



# The effect of early and late pharmacological correction with GABA derivatives of psychoemotional state of offspring of rats with experimental preeclampsia

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## Abstract

**Introduction:** Preeclampsia is a serious complication of pregnancy, which increases the risk of anxiety disorders and depression in children at different stages of ontogenesis.

**Materials and methods:** The psychoemotional state of 70-day-old offspring of rats with experimental preeclampsia (EP) was studied after pharmacological correction from the 40<sup>th</sup> to 70<sup>th</sup> day of offspring life with GABA derivatives – succicard (22 mg/kg), salifen (7.5 mg/kg), phenibut (25 mg/kg) and comparison drug pantogam (50 mg) – in the Open field test, the Elevated plus maze test, and the Marble burying test. The above mentioned tests, together with the Porsolt test, were performed at the age of 18 months.

At the second step, the offspring received succicard (44 mg/kg), salifen (15 mg/kg), phenibut (50 mg/kg) and pantogam (100 mg) from the 24<sup>th</sup> to 25<sup>th</sup> month of life. After that, the animals were tested.

**Results and discussion:** The EP progeny had an increased level of anxiety and depression, as well as obsessive-compulsive disorder.

Early GABA derivatives exposure limited anxiety and depression in the animals aged 70 days and 18 months, with salifen limiting compulsive behavior. Late GABA derivatives “treatment” exerted anti-compulsive and antidepressant effects, with phenibut having a greater degree of anxiolytic activity. Succicard, salifen and phenibut were comparable or superior to pantogam in terms of effectiveness.

**Conclusion:** EP has a negative effect on the psychoemotional state of offspring. Early and late pharmacological correction with derivatives of GABA, such as succicard, salifen and phenibut, reduced anxiety, manifestations of obsessive-compulsive disorder, and depression in offspring of the rats with EP pregnancy.

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## Keywords

anxiety, depression, derivatives of GABA, obsessive-compulsive disorder, offspring, preeclampsia.

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## Introduction

Preeclampsia is a serious multisystem disease which develops during pregnancy. It can cause adverse effects in the offspring at different periods of their life.

Pathogenesis is based on disturbance of placentation and endothelial dysfunction together with an increase in pro-coagulant factors and vasoconstrictors. The fetus suffers from oxidative stress, nonspecific inflammation, and chronic hypoxia (Kovtun and Tsyvian 2019). This can result in abnormal neurogenesis, degeneration and death of neurons. In the postnatal life, this is accompanied by a delay in intellectual development, memory impairment and emotional disturbances (Tuovinen et al. 2014; Phillips et al. 2017; Kay et al. 2019) which clinically can manifest as panic, generalized anxiety, obsessive-compulsive, and anxiety-depressive disorders.

Anxiety precedes the development of depression in patients in 15–33% of cases (Galyamina et al. 2016). Children born to mothers with preeclampsia have an increased risk of developing anxiety disorders and depressive states in adult and old age (Tuovinen et al. 2010).

Since there are currently no drugs with proven efficacy for the correction of post-hypoxic complications in offspring in form of anxiety and depressive states, and the combined manifestation of these psychoemotional disorders is less treatable (Andreescu et al. 2007), the search for substances and ways to correct these effects of preeclampsia is relevant.

In this regard, derivatives of gamma-aminobutyric acid (GABA) which produce neuroprotective and nootropic effects have anti-hypoxic and anxiolytic effects, and improve memory and mental performance are of interest (Tyurenkov et al. 2014a; Muzyko et al. 2020).

The aim of the current study was to evaluate the psychoemotional state of offspring of the rats with EP during the early (from the 40<sup>th</sup> to 70<sup>th</sup> day of life) and late (from the 24<sup>th</sup> to 25<sup>th</sup> month of life) pharmacological correction with derivatives of GABA – succinard, salifen, phenibut, and pantogam as a comparison drug.

## Materials and methods

The experiments were performed on the offspring at the age of 70 days ( $n = 362$ ), 18 months ( $n = 296$ ) and 25 months ( $n = 145$ ) born to white outbred female rats with physiological pregnancy and EP simulated by replacing drinking water with 1.8% NaCl solution from the 1<sup>st</sup> to 21<sup>st</sup> days of gestation (Tyurenkov et al. 2014a). The maintenance and care of the animals in the vivarium of Volgograd State Medical University were carried out in accordance with the recommendations of the National Standard of the Russian Federation GOST R-33044-2014 “Principles of Good Laboratory Practice”, and the International Recommendations of the “European Convention for the Protection of Vertebrate Animals Used for Experiments or Other Scientific Purposes” (The European Convention, 1986).

The experimental study was carried out in accordance with Order No. 199n of the Ministry of Health of the Russian Federation dated 04/01/2016 “On the Approval of Laboratory Practice Rules” and Directive 2010/63/EU of the European Parliament and the Council of the European Union dated 09/22/2010 on the protection of animals used in scientific research. The protocol of the experimental study was approved by the Regional Research Ethics Committee of Volgograd Region (No. 2044-2017 December 25, 2017).

