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PHARMACOLOGICAL CORRECTION OF L-NAME-INDUCED OXIDE DEFICIENCY WITH DERIVATIVES OF 3-(2,2,2-TRIMETHYLHYDRAZINIUM) PROPIONATE

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Abstract. This paper deals with the study of correction of L-NAME-induced endothelial dysfunction by means of 3-(2,2,2-trimethylhydrazinium) propionate derivatives. We have shown that 3-(2,2,2-trimethylhydrazinium) propionate and its derivatives reduced the expression of NO-deficient endothelial dysfunction induced by intraperitoneal administration of N-nitro L-arginine methyl ester (L-NAME), improved the parameters of endothelium-dependent vasodilation in response to administration of acetylcholine, and reduced the coefficient of endothelial dysfunction. It was revealed that the 5-hydroxinicotinate 3-(2,2,2-trimethylhydrazinium) potassium propionate has the most pronounced endothelioprotective effect.
Keywords: endothelial dysfunction; 3-(2,2,2-trimethylhydrazinium) propionate; L-NAME.

Introduction. Currently, the dysfunction of the vascular endothelium is considered one of the leading factors in the pathogenesis of heart and blood vessel diseases [1, 2, 3, 4, 5, 6, 7]. The unique position of endothelial cells at the interface between circulating blood and tissues makes them the most vulnerable to a variety of pathogenic factors present in the system and the tissue blood flow. These cells are the first to meet with reactive free radicals, oxidized low density lipoproteins, hypercholesterolemia, high hydrostatic pressure inside the blood vessels they line (in arterial hypertension), and hyperglycemia (in diabetes mellitus). All of these factors lead to damage of the vascular endothelium, and further to endothelial dysfunction (ED) [8, 9, 10, 11, 12, 13]. Among all the factors synthesized by the endothelium, the main role is played by endothelial relaxation or nitrogen oxide (NO). This compound regulates the activity and the sequence of “launch" of all other endothelium-produced bioactive substances.

NO, synthesized by endothelial NO-synthase (eNOS) is one of the key regulators of vascular tone. Arterial hypertension, a powerful risk factor for cardiovascular diseases, is characterized by the formation of excessive reactive species of oxygen in the body that interact with NO and thereby reduce its bioavailability, and cause oxidative stress when oxidizing NO to peroxynitrite [14, 15].

Increased production of ROS (reactive oxygen species) in vascular disorders is accompanied by severe dysfunction of the vascular endothelium. Production of any of ROSs can cause the formation of several others. All of them are accumulated in the cell membrane, and may have adverse effects on cell functions [15, 16, 17, 18].

Experimental modeling of arterial hypertension in animals showed that an increase in ROS leads to

endothelial dysfunction, as evidenced by the improvement of endothelium-dependent relaxation upon application of antioxidants [4].

Chronic renal failure in animals leads to increased production of ROS and decreased NO bioavailability and therefore to the development of endothelial dysfunction, correctable with antioxidant pre-treatment [16, 17].

In this context, the objective of our study was to investigate endotelio- and cardioprotective activity of 3-(2,2,2-trimethylhydrazinium) propionate (mildronat) and its derivatives (nicotinate, 5-bromonicotinate, 5-hydroxinicotinate, glycinate) 3-(2, 2,2-trimethylhydrazinium) propionate) in the model of L-NAME induced nitrogen oxide deficiency.

Materials and research methods. We studied 4 chemical derivatives of 3-(2,2,2-trimethylhydrazinium) propionate (derivatives of 3-(2,2,2-trimethylhydrazinium) potassium propionate, which are synthesized by the All-Russian Scientific Center of biologically active substances (ARSC BAS) and reference drug Mildronate® (by "Grindeks" JSC).

The study of endothelioprotective activity was conducted on albino male Wistar rats weighing 250±50 g. Endothelial dysfunction was simulated by intraperitoneal administration of nonselective NO-synthase blocker - N-nitro-L-arginine methyl ester (L-NAME) at a dose of 25 mg/kg/day for 7 days.

