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Изменение деформабельности и резистентности мембран эритроцитов у потомства крыс с экспериментальной преэклампсией под действием производных гамма-аминомасляной кислоты

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АННОТАЦИЯ

Введение. Преэклампсия — тяжелое осложнение беременности, которое сопровождается негативными последствиями со стороны матери и ребенка. Такими осложнениями могут служить снижение устойчивости мембран эритроцитов к повреждающим агентам и изменение реологических свойств крови у потомства. Перспективными соединениями для коррекции названных негативных последствий преэклампсии являются производные гамма–аминомасляной кислоты (ГАМК), поскольку в ранее проведенных исследованиях были показаны их мембранопротекторное, антиоксидантное и антигипоксическое действия.

Цель. Оценить влияние Сукцикарда® (4-фенилпирацетам и этан-1,2-дикарбоновая кислота, 2:1), Салифена® (4-амино-3-фенилбутановая кислота и 2-гидроксибензойная кислота, 2:1) и Фенибута® (аминофенилмасляной кислоты), являющихся производными ГАМК, на деформабельность и резистентность мембран эритроцитов у 8- и 14-месячного потомства, рожденного крысами с экспериментальной преэклампсией (ЭП).

Материалы и методы. В исследовании участвовало потомство (самцы и самки) белых неинбредных самок с нормально протекающей беременностью и ЭП, которая была смоделирована посредством замены питьевой воды на 1,8% раствор NaCl в период гестации (1–21 день). В течение 30 дней (с 40 по 70 день жизни) крысята внутрижелудочно один раз в день получали Сукцикард® (22 мг/кг), Салифен® (7,5 мг/кг), Фенибут® (25 мг/кг) и препарат сравнения — Пантогам® (кальция гопантенат) (50 мг/день). Потомству групп позитивного и негативного контролей в аналогичном режиме вводили дистиллированную воду. В возрасте 8 и 14 мес. у потомства определяли резистентность мембран эритроцитов к действию соляной кислоты и их деформабельность.

Результаты. У 8-месячных самцов, рожденных крысами с ЭП, наблюдалось более короткое относительно группы позитивного контроля время достижения половины величины максимальной амплитуды эритрограммы при проведении кислотного гемолиза и уменьшение индекса элонгации эритроцитов. Сукцикард®, Салифен®, Фенибут® и Пантогам® способствовали увеличению продолжительности гемолиза и индекса элонгации эритроцитов у самцов опытных групп в 8 мес. относительно группы негативного контроля. У 14-месячных самцов, и у самок разного возраста статистически значимых отличий между группами не было обнаружено.

Заключение. Изменения жесткости и прочности мембран эритроцитов отмечаются только у самцов, рожденных крысами с ЭП. Сукцикард®, Салифен®, Фенибут® и Пантогам® оказывали мембранопротекторный эффект на эритроциты 8-мес. самцов опытных групп.

Ключевые слова: *экспериментальная преэклампсия; потомство; производные ГАМК; деформабельность и резистентность эритроцитов*

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Changes in the Deformability and Resistance of Erythrocyte Membranes under the Action of Gamma-Aminobutyric Acid Derivatives in the Offspring of Rats with Experimental Preeclampsia

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ABSTRACT

INTRODUCTION: Preeclampsia is a severe complication of pregnancy associated with the negative consequences for the mother and child. Such complications can be a reduction in the resistance of erythrocyte membranes to damaging agents and alteration of rheological properties of the blood in offspring. Promising compounds for the correction of these negative consequences of preeclampsia are gamma-aminobutyric acid (GABA) derivatives, which showed membrane–protective, antioxidant, and antihypoxic effects in previous studies.

AIM: To evaluate the effect of GABA derivatives Succicard® (4-phenylpiracetam and ethane-1,2-dicarboxylic acid, 2:1), Salifen® (4-amino-3-phenylbutanoic acid and 2-hydroxybenzoic acid, 2:1), and Phenibut® (aminophenylbutyric acid) on the deformability and resistance of erythrocyte membranes in 8- and 14-month-old offspring of rats with experimental preeclampsia (EP).

