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Change in physical performance indicators of the progenies of rats with experimental preeclampsia in early and late pharmacological correction by GABA derivatives

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ABSTRACT

The aim of the study was to assess the changes in physical performance parameters in the progeny of rats with experimental preeclampsia (EP) undergoing early and late pharmacological treatment with gamma-aminobutyric acid (GABA) derivatives.

Materials and methods. The experiments were carried out on the progeny of rats aged 3 (n = 358), 18 (n = 288), and 25 (n = 138) months, born to white outbred female rats with EP modeled by replacing drinking water with 1.8% sodium chloride from the 1st to 21st day of gestation. At the first stage, physical performance of 3- and 18-month-old progeny of female rats with EP after early pharmacological treatment (from hte 40th to hte 70th day of life) with GABA derivatives, such as succicard (22 mg / kg), salifen (7.5 mg / kg), phenibut (25 mg / kg) and a comparator drug, pantogam (50 mg) was studied. At the second stage, succicard (44 mg / kg), salifen (15 mg / kg), phenibut (50 mg / kg) or pantogam (100 mg) had been intragastrically administered in the progeny of rats with EP for 30 days (from the 24th to the 25th month of life). The horizontal rope walking test (HRWT), Rotarod performance test, and forced swim test with weight load (FSTwWL) were used in the study.

Results. The HRWT, Rotarod performance rest, and FSTwWL showed a decrease in muscle strength, coordination and motor activity, and aerobic and anaerobic endurance in rats with EP aged 3, 18, and 25 months as compared to the values in the animals born from intact rats. Succicard, a GABA-derivative, and pantogam, a comparator drug, were effective both in early and late pharmacological interventions, whereas salifen and phenibut were effective only when administered during puberty. As the offspring of EP rats were aging, their muscle strength, coordination, and motor activity were decreasing, while their aerobic and anaerobic endurance was increasing.

Conclusion. Physical performance in the progeny of rats with induced EP aged 3, 18, and 25 months tended to decrease. Pharmacological treatment with GABA derivatives in the adolescent period attenuated EP consequences. When administered during puberty, only succicard and the comparator drug pantogam, had a therapeutic effect. This fact provides evidence that a succicard-based drug can be developed for preventive management of preeclampsia consequences.

Key words: experimental preeclampsia, the progeny of rats, GABA derivatives, physical performance.

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Показатели физической работоспособности у потомства крыс с экспериментальной преэклампсией при ранней и поздней фармакологической коррекции производными ГАМК

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РЕЗЮМЕ

Цель исследования – оценить изменения показателей физической работоспособности у потомства крыс с экспериментальной преэклампсией (ЭП) при ранней и поздней фармакологической коррекции производными гамма-аминомасляной кислоты (ГАМК).

Материалы и методы. Эксперименты выполнены на потомстве в возрасте 3 мес (n = 358), 18 (n = 288) и 25 мес (n = 138), рожденном белыми беспородными самками крыс с физиологической беременностью и ЭП, моделированной заменой питьевой воды 1,8%-м раствором натрия хлорида с 1-х по 21-е сут гестации. На первом этапе изучали физическую работоспособность 3- и 18-месячного потомства самок крыс с ЭП после ранней фармакологической коррекции (с 40-х по 70-е сут жизни) производными ГАМК сукцикардом (22 мг/кг), салифеном (7,5 мг/кг), фенибутом (25 мг/кг) и препаратом сравнения пантогамом (50 мг). На втором этапе потомству, рожденному крысами с ЭП, в течение 30 сут (с 24-го по 25-й мес жизни) вводили в желудок сукцикард (44 мг/кг), салифен (15 мг/кг), фенибут (50 мг/кг) или пантогам (100 мг). В исследовании использовали тесты «Удержание тела на горизонтальном веревочном канате» (УТнаГВК), «Ротарод» и «Вынужденное плавание с грузом» (ВПсГ).