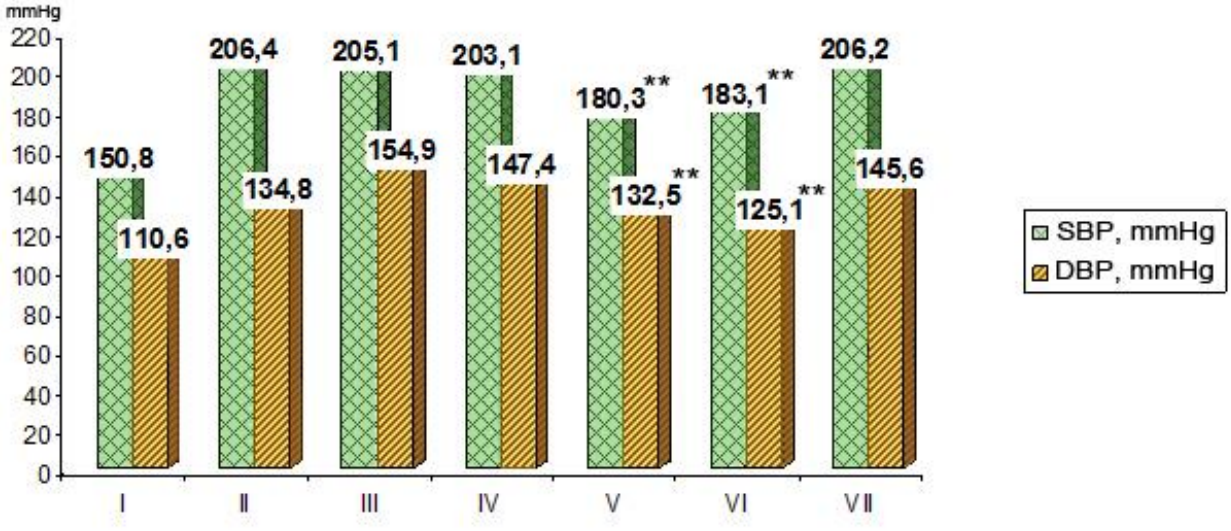
On day 8 of the experiment, a catheter was inserted under anesthetisia (chloral hydrate 300 mg/kg) into the left carotid artery to record blood pressure (BP). Bolus administration of pharmacological agents was into the femoral vein. Hemodynamic parameters: systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were measured continuously with the use of a sensor and the computer program "Biopac Systems, Inc.", USA. In addition to blood pressure measurements, a series of functional tests was performed with subsequent evaluation of changes in hemodynamic parameters (SBP, DBP, HR) in response to an intravenous administration of solution of acetylcholine (ACh) at a dose of 40 mg/kg at the rate of 0.1 ml per 100 g body weight of animal (EDVD) , as well as changes in hemodynamic parameters in response to the intravenous administration of sodium nitroprusside (NP) at a dose of 30 mg/kg at the rate of 0.1 ml per 100 g body weight of animal (EIVD) [17, 19, 20, 21] .

The degree of endothelial dysfunction in experimental animal, as well as the degree of its correction with the studied medications was assessed by the estimated coefficient of endothelial dysfunction (EDC), which represents the ratio of the area of a triangle above the BP recovery curve in response to the NP administration (EIVD) to the area of a triangle above the BP recovery curve in response to the AH administration (EDVD) [1, 3, 4, 7]. Mildronate® and the derivatives were administered intraperitoneally once daily for 7 days. Experimental animals were divided into groups (n=10): I - intact; II - L-NAME-administered; III - with the administration of Mildronate ("Grindeks") at a dose of 90 mg/kg on the background of L-NAME, IV - with the administration of nicotinate 3- (2,2,2-trimethylhydrazinium) potassium propionate at a dose of 189 mg/kg on the background of L-NAME, V - with the administration of bromonicotinate 5-3-(2,2,2-trimethylhydrazinium) potassium propionate at a dose of 189 mg/kg on the background of L-NAME, VI - with the administration of glycinate 3-(2,2,2-trimethylhydrazinium) potassium propionate at a dose of 199 mg/kg on the background of L-NAME, and VII – with the administration of 5-hydroxinicotinate 3-(2,2,2-trimethylhydrazinium) potassium propionate at a dose of 159 mg/kg on the background of L-NAME. Doses of the investigated derivatives were calculated from molar weight by reference drug Mildronate®, in equivalent to laboratory animals.

To evaluate the functionality of the myocardium of animals under controlled respiration, the left ventricular cavity was probed with a needle through the heart top and the parameters of cardiohemodynamics of the left ventricular pressure (LVP) were recorded with the sensor RX104A "Biopac Systems, Inc." and the computer program "Biopac Systems, Inc.", USA. Myocardial functionality was assessed by conducting a series of stress tests in animals: test for adrenoreactivity (a one-time intravenous administration of epinephrine hydrochloride solution $1 \cdot 10^{-5}$ mol/L at the rate of 0.1 ml per 100 g), and the resistance load (ascending aorta compression for 30 seconds).

Results and discussion. It was found that the studied drugs did not prevent development of severe hypertension, and systolic and diastolic blood pressure values were significantly higher than the corresponding values in intact animals in all series of experiments, except for 5-hydroxinicotinate 3- (2,2,2-trimethylhydrazinium) potassium propionate and 5-bromonicotinate 3-(2,2,2-trimethylhydrazinium) potassium propionate, where SBP and DBP were 183.1±3.5 and 125.1±4.3 and 180.3±6.3 and 132.5±4.8, respectively.