On the 39<sup>th</sup> day after birth, the offspring were separated from the female rats. The study was conducted in two steps. At the first stage, the groups of animals were formed: groups 1, 2 – positive control – males ( $n = 30$ ) and females ( $n = 29$ ), born to healthy rats and treated with distilled water; groups 3, 4 – negative control – males ( $n = 30$ ) and females ( $n = 31$ ) – born to the rats with EP and treated with distilled water; experimental groups 5, 6, 7, 8, 9, 10, 11, 12 – males and females born to the females with EP and treated with the following GABA derivatives: succinard (composition of 4-phenylpiracetam and succinic acid in a ratio 2:1, a substance synthesized at the Organic Chemistry Department of the Russian State Pedagogical University named after A.I. Herzen) at a dose of 22 mg/kg (male  $n = 29$  and female  $n = 30$ ), salifen (composition of phenibut and salicylic acid in a ratio 2:1, a substance synthesized at the Organic Chemistry Department of the Russian State Pedagogical University named after A.I. Herzen) at a dose of 7.5 mg/kg (male  $n = 31$  and female  $n = 31$ ), and phenibut ( $\gamma$ -amino- $\beta$ -phenylbutyric acid, a substance synthesized at the Organic Chemistry Department of the Russian State Pedagogical University named after A.I. Herzen) at a dose of 25 mg/kg (male  $n = 31$  and female  $n = 30$ ), as well as pantogam, a comparison drug (hopantenic acid, PIK-FARMA PRO LLC (Russia), syrup 100 mg/ml) at a dose of 50 mg (male  $n = 31$  and female  $n = 29$ ). The derivatives of GABA, pantogam, and distilled water were intragastrically administered to the offspring from the 40<sup>th</sup> to 70<sup>th</sup> day once a day, at the same day time, with the use of a probe. The doses corresponded to half of adult doses, which showed the most pronounced pharmacological activity in previous experiments (Tyurenkov et al. 2014b, c). At the age of 70 days, the psychoemotional state of the offspring was evaluated with the following tests: Open field, Elevated plus maze, Marble burying.

The Open field is a white circular arena with high walls (diameter of 80 cm). The floor of the chamber is divided into equal squares where there are holes at the intersections. Each experimental session lasted 3 min. At the beginning, the rat was placed in the center of the field. The animals were tested in a dim room with a 60 W bulb, placed 1.5 m above the center of the Open field. The parameters recorded in the Open field test were: escape time from the central zone, the number of entries to the central zone, and central zone duration, the number of unsupported rearings and supported rearings, the number of line crossings, the number of peeps into holes, the number of short-term and long-term grooming, the number of urination and defecation (Ostrovskaya et al. 2012).

The elevated plus maze is a plus-shaped apparatus with four long narrow arms (10 cm each) at right angle to each other. The plus maze labyrinth is elevated 100 cm above the floor. Two opposite arms have vertical opaque walls on each side of 40 cm high, while the other two “sleeves” are not walled. At the intersection of the four arms, there is a central zone of 10×10 cm. The animal was placed in the center of the intersection, facing one of the open arms. The session for each animal lasted 3 min, with regular illumination. The list of registration included the following records: latent time before leaving the central area, time spent in the open and closed arms, number of entries into open and closed arms, total number of transitions between the arms, number of rearings in the open and closed arms, number of hangings from the open arms, duration time in the central area and number of entries into it (Voronina et al. 2012). Note that Figures 1, 2 show only the statistically significant indicators.

The Marble burying test was carried out in two steps. Firstly, each rat was placed in the cage for 30 min to familiarize itself with it. Individual polycarbonate cages of 30×20×20 cm were used for rats aged 70 days and 42×26×15 cm cages were used for rats aged 18 and 25 months. In advance, the cage floor had been covered with sawdust packed to form a 5 cm layer. After 30 min of the rat being in the cage, the sawdust was again packed tightly, and 9 glass marbles with a diameter of 1.5 cm (according to the scheme 3 by 3, 5–6 cm apart) were placed on the sawdust surface in a regular spaced pattern for rats aged 70 days, and 18 marbles (scheme 6 by 3, 5–6 cm apart) – for rats aged 18 and 25 months. Secondly, the rat was again placed in the familiar cage with the marbles on the floor of cage. Thirty minutes later, the number of buried marbles was counted (at least 2/3 buried into the bedding) (Witkin 2008). Before starting the test, the sawdust was replaced for each rat.

At the age of 18 months, the above mentioned tests and the Porsolt test were performed in male and female rats of the positive ( $n = 26$  and  $n = 24$ ) and negative ( $n = 28$  and  $n = 26$ ) control groups, and the following experimental groups: 5 ( $n = 24$ ), 6 ( $n = 27$ ), 7 ( $n = 20$ ), 8 ( $n = 22$ ), 9 ( $n = 25$ ), 10 ( $n = 26$ ), 11 ( $n = 24$ ), 12 ( $n = 24$ ).

The Porsolt test was performed in the transparent plastic cylinders 45 cm high and 20 cm in diameter, filled with water (temperature 25 °C). The latent period of immobilization, the number and duration of complete immobility in the water (complete absence of swimming movements while passively holding the animal in the water) were recorded for 3 minutes (Porsolt 2000).

At the second stage of the study, for 30 days (from the 24<sup>th</sup> to 25<sup>th</sup> months of life), the male and female rats of the positive ( $n = 11$  and  $n = 12$ ) and negative ( $n = 16$  and  $n = 13$ ) control groups were intragastrically treated with distilled water. The animals of the experimental groups 5 ( $n = 16$ ) and 6 ( $n = 10$ ) were administrated with succicard at a dose of 44 mg/kg, of groups 7 ( $n = 11$ ) and 8 ( $n = 14$ ) – with salifen at a dose of 15 mg/kg, of groups 9 ( $n = 14$ ) and 10 ( $n = 13$ ) – with phenibut at a dose of 50 mg/kg,

of groups 11 ( $n = 9$ ) and 12 ( $n = 6$ ) – with pantogam at a dose of 100 mg. After that, the Open field test, Elevated plus maze test, Marble burying test and Porsolt test were performed to assess the psychoemotional state of the offspring at the age 25 months. The choice of doses of substances was determined by their most pharmacological activity in adult rats studied in (Tyurenkov et al. 2014b, c).

The statistical processing of the results was carried out with the help of STATISTICA v.12.5 software package (StatSoft Inc., USA) by Mann-Whitney U-test and the Student t-test for paired comparisons, as well as by Newman-Kales criterion, Kruskal-Wallis with Dunnett’s multiple comparison post hoc test. A preliminary check of normality was performed according to the Shapiro-Wilke criterion. Differences were considered significant at  $p < 0.05$ .