Результаты. У потомства самок крыс с ЭП в возрасте 3, 18 и 25 мес уменьшились мышечная сила, координационно-двигательная активность и аэробно-анаэробная выносливость в тестах УТнаГВК, «Ротарод» и ВПсГ по сравнению с показателями у животных, рожденных интактными крысами. Производное ГАМК сукцикард и препарат сравнения «Пантогам» были эффективны как при ранней, так и при поздней фармакологической коррекции, салифен и фенибут – только при введении в пубертатном периоде. С возрастом у потомства крыс с ЭП снижались мышечная сила и координационно-двигательная активность, но аэробно-анаэробная выносливость увеличивалась.

Заключение. У потомства крыс, подвергнутых ЭП, в возрасте 3, 18 и 25 мес ухудшалась физическая работоспособность. Фармакологическая коррекция производными ГАМК в адолесцентном периоде ослабляла последствия ЭП. При введении веществ в пубертатном периоде лечебное действие оказывали только сукцикард и препарат сравнения «Пантогам». Это предполагает возможность создания на основе сукцикарда препарата для превентивной коррекции последствий преэклампсии.

Ключевые слова: экспериментальная преэклампсия, потомство крыс, производные ГАМК, физическая работоспособность.

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INTRODUCTION

Preeclampsia is a severe pregnancy-related multisystem pathology, which increases the risk of development unfavourable consequences in the offspring both at early stages of life and in the long-term perspective. Impaired formation of the fetoplacental complex and endothelial dysfunction typical of preeclampsia contribute to circulatory deterioration in the "mother-placenta-fetus system", which results in the insufficient nutrient delivery to the fetus and development of chronic hypoxia [1]. At the critical stages of prenatal development, preeclampsia is associated with pathological changes in the embryo's organs and tissues. The progeny born to mothers with this pregnancy complication show physical developmental delays, higher risks of disease development in a long-term perspective and decreased physical performance [2].

To date, no medications with proved efficacy in correcting post-hypoxic disorders occurring at different ontogenesis stages in children delivered by women with preeclampsia, have been developed, nor have strategies of treating the complications of this severe pathology been designed. The search for safe and effective agents to manage the complications of preeclampsia is high on the agenda of pediatric and therapeutic practice.

Earlier studies have demonstrated that the derivatives of gamma-aminobutyric acid (GABA) have an endothelium-, neuro-, and cardioprotective action, demonstrate antihypoxic and antioxidant effects, and enhance the physical work capacity in rats [3–5]. These findings suggest that GABA derivatives can be used to manage the preeclampsia consequences in the offspring.

The aim of the study was to assess the physical performance parameters in the progeny of rats with experimental preeclampsia (EP) undergoing early (from the 40th to the 70th day of life) and late (from the 24th to the 25th month of life) pharmacological treatment with GABA derivatives, such as succicard, salifen, phenibut, and the comparator drug pantogam.

MATERIALS AND METHODS

The experiments were conducted on the offspring of white outbred rats with physiological pregnancy and EP modeled by replacing drinking water with 1.8% sodium chloride from the 1st to 21st days of gestation at the age of 3 *(n* = 358), 18 (*n* = 288), and 25 (*n* = 138) months [3]. The animals were obtained from the Rappolovo Breeding Station (Leningrad Region, Russia). The animals were kept and cared for in the vivarium of Volgograd State Medical University in accordance with the Principles of the Good Laboratory Practice of the National Standard of the Russian Federation GOST P-33044-2014, and the international guidelines of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (The European Convention, 1986). The study also complied with the provisions of the Order of the Ministry of Health of RF No. 199n of 01.04.2016 "On Approving Laboratory Practice Regulations" and the directive 2010/63/EU providing the European Union legislation for the Protection of Animals Used for Scientific Purposes of 22.09.2010. The protocol of the experimental study was approved by Research Ethics Review Board of Volgograd region (Protocol No. 2044-2017 of 25.12.2017).

