroprogesterone (5α-DHP) bind with intracellular progesterone receptors (PR), which dimerize and translocate to the nucleus, where they regulate the expression of certain genes [10]. Non-genomic pathway regulation involves activation of membrane progesterone, G protein-coupled receptors (mPR) and membrane progesterone receptor component 1 (PGRMC1), which leads to activation of the MAPK signaling pathway, protein kinase C (PKC) pathway and PI3K/Akt. Unlike other progesterone metabolites, allopregnanolone is a positive modulator of γ-aminobutyric acid type A (GABAA) receptors and is also a ligand for mPR [11].

Due to its small size and lipid solubility, circulating progesterone easily crosses the blood-brain barrier (BBB) by free transmembrane transport and diffuses throughout the nervous tissue. The work of Pardridge W.M., Mietus L.J. demonstrated that 83% of 3 h — labeled progesterone was found in the ipsilateral hemisphere of the rat brain 15 seconds after its administration in an aqueous solution into the common carotid artery. These data serve as justification for the intraperitoneal method of administering progesterone [12].

Progesterone is a neurosteroid because it can be synthesized locally in the nervous system by almost all types of neuronal cells [13]. Also, progesterone received from the systemic circulation can be sequentially metabolized into its neuroactive 5α-reduced metabolites: 5α-reductase metabolizes to 5α-dihydroprogesterone (5α-DHPROG), 3α-hydroxysteroid dehydrogenase (3α-HSD) to 3α-5α-THPROG. Thus, the pool of progesterone and its metabolites in the central nervous system depends on (1) its peripheral synthesis, absorption and accumulation in the brain; (2) its local synthesis; and (3) metabolic features [5].

Depending on its level of concentration in the brain, progesterone can differently activate certain receptors: higher doses of progesterone can saturate nuclear receptors (PRs) while activating membrane mPRs. However, high doses may also cause receptor desensitization or decrease in their expression, saturation of pathways leading to neuroactive metabolites, or induction of inactivating metabolic pathways.

Progesterone and its metabolites are involved in neurohumoral regulation during the body's response to acute stress. Droogleever Fortuyn et al demonstrated that in situations of acute stress the adrenal glands secrete much more allopregnanolone, while its synthesis in brain structures also increases [14].

Currently, accurate data on the mechanism of the neuroprotective action of progestogens are at the stage of accumulating scientific knowledge. Data on the systemic anti-inflammatory effect of progestogens, for example, in patients with rheumatoid arthritis have been accumulated. It has been stated that long-term administration of progesterone leads to activation of the expression of some tissue-specific anti-inflammatory genes. An increase in BDNF expression in the hippocampus in response to allopregnanolone administration has also been described. However, most likely the main contribution to the neuro- and stress-protective effects of progestogens is realized through non-genomic mediated actions [10]. Neurosteroids affect the excitability of nerve cells by increasing the permeability of ion channels through membrane ionotropic receptors such as $GABA_A$ and NMDA receptors, and the stereoselectivity of steroids plays a decisive role in binding with both receptors [15].

Thus, progestogens primarily exert proGABAergic effects with insignificant involvement in the metabolic process of other neurotransmitters and demonstrate sedative, hypnotic, anesthetic, anxiolytic and anticonvulsant properties [3]. We obtained similar pharmacological effects in the results of our work in the model of acute stress of predator presentation. The neuroprotective effects of progesterone have also been studied in models of traumatic brain injury, the therapeutic effects being a reduction in cerebral edema, neuroinflammation and BBB dysfunction, which promoted neuronal survival and functional recovery [16]. An effective cerebroprotective dose of progesterone (8 mg/kg) used in rodent models of both traumatic brain injury and stroke results in plasma progesterone concentrations of 150 nM, a similar dose that we have used in our work [17]. In experimental models of stroke, progesterone levels in brain structures reached 100 nM 2 hours after the last administration of progesterone; these levels are compatible with the activation of progesterone receptors. In our future work, we also plan to determine the levels of progesterone and its metabolites in brain structures (Kd=1 nM) [18, 19].

The neuroprotective effects of progesterone and its derivatives have been studied in various experimental models of neurodegenerative diseases. Brinton laboratory et al Researchers from Briton laboratory treated ovariectomized female 3xTg-AD

mice (a model of Alzheimer's disease) with progesterone alone or in combination with estradiol for 3 months, which specifically attenuated Tau hyperphosphorylation [20–22]. Researchers have demonstrated that neuroactive progesterone derivatives enhance neurogenesis, improve cognitive functions and memory, reduce neuroinflammation and levels of beta-amyloid accumulation in 3xTgAD mice. However, an increasing number of publications demonstrate great importance of allopregnanolone in the processes of neurogenesis [23]. At the cellular level, allopregnanolone reduced the severity of NMDA-mediated excitotoxicity and, in general, reduced presynaptic glutamate release and Ca^{2+} influx through activation of GABA receptors in response to activating stimuli. At the tissue level, this progesterone metabolite activated the induction of proliferation of neural progenitor cells, increasing the survival of newly formed neurons; decreased amyloid generation and microglial activation, increased oligodendrogenesis [24].

Thus, our data confirm that despite the evidence for the neuroprotective effects of allopregnanolone, our experimental findings support the possibility of using progesterone as a stress-preventive drug. Subsequent clinical tasks include specifying the indications, determining the dose, duration and timing of progesterone administration.

CONCLUSIONS

1. Long-term introduction of progesterone (8 mg/kg) for 10 days before exposure to stressor has pronounced anxiolytic, antidepressant effects according to the results of a series of behavioral tests in the predator presentation stress model.

2. These effects appear to be associated with the action of progesterone and its neuroactive metabolites on the GABA system of brain of the experimental animals.

3. Progesterone and its metabolites may provide an alternative direction of research to explore potential methods of treatments of anxiety and depression in patients who had experienced psychotraumatic events.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Experiments with animals were carried out in accordance with international rules (Directive 2010/63/EU of the European Parliament and of the Council of the European Union of September 22, 2010 on the protection of animals used for scientific purposes).

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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