MATERIALS AND METHODS: The study involved offspring (male and female) of white non-inbred female rats with a normal pregnancy and EP that was modeled by replacement of drinking water with a 1.8% sodium chloride solution during gestation (1–21 days). For 30 days (from day 40 to day 70 of life), pup rats intragastrically received Succicard® (22 mg/kg), Salifen® (7.5 mg/kg), and Phenibut® (25 mg/kg), along with a comparison drug Pantogam® (calcium gopantenate) (50 mg/day) once a day. The offspring of the positive and negative control groups were injected with distilled water in a similar mode. In offspring aged 8 and 14 months, the resistance of erythrocyte membranes to the action of hydrochloric acid and their deformability were determined.

RESULTS: In 8-month-old male offspring of rats with EP, a shorter time of achievement of half the maximal amplitude of erythrogram was noted in acid hemolysis relative to the positive control group, and the erythrocyte elongation index was reduced. Relative to the negative control group, Succicard®, Salifen®, Phenibut®, and Pantogam® promoted the prolongation of hemolysis and the erythrocyte elongation index in 8-month-old male rats in the experimental groups. In 14-month-old male and female rats of different ages, no statistically significant differences were found between the groups.

CONCLUSION: Changes in the stiffness and strength of erythrocyte membranes were noted only in male offspring of rats with EP. Succicard®, Salifen®, Phenibut®, and Pantogam® produced membrane-protective effects on the erythrocytes of 8-month-old male rats of the experimental groups.

Keywords: *experimental preeclampsia; offspring; GABA derivatives; deformability and resistance of erythrocytes*

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LIST OF ABBREVIATIONS

GABA — gamma-aminobutyric acid
EEI — erythrocyte elongation index
LP — lipid peroxidation
EP — experimental preeclampsia

INTRODUCTION

Currently, preeclampsia affects approximately 5% of pregnancies worldwide and is one of the main causes of childhood and maternal morbidity. According to previous studies, this pregnancy complication leads to fetal abnormalities and genetic pathologies and increases the risk of cardiovascular and nervous diseases and metabolic and hematological disorders in children at different periods of development [1, 2].

Systemic endothelial dysfunction in preeclampsia leads to insufficient supply of oxygen and nutrients to the developing fetus. Chronic intrauterine hypoxia is associated with oxidative stress that disrupts the structural and functional development of fetal organs [3].

The degree of cell destruction and dysfunction in offspring may be manifested by the reduction of the resistance of erythrocytes to damaging factors, since the erythrocyte membrane is a universal model of the plasma membrane [4]. An important rheological parameter that reflects the adequacy of oxygen supply to organs and tissues is the deformability of erythrocytes. A reduction in this parameter causes an increase in blood viscosity and impairment of microcirculation, which increases the risk of hemodynamic disorders [5].

In this regard, the search for substances that have a membrane-protective effect and reduce blood viscosity is relevant. A study revealed that gamma-aminobutyric acid (GABA) derivatives have endothelium-protective, antioxidant, and antihypoxic effects and stabilize cell membranes [6], which make them promising compounds for the correction of post-hypoxic complications in children of mothers with preeclampsia.

This study **aimed** to evaluate the effects of succicard, salifen, and phenibut, which are derivatives of GABA, on the deformability and resistance of erythrocyte membranes in 8- and 14-month-old offspring of rats with experimental preeclampsia (EP).

MATERIALS AND METHODS

The study was conducted on 84 male (n = 42) and female (n = 42) offspring of white non-inbred rats with uncomplicated pregnancy and EP. The rats were obtained from Rappolovo Breeding House for Laboratory Animals, Rappolovo Village, Leningrad, Russian Federation. EP was modeled by replacing drinking water with 1.8% NaCl solution during the gestation period (1–21 days) [6].

Experiments were conducted in accordance with the requirements and recommendations of the state standard R-33044-2014 "Principles of Good Laboratory Practice," Directive of the European Parliament and of the Council of the European Union 2010/63/EU on the Protection of Animals used for Scientific Purposes, September 22, 2010, and European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, Strasbourg, March 18, 1986. This study was approved by the regional independent ethical committee of the Volgograd Region (Protocol No. 2044-2017 on December 25, 2017).