The animals received GABA derivatives, such as succicard (the composition of 4-phenylpiracetam and succinic acid in the ratio 2:1), phenibut (γ-amino-β-phenylbutyric acid) and salifen (the composition of phenibutr and salicylic acid in the ratio 2:1 ratio). All the substances were synthesized at the Department of Organic Chemistry of Herzen State Pedagogical University. Pantogam served as a comparator drug (hopantenic acid, PIK-PHARMA PRO LTD, Russia; syrup, 100 mg / ml).

The rats' offspring were separated from their mothers on the 39th day after birth. The study involved two stages. At the first stage, the animals were divided into groups: 1, 2 – positive controls – male rats (*n* = 30) and female rats (*n* = 29) delivered by healthy rats and receiving distilled water; 3, 4 – negative controls – male rats (*n* = 30) and female rats (*n* = 30) delivered by the rats with EP and receiving distilled water; 5, 6, 7, 8, 9, 10, 11, 12 – experimental groups – male and female rats (30 animals of each gender) delivered by the rats with EP and receiving the following GABA derivatives: succicard at a dose of 22 mg / kg, phenibut at a dose of 25 mg / kg, salifen at a dose of 7.5 mg / kg or pantogam at a dose of 50 mg / kg. GABA derivatives, pantogam, and distilled water were administered intragastrically once a day the from 40th to

the 70th day of life. The dosage of the agents corresponded to half doses administered in adult rats. These doses of the substances demonstrated the highest pharmacological activity in earlier experiments [3, 4]. Physical performance was explored in rat pups aged 3 months using the horizontal rope walking test (HRWT), when the rats were suspended on a taut horizontal rope grasping it with their forepaws [6], Rotarod performance test [6], and forced swim test with weight load (FSTwWL) [7]. The same tests were employed to study 18-month-old male and female rats from the positive control groups (n = 25 and n = 23), negative control groups (n = 28 and n = 25), and experimental groups 5 (n = 24), 6 (n = 27), 7 (n = 20), 8 (n = 21), 9 (n = 23), 10 (n = 24), 11 (n = 24), and 12 (n = 24).

At the second stage, distilled water was intragastrically administered in male and female rats from the groups of positive (n = 11 and n = 11) and negative control (n = 15 and n = 12). At the same time, males and females in the experimental groups 5 (n = 16) and 6 (n = 9) received succicard at a dose of 44 mg / kg, rats from the experimental groups 7 (n = 11); and 8 (n = 14) received salifen at a dose of 15 mg / kg, animals from the groups 9 (n = 14); and 10 (n = 12) received phenibut at a dose of 50 mg / kg; and groups 11 (n = 7) and 12 (n = 6) received pantogam at a dose of 100 mg. The HRWT, Rotarod performance test, and FSTwWL were used to assess physical performance of the rats at the age of 25 months. The agents were administered at doses which were effective for adult rats [3, 4].

The findings were statistically processed bu STATISTICA v.12.5 software, license number 133-190-095 (StatSoft Inc., USA), using the Mann – Whitney U test, Student's t-test to compare paired samples, Newman – Keuls test, Kruskal – Wallis test with Dunnett's test for multiple comparisons, and Shapiro – Wilk test to assess the samples for normality of distribution. The differences were considered statistically significant at $p < 0.05$. The data are presented in the form $M \pm m$, where M is the mean and m is the error of the mean.

RESULTS

The execution time of HRWT, Rotarod performance test, and FST-wWL in the negative control offspring aged 3, 18, and 25 months was significantly shorter than in the animals delivered by healthy rats. This finding suggests decreased muscle strength, lower balance and motor coordination capacities, and reduced aerobic and anaerobic endurance both at early and late stages of ontogenesis (Table 1, Table 2, Figure).