## Results and discussion

The Open field test showed that male offspring of the negative control group had a significantly lower number of unsupported rearings at the age of 70 days and 18 months. At the age of 70 days, male offspring made supported rearings more often. The number of defecations was higher in 70-day, 18- and 25-month-old male rats. At the age of 70 days and 18 months, the female offspring from the EP females made a significantly lower number of unsupported rearings, compared with the offspring born to healthy females. Female offspring made more supported rearings at the age of 70 days. In females of the negative control group, at the age of 70 days and 25 months, the numbers of short groomings and defecations were significantly greater. This indicates an increase in anxiety of the offspring from the females with EP compared with the females in the positive control group.

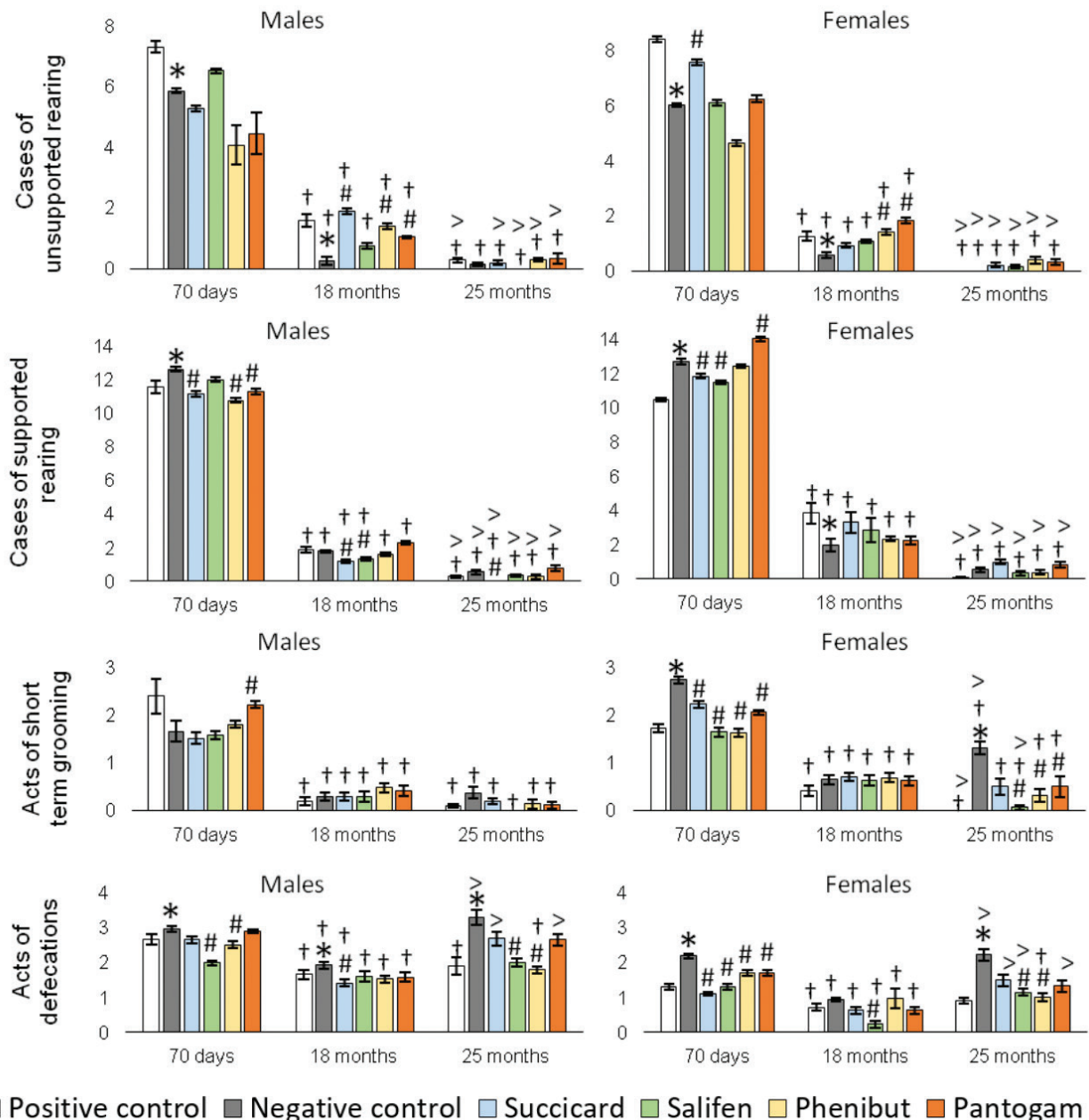
In the Open field test, the level of anxiety in offspring of different ages treated with GABA derivatives was lower than in the rats born to the females with high-risk EP pregnancy.

After early pharmacological correction (from the 40<sup>th</sup> day to the 70<sup>th</sup> day of life), succicard had the most anti-anxiety effect in female offspring at the age of 70 days, as the animals which had received it made more unsupported rearings, made fewer supported rearings, short groomings and defecations compared with the negative control group. Salifen and phenibut also showed a pronounced anxiolytic effect in 70-day-old male offspring. In the Open field test, their anxiety was lower than that in the EP control group. Succicard, salifen and phenibut were superior in effectiveness to pantogam.

In male offspring treated with succicard, the level of anxiety was lower at the age of 18 months. They made more unsupported rearings, fewer supported rearings, and defecations than the offspring of the negative control group. Salifen, phenibut, and pantogam as a comparison drug had an anxiolytic effect in male and female offspring, but it was less pronounced than in offspring at the age of 70 days.

In the offspring at the age of 25 months after a late pharmacological correction, salifen and phenibut only showed an anti-anxiety activity. In addition, it was found that the numbers of supported and unsupported rearings, as well as the number of short groomings, were statistically significantly lower in the offspring of all groups aged 18 and 25 months compared with 3-month-old animals. This is most likely associated with a general decrease in motor activity in old animals. At the same time, the number of defecations, though decreasing by the 18<sup>th</sup> month, was higher in 25-month-old rats in the negative control group, and in the animals treated with succinylcholine and pantogam (Fig. 1).