The effect of Mildronate® and test substances on the initial blood pressure in anesthetized rats with simulated L-NAME-induced pathology are presented in Fig. 1.



I – Intact; II – L-NAME; III – Mildronate® at a dose of 90 mg/kg; IV – nicotinate at a dose of 189.2 mg/kg; V – 5-bromonicotinate at a dose of 237 mg/kg; VI – 5-hydroxinicotinate at a dose of 199.1 mg/kg; VII – glycinate at a dose of 159.6 mg/kg (3-(2,2,2-trimethylhydrazinium) potassium propionate)

Figure 1. The influence of the derivatives of 3-(2,2,2-trimethylhydrazinium) potassium propionate on the systolic and diastolic blood pressure in modeling L-NAME (intraperitoneal administration of L-NAME at a dose of 25 mg/kg for 7 days)-induced deficiency of nitrogen oxide.

Note: *- at p = 0.05 as compared to L-NAME; **- at p = 0.05 as compared to intact animals.

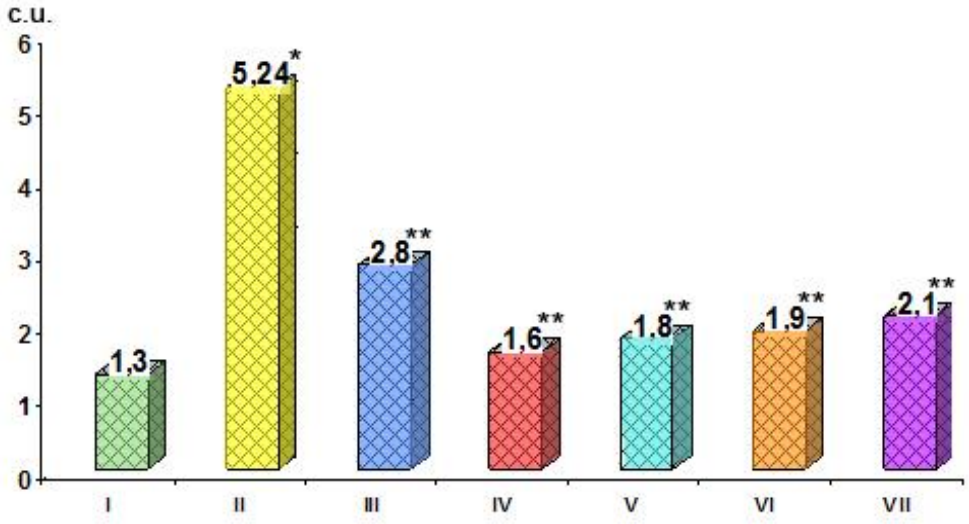
Fig. 2 shows the results of functional tests for endothelium-dependent (acetylcholine, 40 μg/kg i.v.) and endothelium-independent (nitroprusside 30 mg/kg i.v.) vascular relaxation in animals with L-NAME-induced pathology during the treatment with the studied medications, followed by EDC calculation.

It is noteworthy that Mildronate® and all its derivatives led to a significantly pronounced decrease of EDC. We found that Mildronate® reduces EDC up to 2.8±0.1, whereas EDC in the group of animals treated with L-NAME was 5.3±0.6.

The studied derivatives significantly reduced EDC as compared to the control group up to 1.6±0.3, 1.8±0.6, 1.9±0.5, 2.4± 0.5, respectively.

Test for adrenoreactivity revealed a significant decrease in the maximum rise of left ventricular pressure in response to intravenous administration of adrenaline in rats treated with Mildronate® up to 230.8±6.7 mm Hg, as compared to a group of untreated animals - 254.2±7.8 mm Hg ($p<0.05$), which indicates the prevention of increase in adrenoreactivity during treatment. Derivatives of nicotinate and 5-hydroxinicotinate (3-(2,2,2-trimethylhydrazinium) potassium propionate) maximally prevented the increase in adrenoreactivity up to 192.6±5.4 and 163.9 ± 7.1 mm HG caused by L-NAME-induced pathology. Adrenoreactivity of 5-bromonicotinate and glycinate (3- (2,2,2-trimethylhydrazinium) potassium propionate) was 223.5±8.4 and 213.4±6.9 mm Hg, respectively.

