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Research Article

Chronic mental stress in early ontogenesis increased risks of development for chemical and non-chemical forms of addiction

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BACKGROUND: Exposure to acute or chronic stress contributes to the occurrence of various disorders of the central nervous system, psycho-emotional sphere, as well as increases the risks of development of various forms of addiction.

AIM: The aim of the study is analyze the influence of maternal deprivation on voluntary alcohol consumption in adolescents and to determine the degree of the signs of compulsive behavior in experimental animals.

MATERIALS AND METHODS: Thirty male Wistar rats were taken in the research. A maternal deprivation model was carried out from day 2 to day 12 of the postnatal period (MD). Compulsivity (compulsive tendency) was evaluated in the ball burial test. Voluntary alcoholization with 10% ethyl alcohol solution in a two-bottle test was employed. Level of progesterone in blood plasma was determined by enzyme- immune analyses.

RESULTS: Changes in the level of progesterone in blood plasma in MD and control group of animals were detected. In the test of two bottles 10% of ethanol solution presented on days 2 and 3, statistically significant differences in consumption were determined in contrast to the control group. In the test of balloon diapering, MD group of animals showed a statistically proved significant increase in compulsiveness both before the beginning of voluntary alcoholization and on day 3 from the start.

CONCLUSIONS: The increase in compulsivity and voluntary ethanol consumption was significantly higher in the MD group, that is comparable to the increased level in blood plasma progesterone samples.

Keywords: psychogenic stress; maternal deprivation; alcoholization; progesterone.

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Научная статья

Действие хронического психического стресса в раннем онтогенезе повышает риски развития химической и нехимической форм зависимости

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Актуальность. Воздействие острого или хронического стресса способствует возникновению различных нарушений со стороны центральной нервной системы, психоэмоциональной сферы, а также повышает риски развития различных форм зависимости.

Цель — проанализировать влияние материнской депривации на добровольное потребление алкоголя подростками, а также выяснить степень выраженности компульсивного поведения у экспериментальных животных.

Материалы и методы. В работе было использовано 30 крыс-самцов линии Вистар. Была осуществлена модель материнской депривации со 2-го по 12-й день постнатального периода (MD). Проведена оценка компульсивности в тесте закапывания шариков. Применяли добровольную алкоголизацию 10 % раствором этилового спирта в тесте «двух бутылок». Определение уровня прогестерона в плазме крови проводили методом иммуноферментного анализа.

Результаты. Обнаружены изменения уровня прогестерона в плазме крови у животных с MD и контролем. В тесте «двух бутылок» на 2-й и 3-й день предоставления 10 % раствора этанола определены статистически значимые отличия потребления по сравнению с группой контроля. В тесте закапывания шариков животные группы MD показали статистически достоверное возрастание компульсивности как до, так и на 3-й день от начала добровольной алкоголизации.

Выводы. Повышение компульсивности и добровольное потребление этанола значительно выше у группы MD, что сопоставимо с увеличением уровня плазменного прогестерона.

Ключевые слова: психогенный стресс; материнская депривация; алкоголизация; прогестерон.

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ЭКО•ВЕКТОР

BACKGROUND

Exposure to acute and/or chronic stress contributes to the emergence of various disorders or subclinical changes in the nervous, endocrine, and immune systems, which are manifested primarily in the changes in the psychoemotional sphere, as well as increased risks of developing various forms of addiction [1]. Presently, several models of stress effects on the body of newborn model animals have been proposed [2], of which, the most interesting are the models of maternal neglect and deprivation of newborn rats from the mother for a certain period [3].

Maternal care at an early age affects endocrine function and the reproductive development by programming the functions of the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-adrenal axes [4].

In rodents, maternal care involves several components that exhibit the following behavioral patterns: licking, feeding, incubating, and retrieving rats [5]. Maternal care also affects the timing of reproductive maturity in rats [6]. The opening of the vagina, which is an indicator of female puberty in rats, occurs earlier in females that received low maternal care relative to those who received high care, which is most likely related to the maturity of hypothalamic structures responsible for the synthesis of kisspeptin protein that regulates puberty mechanisms [7]. Considering that the correlations among reproductive development programming, endocrine function features in female rats, and maternal care at an early age have been described in independent studies, the data on the influence of these factors on the endocrine functions of males are extremely scarce. It is also of interest that sensitivity to ethanol is largely modulated by endogenous steroid levels, including corticosterone and sex steroids such as testosterone, progesterone, and its metabolite allopregnanolone [8].