When executing the HRWT test, 3-month-old offspring receiving GABA derivatives and the comparator drug pantogam, demonstrated a significantly longer time of hanging on a horizontal rope than the rats from the negative control group. At the age of 18 months, the suspension time increased in the male rats receiving succicard and pantogam and female rats receiving salifen and phenibut. At the age of 25 months, the male rats, to whom succicard, phenibut, and pantogam were administered, tended to hang on a horizontal rope longer. The test execution time for the offspring of all groups aged 18 and 25 months was significantly shorter than in the 3-month-old animals. 25-month-old rats showed a shorter suspension time as compared to 18-month-old-rats. This tendency was observed in the male and female rats delivered by rats with EP and females receiving salifen and phenibut (table 1).

Table 1

Dynamics of the muscle strength changes in the offspring of rats with experimental preeclampsia undergoing early and late pharmacological treatment with GABA derivatives ($M \pm m$) during the horizontal rope test

Groups of animals	Gender of rats	Test execution time, s		
		3 months	18 months	25 months
Positive control	Males	50.27 ± 1.58	10.08 ± 0.83 &	7.60 ± 0.91 &
	Females	62.03 ± 1.80	6.83 ± 0.73 &	6.82 ± 0.87 &
Negative control	Males	27.31 ± 1.61 *	6.46 ± 0.64 $&	3.80 ± 0.31 $&>
	Females	37.07 ± 1.99 *	6.33 ± 0.45 &	4.50 ± 0.31 *&<
Progeny of rats with experimental preeclampsia receiving succicard	Males	42.07 ± 1.66 #	8.50 ± 0.69 #&	8.33 ± 0.62 ^&
	Females	57.09 ± 1.77 #	7.19 ± 0.53 &	6.43 ± 0.53 &
Progeny of rats with experimental preeclampsia receiving salifen	Males	41.31 ± 1.35 #	6.25 ± 0.69 &	5.55 ± 0.55 &
	Females	56.37 ± 1.62 #	11.57 ± 0.85 #&	5.71 ± 0.60 &<
Progeny of rats with experimental preeclampsia receiving phenibut	Males	43.55 ± 1.19 #	6.39 ± 0.61 &	6.38 ± 0.43 ^&
	Females	52.13 ± 1.55 #	9.61 ± 0.74 #&	6.00 ± 0.51 &<

Table 1 (continued)

Groups of animals	Gender of rats	Test execution time, s		
		3 months	18 months	25 months
Progeny of rats with experimental preeclampsia receiving pantogam	Males	34.48 ± 1.60 #	8.54 ± 0.68 #&	6.57 ± 0.75 ^&
	Females	51.38 ± 1.49 #	6.96 ± 0.48 @	5.83 ± 0.48 &

Note. The differences are statistically significant ($p < 0.05$) compared with the positive control group: $ – by the Mann – Whitney test, * – by the Student's t-test; compared with the negative control group: ^ – by the Kruskal – Wallis test with the Dunnett's (post hoc) test, # – by the Newman – Keuls test; compared to offspring at the age of 3 months: @ – by the Mann – Whitney test, & – by the Student's t-test; compared with offspring at the age of 18 months: > – by the Mann – Whitney test, < – by the Student's t-test.

The assessment of balance and coordination capacities by the Rotarod performance test demonstrated that 3-month-old male rats receiving salifen and phenibut stayed on the rotating rod significantly longer than the negative control animals. At the age of 18 months, males receiving succicard, salifen, and pantogam and females receiving pantogam managed to stay longer; at the age of 25 months, the length of time the animals stayed on the rod increased in males receiving succicard and pantogam and females receiving succicard.

The test execution time in the offspring aged 18 and 25 months was shorter than in 3-month-old rats (Figure).