Each group included seven animals:

- ***Groups 1 and 2*** (positive control) included male and female offspring, respectively, of rats with uncomplicated pregnancy. They were given distilled water intragastrically daily at the same time within 30 days (i.e., from 40 to 70 days of life).

- ***Groups 3 and 4*** (negative control) included male and female offspring, respectively, of rats with EP and given distilled water in the same regimen.

The experimental groups included male and female offspring of rats with EP:

- ***Groups 5*** (male) ***and 6*** (female) included rats that were given succicard 22 mg/kg (4-phenyl pyracetam and ethane-1,2-dicarboxylic acid, 2:1 ratio).

- ***Groups 7*** (male) ***and 8*** (female) included rats that were given salifen 7.5 mg/kg (4-amino-3-phenyl butanoic acid and 2-hydroxybenzoic acid, 2:1 ratio).

- ***Groups 9*** (male) ***and 10*** (female) included rats that were given phenibut 25 mg/kg (4-amino-3-phenylbutyric acid).

All drugs for groups 5–10 were supplied by Herzen State Pedagogical University of Russia, St. Petersburg.

- ***Groups 11*** (male) ***and 12*** (female) included animals that were given pantogam® (calcium hopantenate) 50 mg/day (syrup 100 mg/mL, PIC-PHARMA PRO OOO, Russian Federation) as a comparison drug.

The deformability and resistance of erythrocyte membranes in the 8-month-old offspring were determined. For this, blood was taken from the sublingual vein and stabilized with 3.8% sodium citrate

solution (Vecton, Russia) in a 9:1 ratio, and it was gently mixed without foam formation.

The resistance of erythrocyte membranes to hydrochloric acid was evaluated by the method of Tersky and Gitelzon (1961). After three washes in saline, 10 μL of erythrocytes were resuspended in 5 mL of 0.9% NaCl solution (Escom NPK, Russian Federation). The erythrocyte suspension (290 μL) was introduced into a cuvette and placed for 1 min in a thermostatically controlled cell of a laser aggregation analyzer with a built-in 220 LA magnetic stirrer (NPF Biola, Russian Federation). Then, 10 s after the recording was turned on, 10 μL of 0.1 normal HCl solution was added to the cuvette. The time to reach one-half of the maximum amplitude in the erythrogram (T1/2 of hemolysis) served as an indicator of the *resistance of erythrocytes to the action of hydrochloric acid*.

Deformability of erythrocytes was evaluated by erythrocyte elongation index (EEI) in a flow microchamber. After filling the microchamber of erythrocytes with 0.9% NaCl solution and 0.1% bovine serum albumin (Sigma-Aldrich, USA), pressure was applied. The shearing stress (τ) was calculated as follows:

$$\tau = \frac{6\eta Q}{Wh^2}$$

where n is the suspension viscosity (approximately 1.0 mPa × c at 20°C); Q, volume flow; W, width of the flow channel; h, height of the channel equaling the thickness of the wafer.

The obtained image was recorded and analyzed in Adobe Photoshop CC program (2021, trial version), and the length and width of elongated erythrocytes were measured. On the basis of the data obtained, the EEI was calculated as follows:

$$EEI = \frac{L - W}{L + W}$$

where L indicates the length of the deformed cell and W is the width of the deformed cell.

At age 14 months, the aforementioned tests were repeated in male and female rats of the positive (n = 6 and n = 6) and negative (n = 7 and n = 6) control groups and experimental groups 5 (n = 6), 6 (n = 7), 7 (n = 7), 8 (n = 6), 9 (n = 6), 10 (n = 7), 11 (n = 6), and 12 (n = 6).

The results of the experimental study were statistically processed using Statistica version 12.5 (License no. 133-190-095, StatSoft Inc., USA). For paired and multiple comparisons of samples, Student's and Newman–Keuls tests were used, respectively. The difference was considered significant at $p < 0.05$.

RESULTS

In 8-month-old male offspring of rats with EP, the resistance of erythrocyte membranes to hydrochloric acid decreased. The time to reach one-half of the maximal amplitude in the erythrogram in them was 17.7% ($p = 0.0196$) shorter relative to the positive control group. At 14 months, the offspring of the negative control group showed a tendency to reduce T1/2 of hemolysis.