70-day, 18- and 25-month-old animals of the negative control group showed increased anxiety in the Elevated plus maze test and in the Open field test compared to offspring of the healthy females. Males born to the rats with EP performed significantly fewer hangings from the open arms at the age of 70 days and made more entries to the closed arms at the age of 70 days and 18 months than the offspring of the positive control group. Young and old female offspring of the rats with EP spent significantly less time in the open arms and made fewer hangings from the open arms. At the age of 70 days and 25 months, the number of entries into



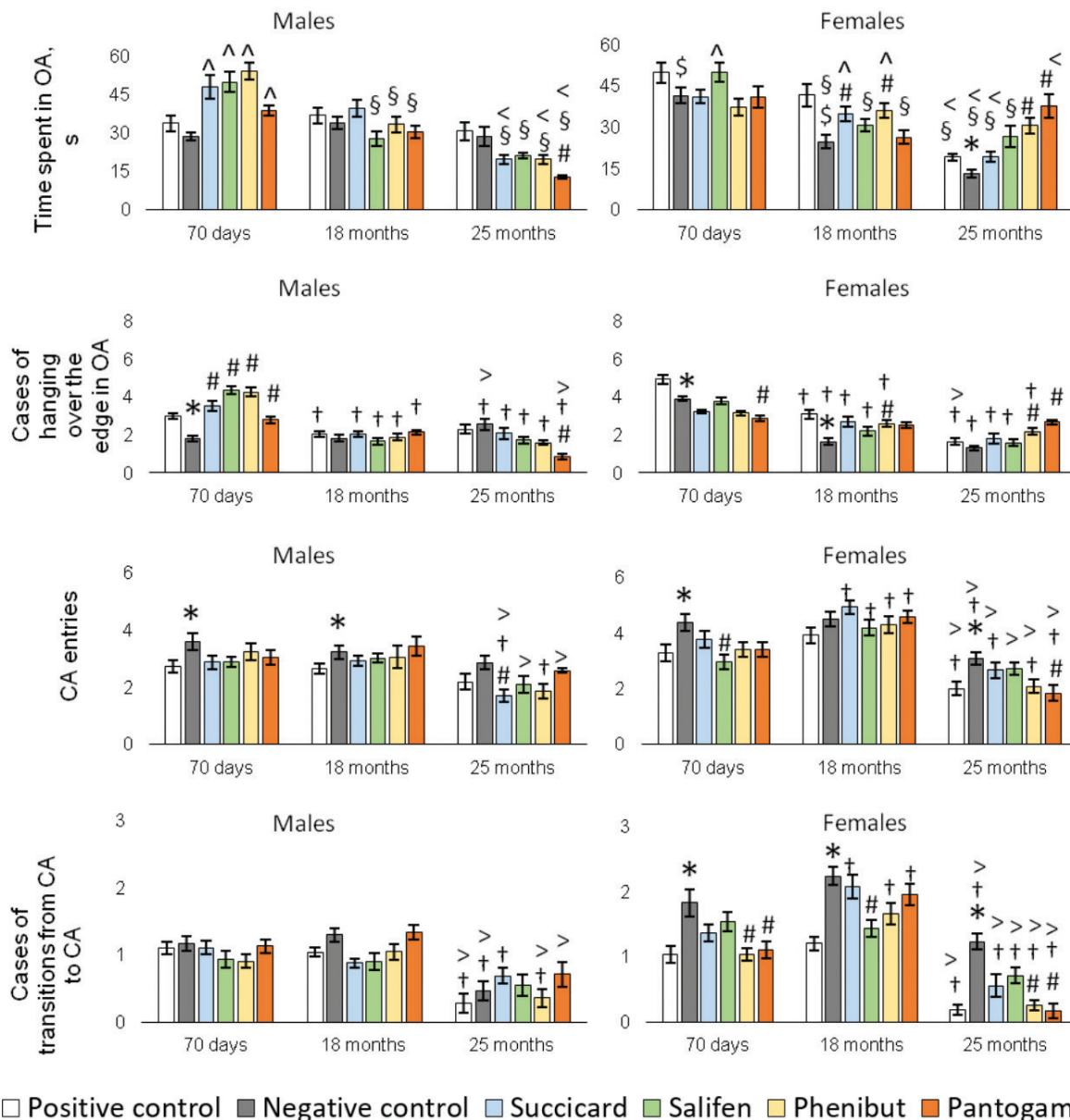
**Figure 1.** The effect of early and late pharmacological correction by GABA derivatives on anxiety indicators in offspring of females with experimental preeclampsia in the Open field test ( $M \pm m$ ). **Note.** The differences are statistically significant compared with the positive control group: \* – by Mann-Whitney U-test; compared with the negative control group: # – by Kruskal-Wallis test with Dunn's multiple comparison (post hoc) test; compared with offspring at the age of 3 months: † – by the Mann-Whitney U-test; compared with offspring at the age of 18 months: > – by to the Mann-Whitney U-test.  $p < 0.05$ .

closed arms by females of the negative control group was higher than that by the animals born to healthy rats, as well as the number of transitions from one closed to the other closed arms made by offspring of 70 days, 18 and 25 months old.

In offspring of females with EP at the age of 70 days, administration of succinard, salifen, phenibut, and pantogam as a comparison drug produced an anti-anxiety effect. By the age of 18 months, the anxiolytic effect persisted only in female offspring administered with the studied GABA derivatives, mostly succinard and phenibut, and at the age of 25 months – in the female offspring administered with phenibut and pantogam. In the male offspring,

the positive effect of early pharmacological correction (from the 40<sup>th</sup> day to the 70<sup>th</sup> day of life) by GABA derivatives weakened by the age of 18 months, and late administration (from the 24<sup>th</sup> to 25<sup>th</sup> months of life) did not significantly change the studied parameters.

For male and female offspring of different groups aged 18 and 25 months, the time spent in the open arms and the number of hangings from them were fewer in comparison to those by the 70-day-old offspring. The numbers of transitions and entries into the closed arms were also fewer in 25-month-old rats than that in the animals aged 70 days and 18 months, which is due to a decrease in motor activity in old animals (Fig. 2).