Ethanol-induced hypnotic, anticonvulsant, and sedative effects correlate with ethanol-induced allopregnanolone levels in the brain [9, 10]. Both human and rodent studies have reported that testosterone can influence sensitivity to ethanol-induced hypnosis and ethanol consumption [11].

Thus, changes in the endogenous levels of male progesterone, testosterone, and corticosterone may represent the mechanism through which maternal care modulates sensitivity to ethanol-induced hypnosis.

Early life difficulties, especially during the first few years of life, have been associated with the early onset of problematic alcohol use in adolescence and alcohol dependence in early adulthood [12].

It has been reported that mental disorders associated with excessive alcohol consumption include chronic, relapsing disorders characterized by compulsive drinking, loss of control over drinking, and negative emotional states during abstinence [13–15].

The neurochemical action mechanism of ethanol and partial neurosteroids on the central nervous system is mainly occurs through the potentiation of the functions of γ-aminobutyric acid type A ($GABA_A$) receptors [16]. The GABAergic system serves as the main mediator of the rapid inhibition in the central nervous system. The fully functional GABA-receptor complex is pentameric and includes five of the 19 known subunits; α (1–6), β (1–3), γ (1–3), δ, ε, ρ, and θ (1–3). The composition of the subunits of the GABA-receptor complex can determine various characteristics of the receptor, such as its location in the brain, cellular localization (synaptic or extrasynaptic), physiological functions (phasic o–r tonic inhibition), and its kinetic and pharmacological properties (agonist and antagonist) [17, 18].

The aim was to analyze the effect of maternal deprivation on voluntary alcohol consumption by sexually mature offspring and to determine the severity of compulsive behavior in the experimental animals.

MATERIALS AND METHODS

Ethical rules and regulations

This work was conducted in accordance with the ethical principles established by the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (adopted in Strasburg, 18.03.1986 and confirmed in Strasburg, 15.06.2006) and approved by the local ethical committee. Each animal group was maintained under the conditions of 4–6 same-sex individuals per group with free access to water and *ad libitum* access to food. The study plan, standardized operating procedures, and the accompanying documentation were subjected to ethical review by the local ethical committee at St. Petersburg State Pediatric Medical University, Ministry of Health Care of the Russian Federation.

General design of the experimental study

This study is a two-stage experimental observation, wherein the first stage involved mating of the laboratory animals to produce offspring, while the second stage involved reproduction of the maternal deprivation model on male offspring, followed by testing of the laboratory animals. After the animals were removed from the experiment, their hormone levels were measured.

Obtaining offspring

At the first stage of the study, 10 sexually mature female Wistar rats of bodyweight 270 ± 20 g were obtained from the cattery of laboratory animals at the Pushchino Branch of IBH RAS (Moscow Region). After a two-week quarantine period, a male was added to the groups of females during the estrus phase for one day. This procedure was repeated until spermatozoa were detected in the vaginal smears; this day was considered as day

zero (0) of pregnancy. Next, the females were seated in individual plastic containers with free access to water and food under inverted light conditions 8:00–20:00 at 22 ± 2°C.

Maternal deprivation modeling (MD)

In the second stage of this study, only P1 male offspring were included. After their delivery, the rats were counted, weighed, and sexually differentiated, and the general condition of the newborns, their mobility, and skin coloration were evaluated. Thirty male rats were directly included in the work. The cubs were deprived of their mother (MD) daily for 3 h from days 2 to 12 postnatal. At this time, the rats were placed in individual plastic containers to avoid contact with each other, assigned an individual number, and applied to the skin of the rats. Upon completion of the deprivation session, the brood was returned to its home cage [1]. At the end of the deprivation period, two experimental groups of animals were created: a control group without MD (Control) and an experimental group with MD, each with 15 rats (Table 1).

The experimental and control groups were created through randomization using the closed envelope method in the ratio of 1:1.

The marble test

On day 90 of the postnatal period, the animals were examined to quantify their status of anxiety, obsessive-compulsive behavior, or repetitive behavior. A 5-cm layer of sawdust was placed in into a 20 × 25 × 17-cm cage and 20, 1-cm-diameter glass beads were placed equidistantly. The rat was placed in the cage for 30 min. After which, the number of balls covered by sawdust by more than 2/3 was counted. In this experiment, each animal was tested thrice [19].