Succicard, salifen, phenibut, and Pantogam increased the duration of reaching one-half of the maximal amplitude in erythrogram in 8-month-old male offspring of the experimental groups by 24.3% ($p = 0.0006$), 25.9% ($p = 0.0003$), 14.7% ($p = 0.0281$), and 20.3% ($p = 0.0041$), respectively, as compared with the data of the negative control group. In 14-month-old male and female offspring that received the above GABA derivatives at different time points, no differences were found in the offspring of rats of the control group with EP (Figure 1).

The EEI was 20.0% lower in 8-month-old male offspring of pregnant rats with EP ($p = 0.0034$) than in the offspring of healthy rats. In 14-month-old rats, no reliable differences were found among the positive control group, negative control group, and experimental groups.

Succicard, salifen, phenibut, and Pantogam increased the deformability of erythrocyte membranes in 8-month-old male rats of the experimental groups, and the EEI was greater than that in the negative control group by 17.9% ($p = 0.0013$), 15.1% ($p = 0.0016$), 22.2% ($p = 0.0002$), and 17.6% ($p = 0.0009$), respectively. By age 14 months, the effect of therapy with these GABA derivatives starting at an early age leveled out, and no significant differences were found between the groups (Figure 2).

DISCUSSION

According to the results of this study, in 8-month-old male offspring of the negative control group, the resistance of erythrocyte membranes to damaging agents was reduced and membrane deformability was impaired, as evidenced by the short time needed to reach one-half of the maximal amplitude in erythrogram and by the reduction of EEI when compared with the values obtained in the offspring of healthy rats. This may be due to the insufficient uteroplacental circulation in the mother with EP and the insufficient oxygen supply to the fetus. In the first days of life of rats exposed to intrauterine hypoxia, the processes of erythropoiesis were enhanced; however, it leads to the depletion of the functional reserves of the erythrocyte system [7] and insufficient perfusion and oxygenation of the tissues of the offspring of rats with EP. Hypoxia mediates the development of oxidative damage to membranes and

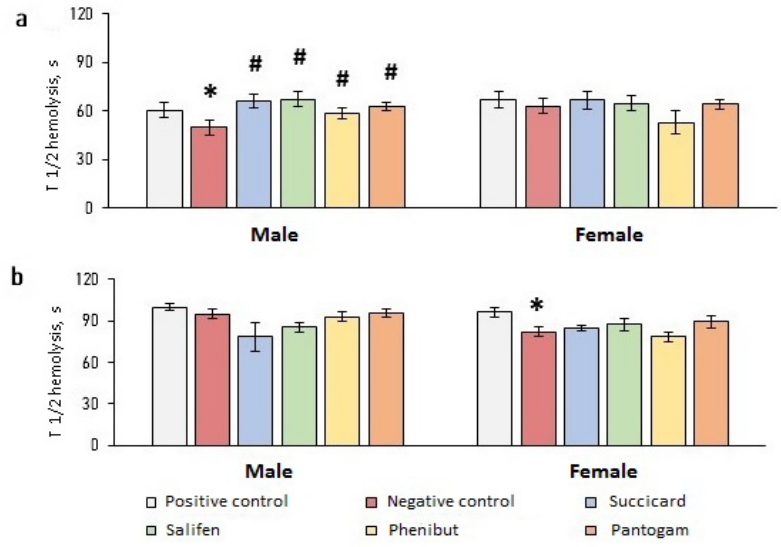

Fig. 1. Effect of gamma-aminobutyric acid derivatives on the duration of reaching one-half of the maximal amplitude in the erythrogram (T1/2 of hemolysis) in 8-month-old (A) and 14-month-old (B) offspring of rats with experimental preeclampsia (M ± m).
Note: * p < 0.05 in comparison with the data of the positive control group (Student's t-test); # p < 0.05 in comparison with the data of the negative control group (Newman–Keuls test).