**Figure 2.** The effect of early and late pharmacological correction of anxiety indicators by GABA derivatives in offspring of females with experimental preeclampsia in the Elevated plus maze test ( $M \pm m$ ). **Note.** OA – open arms, CA – closed arms. The differences are statistically significant compared with the positive control group: \* – by Mann-Whitney U-test, \$ – by Student t-test; compared with the negative control group: # – by Kruskal-Wallis test with Dunn’s multiple comparison (post hoc) test, ^ – by the Newman-Kuels test; compared with offspring at the age of 3 months: † – by the Mann-Whitney U-test, § – by the Student t-test; compared with offspring at the age of 18 months: > – by to the Mann-Whitney U-test, < – by to the Student t-test.  $p < 0.05$

The Marble burying test showed that the offspring of rats with EP aged 70 days, 18 and 25 months buried significantly more marbles compared to the positive control group. The proportion of the animals which buried the marbles was also significantly larger. At the age of 70 days, male and females administered with salifen buried fewer marbles compared to the negative control group. In 18-month-old female offspring treated with succicard and salifen, this indicator was significantly lower than in the animals born to females with high-risk pregnancy. At the age of 25 months, the offspring after an injection of the studied GABA derivatives and pantogam demonstrated a decrease in the number of buried marbles, and the percentage of males which had buried the marbles was significantly lower in this age group compared to the negative control group (Fig. 3).

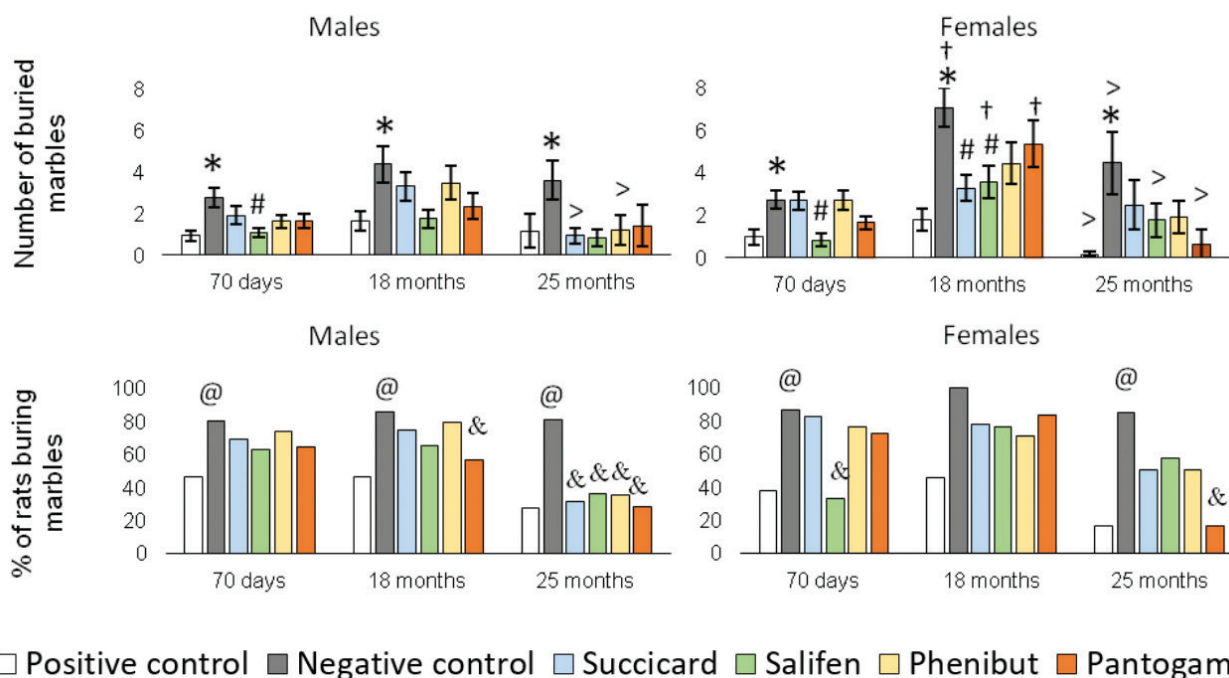
In the Porsolt test, 18-month-old male and female offspring born to the rats with EP had a shorter latent period and immobility time, as well as the number of freezings, compared to the rats of the positive control group. At the age of 25 months, the female born to the rats with EP pregnancy demonstrated a more expressed depressive behavior, which is probably associated with an age-related decrease in the production of sex hormones. At the age of 18 and 25 months, offspring treated with succicard, salifen, phenibut, and pantogam had a lower level of depression compared to the rats of the negative control group. At the same time, 25-month-old offspring corrected with the GABA derivatives showed that immobility time was shorter compared to offspring at the age of 18 months (Table 1).

Today, there are a large number of studies confirming the relationship between prenatal hypoxia and depressive and anxiety disorders in offspring at different periods of their life. The latter include a wide range of diseases, for example, generalized anxiety, panic, post-traumatic stress, childhood anxiety, obsessive-compulsive disorders, and various phobias.

According to Tuovinen et al. (2010, 2012, 2014), hypertensive pregnancy diseases increase the risk of depression and anxiety in children. The experimental study by Trofimova et al. (2010) showed that intrauterine intermittent hypoxia triggered a decrease in motor activity of rat offspring and an increase in their anxiety. Our previous studies also indicated the negative impact of EP on the psycho-emotional state of offspring (Tyurenkov et al. 2014a; Muzyko et al. 2020).

The experimental data obtained in the Open field, Elevated plus maze, Marble burying and Porsolt tests indicate that offspring of females with EP showed an increased level of anxiety and obsessive-compulsive disorder at the age of 70 days, 18 and 25 months, as well as depressive behavior at the age of 18 and 25 months.