The "two bottles" test

As taste is a predominant component of eating behavior, the two-bottle test provides a broad measure of taste sensitivity, that is, it estimates whether the tested liquid is preferable to water. In our work, we used a 2 h test for this purpose.

In the first test, the test animals were administered a bottle of water and a bottle of 10% ethanol solution. Each animal was kept individually, with access to the bottles with liquids. The drinkers were left in place for 2 h, after which their fluid volume was recorded. To avoid the formation of a preference reaction, the water and alcohol drinkers were swapped after 1 h, followed by estimating the liquid volume (Fig. 1).

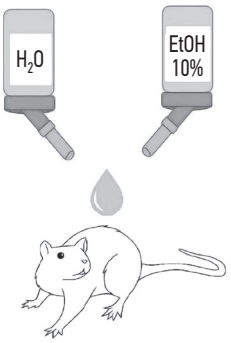

Fig. 1. Depiction of the "two bottles" test
Рис. 1. Тест «двух бутылок»

Table. Characteristics of the experimental groups of animals
Таблица. Характеристика экспериментальных групп животных

Conditional serial number of the female	Total number of offspring	The sex of the offspring		Offspring included in further study
		♀	♂	
1	11	5	6	3
2	9	3	6	3
3	8	5	3	3
4	10	4	6	3
5	9	2	7	2
6	8	4	4	4
7	10	2	8	2
8	6	1	5	1
9	11	6	5	4
10	13	6	7	5

Immunoassay

The blood samples were collected immediately after decapitation through direct withdrawal from the gaping vessels of the neck into tubes with ethylenediaminetetraacetic acid. Then, blood was centrifuged in a laboratory clinical centrifuge.02 (Dastan, Russia) for 15 min at 3000 rpm to obtain the plasma with further freezing in a freezer at –20°C. The hormone levels were measured by using an enzyme immunoassay reagent kit (SteroidIFA-progesterone, AlkorBio, Russia) for quantitative enzyme immunoassay for prolactin and free thyroxine in the blood serum.

Statistical processing

The methods of descriptive statistics include the estimation of the mean (*M*), the standard error of the mean (*SE*), and the standard error of the mean (*m*). The data obtained were analyzed using the GraphPad PRISM 6.0 statistical software package. The differences in the monoamine metabolism of the brain structures were assessed by single-factor analysis of variance using Bonferroni correction for multiple comparisons. The critical significance of the null statistical hypothesis (the absence of significant differences or factor influences) was considered as 0.05.

RESULTS AND DISCUSSION

In accordance with the results of statistical analysis, the numbers of balls buried more than 2/3 in the experimental animals was 50% higher than in the control animals ($p < 0.05$). The tendency to an increase in the compulsive behavior in this test was observed on the third day of voluntary alcoholization, which constituted 100% of the results of the control group of animals, as also confirmed by the results of statistical analysis ($p < 0.05$). No significant statistical differences were identified between the indicators before and on the third day of voluntary alcoholization, albeit there was a tendency of an increase in compulsiveness in the behavior of the animals (Fig. 2).

The ethanol consumption reaction in the "two-bottle" test reproduces the physiological pathway of alcohol consumption. Our experiment involved two stages: the task of the first stage was to determine the degree of compulsiveness in animals who experienced a psychotraumatic event in early ontogenesis when compared to that in the intact group of animals. The task of the second stage was to determine the individual sensitivity of rats to the reinforcing effect of the preferred alcohol concentration in the groups of animals exposed to MD from days 2 to 12 postnatal and in the animals of the control (intact) group.

The consumption of 10% ethyl alcohol solution in the two-bottle preference test was performed on days 1, 3, and 7 of the experiment.

The results of voluntary alcoholization on day one of the study indicated no statistically significant differences in the consumption of 10% ethanol solution and water between the control and stressed rats.

Furthermore, on the third day of the experiment, we obtained reliable differences ($p < 0.05$) in the volume of fluid consumed. In the group of animals subjected to MD, the volume of consumed 10% ethanol solution during the observation was 0.57 ± 0.065 mL, which reliably differed from the voluntary consumption of 10% ethanol solution by 0.41 ± 0.10 mL in animals of the control (intact) group, $p < 0.05$ (Fig. 3).