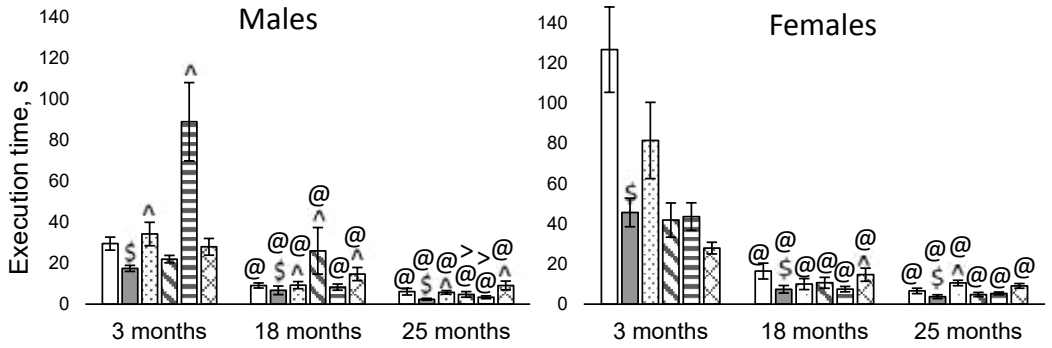

Fig. 1. Dynamics of the coordination and motor activity changes in the offspring of rats with experimental preeclampsia undergoing early and late pharmacological treatment with GABA derivatives ($M \pm m$) during the Rotarod performance test:

The differences are statistically significant ($p < 0.05$) compared with the positive control group: $ – by the Mann – Whitney test, * – by the Student's t-test; compared with the negative control group: ^ – by the Kruskal – Wallis test with the Dunnett's (post hoc) test, # – by the Newman – Keuls test; compared with offspring at the age of 3 months: @ – by the Mann – Whitney test, & – by the Student's t-test; compared with offspring at the age of 18 months: > – by the Mann – Whitney test

When undergoing the FSTwWL test, 3-month-old males rats receiving succicard, salifen, and pantogam, alongside the females receiving succicard, salifen, and phenibut were able to swim much longer compared to the animals of the negative control group. At the age of 18 months, the time of swimming increased in males receiving all the GABA derivatives under study and pantogam, as well as in females receiving salifen; at the age of 25 months, the time of swimming was longer in females receiving succicard and pantogam. In all groups of rats aged 18 and 25 months, the test execution time increased as compared to 3-month-old offspring.

The swimming time of rats aged 25 months showed a statistically significant decrease only in negative control females receiving salifen compared to 18-month-old rats (Table 2).

Table 2

Dynamics of aerobic-anaerobic endurance changes in the offspring of rats with experimental preeclampsia undergoing early and late pharmacological treatment with GABA derivatives ($M \pm m$) during the forced swim test with weight load

Groups of animals	Gender of rats	Test execution time, s		
		3 months	18 months	25 months
Positive control	Males	129.72 ± 2.97	155.88 ± 8.56 &	166.50 ± 7.20 @
	Females	153.38 ± 3.78	189.61 ± 11.48 &	193.56 ± 9.30 &

Table 2 (continued)

Groups of animals	Gender of rats	Test execution time, s		
		3 months	18 months	25 months
Negative control	Males	92.23 ± 2.78 $	125.74 ± 5.02 * &	134.53 ± 4.95 *&
	Females	99.67 ± 2.79 *	148.71 ± 4.17 * &	116.67 ± 4.90 *&<
Progeny of rats with experimental preeclampsia receiving succicard	Males	108.52 ± 3.41 ^	145.71 ± 5.77 # &	154.47 ± 6.40 &
	Females	111.93 ± 2.98 #	166.33 ± 9.48 &	173.00 ± 12.08 #&
Progeny of rats with experimental preeclampsia receiving salifen	Males	127.40 ± 7.78 ^	150.05 ± 8.58 #	147.40 ± 8.83
	Females	124.10 ± 5.26 #	184.38 ± 8.88 #&	148.42 ± 8.28 &<
Progeny of rats with experimental preeclampsia receiving phenibut	Males	99.28 ± 3.26	164.96 ± 6.81 #&	155.50 ± 6.28 &
	Females	121.53 ± 3.23 #	161.74 ± 9.66 @	153.92 ± 9.07 &
Progeny of rats with experimental preeclampsia receiving pantogam	Males	109.84 ± 3.24 ^	156.08 ± 8.30 #&	135.71 ± 7.97 &
	Females	99.38 ± 2.32	169.43 ± 9.52 &	174.20 ± 11.06 #&

Note. All symbols are similar to those in Figure, except: & – the differences are statistically significant ($p < 0.05$) by the Student's t-test compared with offspring at the age of 3 months, < – the differences are statistically significant by the Student's t-test compared with offspring at the age of 18 months.