Obviously, preeclampsia is associated with intrauterine hypoxia, which is a characteristic complication of such a type of high-risk pregnancy. The insufficient supply of oxygen to the developing fetus can affect the nervous system development and its differentiation, as well as may cause the death of neurons of various neurotransmitter systems, triggering a lag in mental development in the postnatal life (Kay et al. 2019).



**Figure 3.** The effects of early and late pharmacological correction by GABA derivatives of obsessive-compulsive disorder in offspring of females with experimental preeclampsia in the Marble burying test ( $M \pm m$ ). **Note.** The differences are statistically significant compared with the positive control group: \* –  $p < 0.05$  by Mann-Whitney U-test, @ –  $\varphi > 2.31$  by Fisher F-test; compared with the negative control group: # –  $p < 0.05$  by Kruskal-Wallis test with Dunn's multiple comparison (post hoc) test, & –  $\varphi > 2.31$  by Fisher F-test; compared with offspring at the age of 3 months: † –  $p < 0.05$  by the Mann-Whitney U-test; compared with offspring at the age of 18 months: > –  $p < 0.05$  by the Mann-Whitney U-test.

**Table 1.** Effect of Early and Late Pharmacological Correction with GABA Derivatives of Depressive Behavior in Offspring of Females with Rxperimental Preeclampsia in the Porsolt Test ( $M \pm m$ ).

Age	Groups of animals	Sex of rat	Latent period of immobilization, s	Immobility time, s	Cases of freezing
18 months	Positive control	Males	91.36±5.65	12.48±0.99	3.48±0.25
		Females	84.65±5.67	9.87±0.52	3.35±0.16
	Negative control	Males	64.29±5.98\$	25.29±6.49*	6.68±0.43*
		Females	56.88±4.11\$	19.33±1.48\$	6.00±0.38\$
	Progeny of rats with experimental preeclampsia receiving succicard	Males	99.58±6.83^	11.83±1.14#	4.17±0.35#
		Females	80.19±6.49^	10.67±0.97^	4.30±0.30^
	Progeny of rats with experimental preeclampsia receiving salifen	Males	84.65±7.24^	16.55±1.23	4.15±0.25#
		Females	92.10±6.21^	9.78±1.05^	3.14±0.19^
	Progeny of rats with experimental preeclampsia receiving phenibut	Males	104.13±5.92^	10.61±1.62#	4.17±0.88#
		Females	77.22±4.64^	13.17±0.59^	4.57±0.37^
Progeny of rats with experimental preeclampsia receiving pantogam	Males	93.71±5.96^	8.38±0.90#	3.25±0.29#	
	Females	72.04±5.80^	14.42±0.83^	4.71±0.37^	
25 months	Positive control	Males	87.56±6.46	18.56±1.85>	4.22±0.49
		Females	100.00±7.72	6.18±0.54<	3.09±0.20
	Negative control	Males	72.67±7.12	20.40±2.04	4.60±0.27>
		Females	52.58±6.55\$	22.33±2.86\$	4.67±0.36*>
	Progeny of rats with experimental preeclampsia receiving succicard	Males	108.87±9.56#	8.00±0.50^>	2.60±0.20#>
		Females	94.63±7.43^	6.75±0.41^>	2.75±0.25#>
	Progeny of rats with experimental preeclampsia receiving salifen	Males	102.09±6.52	9.09±0.40^>	3.18±0.38
		Females	107.42±4.52^	7.08±1.48^	2.50±0.19#>
	Progeny of rats with experimental preeclampsia receiving phenibut	Males	95.08±7.20	8.54±0.69^	2.77±0.30#
		Females	93.67±9.54^	9.25±0.57^<	2.92±0.26#>
Progeny of rats with experimental preeclampsia receiving pantogam	Males	115.14±3.97#	13.14±0.53^>	3.43±0.38	
	Females	95.83±9.03^	6.50±0.18^<	2.50±0.22#>	

**Note.** The differences are statistically significant compared with the positive control group: \* – by Mann-Whitney U-test, \$ – by Student t-test; compared with the negative control group: # – by Kruskal-Wallis test with Dunn's multiple comparison (post hoc) test, ^ – by the Newman-Kales test; compared with offspring at the age of 3 months: † – by the Mann-Whitney U-test, § – by the Student t-test; compared with offspring at the age of 18 months: > – by the Mann-Whitney U-test, < – by the Student t-test.  $p < 0.05$ .

It has been shown that preterm delivery, often resulting from preeclampsia, leads to a high risk of anxiety in pre-term infants and reduces their social adaptation and self-esteem, causes emotional dysregulation, attention deficit hyperactivity disorder, and depressive disorders (Arpi and Ferrari 2013; Mahoney et al. 2013; Dudova et al. 2014; Dobson et al. 2016). Morphologically, there is a decrease in the thickness of gray matter (Gimenez et al. 2006) and decrease in amygdala (Nosarti et al. 2014), which is central for the fear and anxiety processing.

Prenatal stress disturbs the production of a corticotropin-releasing hormone by the paraventricular nucleus and amygdala in rats, which leads to anxiety, fear, anxiety, and stress in affected animals (Brunton et al. 2011; Zohar and Weinstock 2011). It has been shown that changes in the DNA demethylation of the corticotrophin-releasing hormone Crhr 1 gene was observed in male rats subjected to intermittent hypoxia in the prenatal life. These data suggest that intermittent hypoxia in the prenatal life triggered anxious behavior in adulthood (Wang et al. 2013).

As a result of our study, it is shown that the early (from the 40<sup>th</sup> to the 70<sup>th</sup> day of life) pharmacological treatment with succicard, salifen, and phenibut exerts an anti-anxiety effect (at the age of 70 days) on offspring of females with EP, exceeding that of a comparison drug pantogam. By the age of 18 months, the anxiolytic effect persisted to a greater extent in the animals treated with succicard and phenibut. Among the derivatives of GABA which reduce anxiety in offspring of EP females during the late “therapy” (from the 24<sup>th</sup> to 25<sup>th</sup> month of life), phenibut showed the highest effectiveness.