One week later, we noted that the volume of ethanol solution drunk in the MD group was 1.6 ± 0.12 mL, whereas

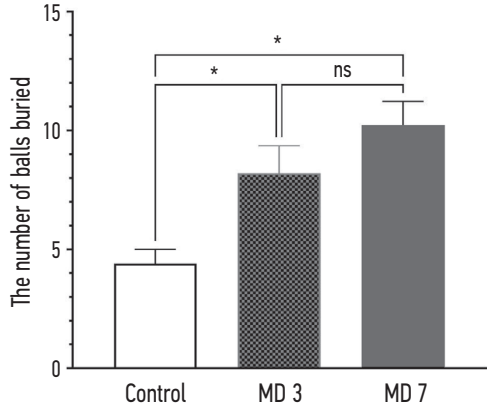

Fig. 2. The effect of MD and voluntary alcoholization on compulsive behavior in the balloon burial test. *$p \leq 0.05$ compared with intact control. MD 3, MD 7, maternal deprivation days 3 and 7; ns, not significant ($p > 0.05$)

Рис. 2. Влияние материнской депривации и добровольной алкоголизации на компульсивное поведение в тесте закапывания шариков. *$p \leq 0{,}05$ в сравнении с интактным контролем. MD 3, MD 7 – 3-й и 7-й дни депривации от матерей; ns – не достоверно ($p > 0{,}05$)

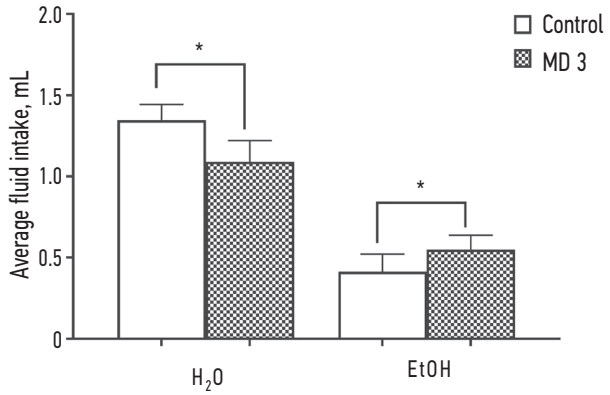

Fig. 3. The volume of fluid intake in experimental and control groups of animals on day 3 of the study. *$p \leq 0.05$ compared with the intact control

Рис. 3. Объем потребляемой жидкости в экспериментальной и контрольной группах животных на 3-й день исследования. *$p \leq 0{,}05$ в сравнении с интактным контролем

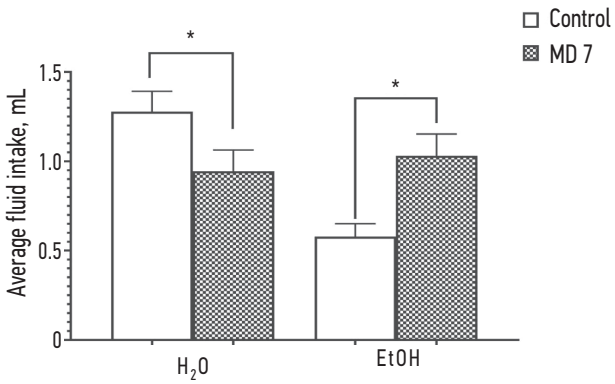

Fig. 4. The volume of fluid intake between the experimental and control groups of animals on day 7 of the study. *$p \leq 0.05$ compared with intact control

Рис. 4. Объем потребляемой жидкости в экспериментальной и контрольной группах животных на 7-й день исследования. *$p \leq 0,05$ в сравнении с интактным контролем

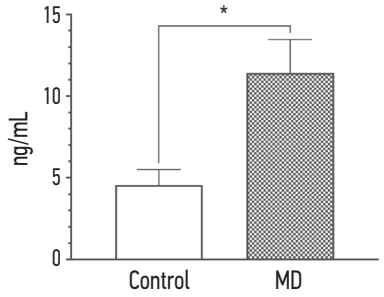

Fig. 5. The effect of MD stress on the plasma progesterone level. *$p \leq 0.05$ versus intact control

Рис. 5. Влияние стресса материнской депривации на концентрацию прогестерона в плазме крови. *$p \leq 0,05$ в сравнении с интактным контролем

that in the control (intact) group was 0.57 ± 0.07 mL, $p < 0.05$ (Fig. 4).

Statistically significant differences ($p \leq 0.05$) were detected in the results of the enzyme immunoassay of animal blood. We observed significant effects of MD on the increase in the progesterone concentration in the plasma in relation to that in the control animals (Fig. 5).