DISCUSSION

Preeclampsia results in impaired nutrient and oxygen delivery to the developing embryo. Metabolic changes are associated with acidosis and oxidative stress, which contribute to the damage of cell structures and organ and tissue enzymes and may lead to their dysfunction in the postnatal ontogenesis [2]. These factors increase the likelihood of the development of nervous, cardiovascular, respiratory, and other pathologies [8–11] with decreased physical performance at different life stages.

The findings of the conducted experiments have demonstrated that the physical work capacity of the progeny of rats with EP is lower compared to the animals delivered by healthy rats both at early stages (3 months) and later stages (18 and 25 months) of ontogenesis. This was proved by the differences in the execution time of the HRWT, Rotarod performance test, and FSTwWL.

As is known, GABA derivatives have a positive effect on the physical performance parameters and adaptability to physical exertion and increase the physical endurance of rats performing forced dynamic and static activities [5].

In our experiments, early (from the 40th to the 70th day of life) and late (from the 24th to the 25th month of life) pharmacological treatment with succicard, a GABA derivative, resulted in enhanced muscle strength, coordination and motor activity, aerobic and anaerobic endurance as demonstrated by the HRWT, Rotarod performance test, and FSTwWL in 3-, 18- and 25-month-old progeny, respectively, as opposed to the values in the negative control group. Muscle strength and aerobic and anaerobic endurance were significantly higher in 3- and 18-month-old rats which received salifen and phenibut from the 40th to 70th day of life than in the animals delivered by female rats with EP. Late pharmacological treatment with these GABA derivatives did not have a significant effect on the physical performance of rats with EP. The effect of pantogam, the comparator drug, was similar to that of succicard.

Therefore, succicard and the comparator drug pantogam were effective both in early (from the 40th to the 70th day of life) and late (from the 24th to 25th month of life) pharmacological correction, salifen and phenibut were effective only when administered in the puberty period.

The therapeutic effect of GABA derivatives is conditioned by their polytropic pharmacological action. The agents of this group have endothelium-, neuro-, and cardioprotective, as well as antihypoxic and antioxidant effects [3, 4]. Moreover, GABA derivatives have an impact on glucose transport and utilization, increase ATP synthesis in hypoxia, help to overcome energy deficit in cells, and regulate muscle contractions [5, 12]. All these factors contribute to a rise in physical work capacity in the progeny of rats with EP.

In aging rats, there was a decrease in muscle strength, coordination, and motor activity, whereas their aerobic and anaerobic endurance increased. It is likely that the values obtained during the FSTwWL test were influenced by the fact that it was executed at the age of 6 and 12 months, which could be practice for rats [13].

Physical performance was significantly lower in 25- and 18-month-old negative control animals and rats receiving salifen and phenibut. This finding demonstrates the negative effect of EP on muscle

strength, balance and coordination capacities, and aerobic and anaerobic endurance and proves the inefficacy of late (from the 24th to 25th month of life) pharmacological correction of EP consequences using salifen and phenibut.

CONCLUSION

The physical performance of 3-, 18-, and 25-month-old animals delivered by rats with EP is decreased as compared to the progeny of healthy females. GABA derivatives, such as succicard, salifen and phenibut, reduce the negative impact of EP on the offspring undergoing early (from the 40th to the 70th day of life) pharmacological correction. This fact provides evidence that a succicard-based drug can be developed for preventive treatment of preeclampsia consequences in the progeny.

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Authors contribution

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