The most decrease in the manifestations of obsessive-compulsive disorder in EP offspring was observed in 70-day and 18-month-old animals treated with salifen. Late treatment with succicard, salifen, phenibut, and pantogam limited compulsive behavior at the age of 25 months.

The antidepressant effects of the studied GABA derivatives and pantogam were registered after the early (from the 40<sup>th</sup> to 70<sup>th</sup> day of life) and late (from the 24<sup>th</sup> to 25<sup>th</sup> month of life) treatment of offspring aged 18 and 25 months, respectively.

The improvement in the psychoemotional state of offspring of rats with EP treated with the studied compounds can probably be explained by the fact that GABA derivatives have nootropic, neuro- and endothelioprotective, antihypoxic and anxiolytic effects as was shown in the previous studies (Tyurenkov et al. 2014a; Muzyko et al. 2020). Besides, the substances of this pharmacological group improve the processes of respiration and oxidative phosphorylation by reducing energy deficiency of neurons in hypoxia. They improve glucose utilization, stimulate protein synthesis in the brain cells and stabilize the functions of neuron membranes in chronic cerebral ischemia (Burchynskyi 2015).

## Conclusion

Thus, EP produced a negative effect on the psychoemotional state of offspring at the age of 70 days, 18 and 25 months. Early pharmacological correction (from the 40<sup>th</sup> to 70<sup>th</sup> day of life) with GABA derivatives, such as succicard,

salifen, and phenibut, limits anxiety and depressive behavior in rats born to females with EP. Treatment with salifen decreased manifestations of obsessive-compulsive disorder in animals aged 70 days and 18 months. In late "therapy" (from the 24<sup>th</sup> to 25<sup>th</sup> month of life), the studied derivatives of GABA exerted anti-compulsive and anti-depressant effects, with phenibut having the most pronounced anxiolytic effect. Because succinylcholine, salifen, and phenibut were comparable or superior to pantogam in terms of their effective-

ness, this suggests the chance to create medicines based on them to correct psychoemotional disorders in offspring in early and late periods of their life.

## Conflict of interest

The authors declare no conflict of interest.

## References

- Andreescu C, Lenze EJ, Dew M, Begley AE, Mulsant BH, Dombrowsky AY, Pollock BG, Stack J, Miller MD, Reynolds CF (2007) Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: controlled study. *The British Journal of Psychiatry: the Journal of Mental Science* 190: 344–349. <https://doi.org/10.1192/bjp.bp.106.027169> [PubMed]
- Arpi E, Ferrari F (2013) Preterm birth and behaviour problems in infants and preschool-age children: a review of the recent literature. *Developmental Medicine and Child Neurology* 55(9): 788–796. <https://doi.org/10.1111/dmcn.12142> [PubMed]
- Brunton PJ, Donadio MV, Russell JA (2011) Sex differences in prenatally programmed anxiety behaviour in rats: differential corticotropin-releasing hormone receptor mRNA expression in the amygdaloid complex. *Stress: The International Journal on the Biology of Stress* 14(6): 634–643. <https://doi.org/10.3109/10253890.2011.604750> [PubMed]
- Burchynskyi SH (2015) GABA-ergic agents in the pharmacotherapy of chronic cerebral ischemia. *International Neurological Journal* 1(71): 101–105. [in Russian]
- Dobson KG, Schmidt LA, Saigal S, Boyle MH, Van Lieshout RJ (2016) Childhood cognition and lifetime risk of major depressive disorder in extremely low birth weight and normal birth weight adults. *Journal of Developmental Origins of Health and Disease* 7(6): 574–580. <https://doi.org/10.1017/S2040174416000374> [PubMed]
- Dudova I, Markova D, Kasparova M, Zemankova J, Beranova S, Urbanek T, Hrdlicka M (2014) Comparison of three screening tests for autism in preterm children with birth weights less than 1,500 grams. *Neuropsychiatric Disease and Treatment* 10: 2201–2208. <https://doi.org/10.2147/NDT.S72921> [PubMed] [PMC]
- Galyamina AG, Kovalenko IL, Smagin DA, Kudryavtseva NN (2016) Relationship of anxiety and depression in the development of mixed anxiety/depression disorder. An experimental study of comorbidity mechanisms (review). *Neuroscience and Behavioral Physiology* 66(2): 181–201. <https://doi.org/10.7868/S0044467716020039> [PubMed] [in Russian]
- Gimenez M, Junque C, Vendrell P, Narberhaus A, Bargalló N, Botet F, Mercader JM (2006) Abnormal orbitofrontal development due to prematurity. *Neurology* 67: 1818–1822. <https://doi.org/10.1212/01.wnl.0000244485.51898.93> [PubMed]
- Kay VR, Ratsep MT, Figueiro-Filho EA, Croy BA (2019) Preeclampsia may influence offspring neuroanatomy and cognitive function: a role for placental growth factor. *Biology of Reproduction* 101(2): 271–283. <https://doi.org/10.1093/biolre/iox095> [PubMed]
- Kovtun OP, Tsyvian PB (2019) Preeclampsia in a mother and programming of the child's cardiovascular health. *Russian Bulletin of Perinatology and Pediatrics* 64(4): 19–25. <https://doi.org/10.21508/1027-4065-2019-64-4-19-25> [in Russian]
- Mahoney AD, Minter B, Burch K, Stapel-Wax J (2013) Autism spectrum disorders and prematurity: a review across gestational age subgroups. *Advances in Neonatal Care: Official Journal of the National Association of Neonatal Nurses* 13: 247–251. <https://doi.org/10.1097/ANC.0b013e31828d02a1> [PubMed]
- Muzyko EA, Tkacheva GA, Perfilova VN, Matvienko LS, Naumenko LV, Vasil'eva OS, Tyurenkov (2020) Effects of GABA derivatives on anxious and compulsive behavior in offspring of rats with experimental preeclampsia. *Bulletin of Experimental Biology and Medicine* 168(4): 457–464. <https://doi.org/10.1007/s10517-020-04731-x> [PubMed]
- Nosarti C, Giouroukou E, Healy E, Rifkin L, Walshe M, Reichenberg A, Chitnis X, Williams SC, Murray RM (2008) Grey matter distribution in very preterm adolescents mediates neurodevelopmental outcome. *Brain: a Journal of Neurology* 131: 205–217. <https://doi.org/10.1093/brain/awn282> [PubMed]
- Ostrovskaya RU, Raevsky CS, Voronina TA, Garibova TL, Kovalev GI, Kudrin VS, Narkevich WB, Klodt PM (2012) Guidelines for the study of the antipsychotic activity of drugs. In: Mironov AN (Ed.) *Guidelines for Preclinical Drug Research, Part 1*. Grif & Co., Moscow, 251–263. [in Russian]
- Porsolt RD (2000) Animal models of depression: utility for transgenic research. *Reviews in the Neurosciences* 11(1): 53–58. <https://doi.org/10.1515/REVNEURO.2000.11.1.53> [PubMed]
- Phillips T, Scott H, Menassa D, Bignell A, Sood A, Morton J, Akagi T, Azuma K, Rogers M, Gilmore C, Inman G, Grant S, Chung Y, Aljunaidy M, Cooke C, Steinkraus B, Pocklington A Logan A, Collett G, Kemp H, Holmans P, Murphy M, Fulga T, Coney A, Akashi M, Davidge S, Case C (2017) Treating the placenta to prevent adverse effects of gestational hypoxia on fetal brain development. *Scientific Reports* 7(1): 1–9079. <https://doi.org/10.1038/s41598-017-06300-1> [PubMed] [PMC]
- Trofimova LK, Graf AV, Maslova MV, Dunaeva TU, Maklakova AS, Sokolova NA (2010) Postnatal behavioural consequences of antenatal intermittent hypoxia experienced during early organogenesis in mature rats. *Bulletin of the Russian Academy of Sciences. Biology [Izvestiia Akademii nauk. Seriya biologicheskaya]* 1: 54–59. [in Russian] <https://doi.org/10.1134/S1062359010010061>
- Tuovinen S, Eriksson JG, Kajantie E, Räikkönen K (2014) Maternal hypertensive pregnancy disorders and cognitive functioning of the offspring: a systematic review. *Journal of the American Society*