The present results suggest that, initially, the animals that survived the action of a psychotraumatic event in early ontogeny exhibited a more anxious and compulsive behavior in the balloon burial test, which was before the onset of voluntary alcoholization.

In the present study, we demonstrated how stress due to MD leads to an increase in the levels of plasma progesterone and to increased compulsive behavior in model animals and also how early stress can influence increased voluntary consumption of a 10% ethanol solution in rats.

Accordingly, we hypothesized that low levels of maternal care can increase the behavior of voluntary ethanol consumption in adolescents, which may be related to the differences in the plasma gonadal hormone levels and $GABA_A$ receptor subunit expression as they are affected by maternal care in the early neonatal period [20].

Consequently, when the baseline plasma levels of progesterone were measured in the animals participating in the experiment, higher levels of progesterone were recorded, which possibly affected the expression of the $GABA_A$ subunit in the brain tissues, contributing to the sensitivity to the depressogenic effect of ethanol. A key feature of the endocrine stress response is the increased secretion of corticosterone from the adrenal cortex into the bloodstream. In the absence of stress, the concentration of circulating progesterone is higher in women than in men. However, after exposure to stress, the circulating progesterone concentrations were found to increase in both the sexes, with a significantly greater response in females. Stress can also increase the levels of progesterone in both the sexes, as specifically recorded in the brain structures of the experimental animals [21].

Several studies have reported a positive correlation between the circulating blood progesterone levels and the progesterone levels in the brain structures, which possibly indicates that the source of neuroprogesterone in the brain is adrenal progesterone from the periphery [22]. Progesterone mediates rapid nongenomic effects indirectly through its downstream neuroactive metabolites, such as allopregnanolone, which acts as an allosteric modulator of the $GABA_A$ receptor activity to enhance inhibitory GABA neurotransmission.

Chronic maternal separation stress at an early age has been associated with changes in the development and formation of several neurotransmitter systems involved in the stress response. Thus, several studies have demonstrated that MD can significantly affect the development of the dopaminergic, serotoninergic, and glutamatergic systems, which are known to be involved in the effects of alcohol and vulnerability [23].

Literature evidence suggests impairment in the endogenous cannabinoid system due to exposure to chronic stress during active neurogenesis of the brain structures. Particularly, the endocannabinoid system is of interest in the present context as it has been proposed as one of the main mechanisms of alcohol use and abuse and, more recently, as a putative candidate for the propensity to drink observed in animals subjected to certain maternal separation protocols [24, 25].

According to the literature on the effects of ontogenetic changes on brain functions, incomplete maturation of the neural systems that regulate the emotional and inhibitory behavior reflects the behavioral phenotype on reaching adolescence [26]. Decades of research have demonstrated the impact of impaired neonatal care in rodents in terms of the behavioral and neurobiological

outcomes in adulthood. A better understanding of the changes in specific genes or neuroendocrine targets is thus needed.

We thereby demonstrated that periodicity in the provision of alcohol corresponds to an increase in compulsive behavior and hence an increase in the voluntary ethanol consumption during the following sessions. These data together illustrate a compulsive consumption response in ethanol-drinking rats, which was not observed in the control animals [27].

CONCLUSION

In the present study, we noted that exposure to chronic stress deprivation from maternity from days 2 to 12 postnatal promoted increased compulsive behavior in the balloon burial test relative to that in the control animals. These experimental animals showed increased plasma progesterone content, which may indicate a stress-protective effect of progesterone neurometabolites, such as allopregnanolone, which contributes to an increase in the plasticity of the brain structures. A correlation was thereby recorded with an increase in compulsivity in the behavior of animals that experienced a psychotraumatic event during early ontogenesis and voluntary consumption of 10% ethanol solution. Significant statistical changes were observed from the 2nd day of alcohol presentation. On the third day, the maximum amount of both the ethanol consumed and the buried balls reflects the delayed development of the anxiety state.

ADDITIONAL INFORMATION

Authors' 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. The contribution of each author: S.S. Purveev, M.S. Nekrasov, N.S. Dedanishvili, A.S. Nekrasova, T.V. Brus, N.V. Lavrov, A.V. Podrezova, R.I. Glushakov — manuscript drafting, writing and pilot data analyses; A.A. Lebedev, P.D. Shabanov — paper reconceptualization and general concept discussion.

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

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Ethic committee. The investigation was approved by Local Ethic Committee of Institute of Experimental Medicine (Protocol No. 10, 12.10.2020)

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