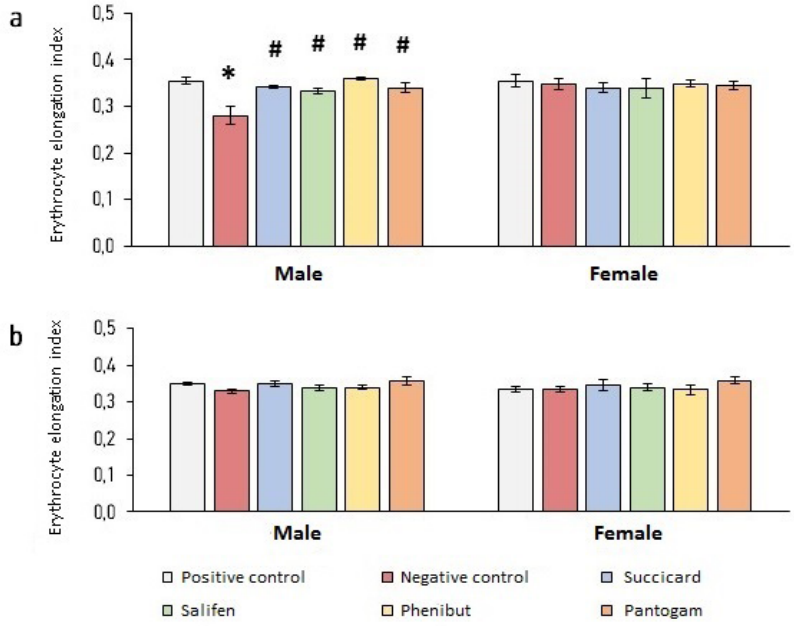

Fig. 2. Effect of gamma-aminobutyric acid derivatives on erythrocyte elongation index in 8-month-old (A) and 14-month-old (B) offspring of rats with experimental preeclampsia (M ± m).
Note: * p < 0.05 in comparison with the data of the positive control group (Student's t-test); # p < 0.05 in comparison with the data of the negative control group (Newman–Keuls test).

pathological modification of erythrocyte proteins [8]. The accumulation of oxidation products in erythrocyte membranes is associated with the changes in their fluidity and deformability [9]. Consequently, the structure of erythrocyte membranes becomes more rigid and fragile, and the membrane potential and permeability to ions change, which leads to intravascular hemolysis. In our previous studies, we found that the offspring of rats with EP have increased plasma levels of the lipid peroxidation product malondialdehyde and reduced activities of superoxide dismutase and catalase compared with the values of these parameters in animals born to rats with physiological pregnancy [10].

In male offspring aged 8 months, succicard, salifen, phenibut, and Pantogam enhanced the deformability of erythrocyte membranes and their resistance to

hydrochloric acid. This is apparently associated primarily with their ability to limit peroxide oxidation of lipid processes and increase the activity of antioxidant system enzymes. In addition, the normalizing effect of GABA derivatives on the microcirculation, their antihypoxic activity, and membrane-protective effect are known [11].

Moreover, no significant differences were observed in female rats of different ages and groups, which may be due to the effects of sex hormones during the estrous cycle. The protective effect of endogenous estrogens is related to the deformability of erythrocytes [12, 13]. In the study by Mladenovic et al., estradiol was shown to limit the oxidative injury of erythrocytes by acting synergistically with glutathione and vitamin E [14].

CONCLUSION

Male offspring of rats with EP showed an increase in stiffness and a decrease in the strength of erythrocyte membranes relative to the offspring of healthy rats at 8 months. The derivatives of GABA, namely, succicard, salifen, and phenibut, and the comparison drug Pantogam demonstrated membrane-protective effects on the erythrocytes of 8-month-old male offspring of the experimental groups.

ADDITIONAL INFORMATION

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Contribution of the authors: *E. A. Muzyko* — implementation of the main stages of the experiments, analysis and interpretation of the data, writing the article; *L. V. Naumenko* — implementation of the main stages of the experiments, analysis and interpretation of the data; *V. N. Perfilova* — analysis and interpretation of the data, revision of the crucially important conceptual content, approval of the manuscript for publication; *V. E. Zavadskaya, S. V. Varlamova* — implementation of the main stages of the experiments; *I. N. Tyurenkov* — development of the concept and design of the study, revision of the crucially important conceptual content, final approval of the manuscript for publication; *O. S. Vasilyeva* — analysis and interpretation of the data, revision of the crucial conceptual content. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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