- of Hypertension: JASH 8(11): 832–847. <https://doi.org/10.1016/j.jash.2014.09.005> [PubMed]
- Tuovinen S, Räikkönen K, Kajantie E, Pesonen AK, Heinonen K, Osmond C, Barker DJ, Eriksson JG (2010) Depressive symptoms in adulthood and intrauterine exposure to preeclampsia: the Helsinki Birth Cohort Study. *BJOG: an International Journal of Obstetrics and Gynaecology* 117(10): 1236–1242. <https://doi.org/10.1111/j.1471-0528.2010.02634.x> [PubMed]
  - Tuovinen S, Raikkonen K, Pesonen AK, Lahti M, Heinonen K, Wahlbeck K, Kajantie E, Osmond C, Barker DJ, Eriksson JG (2012) Hypertensive disorders in pregnancy and risk of severe mental disorders in the offspring in adulthood: the Helsinki Birth Cohort Study. *Journal of Psychiatric Research* 46(3): 303–310. <https://doi.org/10.1016/j.jpsychires.2011.11.015> [PubMed]
  - Tyurenkov IN, Perfilova VN, Mikhailova LI, Zhakupova GA, Lebedeva SA (2014a) Comparative study of the effects of new neuroactive amino acid derivatives on the postnatal development of the rat's offspring with experimental preeclampsia. *Annals of the Russian Academy of Medical Sciences [Vestnik Rossijskoj Akademii Meditsinskikh Nauk]* 69(9–10): 123–130. <https://doi.org/10.15690/vramn.v69i9-10.1141> [PubMed] [in Russian]
  - Tyurenkov IN, Perfilova VN, Reznikova LB, Smirnova LA, Ryabukha AF, Suchkov EA, Kuznetsov KA (2014b) GABA derivatives citrocard and salifen reduce the intensity of experimental gestosis. *Bulletin of Experimental Biology and Medicine* 157(1): 42–44. <https://doi.org/10.1007/s10517-014-2487-z> [PubMed]
  - Tyurenkov IN, Perfilova VN, Karamysheva VI, Popova TA, Lebedeva SA, Mihajlova LI, Zhakupova GA (2014c) Gravidaprotective action of phenibut in experimental pre-eclampsia. *Russian Journal of Experimental and Clinical Pharmacology [Eksperimental'naja i Klinicheskaia Farmakologija]* 77(11): 6–10. <https://doi.org/10.30906/0869-2092-2014-77-11-6-10> [PubMed] [in Russian]
  - Voronina TA, Ostrovskaya RU, Garibova TL (2012) Guidelines for the preclinical study of drugs with nootropic type of action. In: Mironov AN (Ed.) *Guidelines for Preclinical Drug Research, Part 1*. Grif & Co., Moscow, 276–296. [in Russian]
  - Wang X, Meng FS, Liu ZY, Fan JM, Hao K, Chen XQ, Du JZ (2013) Gestational hypoxia induces sex-differential methylation of Crhr1 linked to anxiety-like behavior. *Molecular Neurobiology* 48(3): 544–555. <https://doi.org/10.1007/s12035-013-8444-4> [PubMed]
  - Witkin JM (2008) Animal models of obsessive-compulsive disorder. *Current Protocols in Neuroscience* 45: 9.30.1–9.30.9. <https://doi.org/10.1002/0471142301.ns0930s45> [PubMed]
  - Zohar I, Weinstock M (2011) Differential effect of prenatal stress on the expression of corticotrophin-releasing hormone and its receptors in the hypothalamus and amygdala in male and female rats. *Journal of Neuroendocrinology* 23(4): 320–328. <https://doi.org/10.1111/j.1365-2826.2011.02117.x> [PubMed]

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