Test for resistance load showed that Mildronate® and all its derivatives prevented the drop of contractility in the period from 5 to 25 second of aortic compression on the background of endothelial dysfunction modeling. So, myocardial reserve on the 25th second of the test was 83.6±2.1% of the value at the 5th seconds in intact animals.In the control group (L-NAME-induced nitrogen oxide deficiency) – 66.0±2.3% administration of Mildronate® to rats contributed to the maintenance of myocardial reserve at a level of 78.5±4.1. Pretreatment with the derivatives (nicotinate, 5-bromonicotinate, 5-hydroxinicotinate, glycinate) 3-(2,2,2-trimethylhydrazinium) potassium propionate) during the resistance load test approximated the values to the level of intact animals: 72.5±2.1%, 82.3±3.9%, 78.1±6.1% and 70.9±5.8%, respectively.



I – Intact; II – L-NAME; III – Mildronate® at a dose of 90 mg/kg; IV – nicotinate at a dose of 189.2 mg/kg; V – 5-bromonicotinate at a dose of 237 mg/kg; VI – 5-hydroxinicotinate at a dose of 199.1 mg/kg; VII – glycinate at a dose of 159.6 mg/kg (3-(2,2,2-trimethylhydrazinium) potassium propionate)

Figure 2. The influence of the derivatives of 3-(2,2,2-trimethylhydrazinium) potassium propionate on the endothelial dysfunction coefficient in modeling L-NAME (intraperitoneal administration of L-NAME at a dose of 25 mg/kg for 7 days)-induced deficiency of nitrogen oxide.

Note: *- at p = 0.05 as compared to L-NAME; **- at p = 0.05 as compared to intact animals.

Currently, it is considered promising to correct the conditions involving endothelial dysfunction with the drugs having antioxidant activity, as the main mechanism underlying endothelial dysfunction is a reduction of production and bioavailability of NO under simultaneous increase in the level of superoxide anion due to increased oxidative activity of NADP [17, 20, 21].

3-(2,2,2-trimethylhydrazinium propionate), which itself does not have antioxidant properties, increases the body's concentration of gamma-butyrobetaine (GBB), due to being oxidized to carnitine slower than usual under the influence of 3-(2,2,2-trimethylhydrazinium propionate). The GBB, in turn, can induce the formation of NO, which is one of the most efficient absorbents of free radicals in the body. 3-(2,2,2-trimethylhydrazinium propionate), by increasing the number of GBBs, is able to protect cells from free radical effects, but this is realized indirectly through the induction of NO biosynthesis. Therefore, 3-(2,2,2-trimethylhydrazinium propionate) contributes to the development of physiologically controlled amount of NO, allowing the body to ensure the necessary level of protection from radicals. There are lot of researhes devoted to the application of 3-(2,2,2-trimethylhydrazinium) propionate in cardiovascular diseases. It is generally known that 3-(2,2,2-trimethylhydrazinium) propionate leads to restricted flow of fatty acids through the mitochondrial membrane and protects cell from death under oxygen deficiency. A question of a new mechanism of action of 3-(2,2,2-trimethylhydrazinium) propionate by the type of ischemic preconditioning is under study. Analyzing the implementation stage of the protective effects by preconditioning type, many researchers pay attention to the significant role of ATP-dependent potassium channels (K_{ATF} channels) through the activation of NO [22, 23].

By introduced into the molecule of 3-(2,2,2-trimethylhydrazinium propionate) the nicotinic acid and its derivatives, namely 5-bromonicotinate, 5-hydroxinicotinate, and glycinate having various degrees of antioxidant activity, it is expected to identify new properties and strengthening of effects in the treatment of cardio-vascular diseases.

For example, such substances as 5-hydroxinicotinate, 5-bromonicotinate (3-(2,2,2-trimetilgidroziny) potassium propionate), have significantly, unlike other substances, affected the hemodynamic parameters in the model of L-NAME-induced NO deficiency and lowered systolic and diastolic blood pressure up to the following values: 183.1±3.5 and 125.1±4.3 mm Hg, and 180.3±6.3 and

132.5±4.8 mm Hg, respectively. The maximum decrease in EDC is typical of the three presented modifications: nicotinate, 5-bromonicotinate, and 5-hydroxinicotinate (3-(2,2,2-trimetilgidroziny) potassium propionate), 1.6±0.3, 1.8±0.6, and 1.9±0.5, respectively.

The conducted experimental studies allow suggesting that both Mildronate® and all its derivatives have a pronounced endothelium- and cardioprotective effect on the model of L-NAME-induced NO deficiency, which was reflected in the predominance of endothelium-dependent relaxation of blood vessels and reduced coefficient of endothelial dysfunction, the prevention of increase in adrenoreactivity and the drop of LV contractility and pressure.

Given the important role of ED in the development of oxidative stress, it can be assumed that the substances with antioxidant effect may affect the various elements of ED development such as NO synthesis and bioavailability system, hemorheological parameters of blood, lipid and carbohydrate metabolism, inflammation, and proliferation. Therefore, the search for highly active endotelioprotectors among the compounds with antioxidant activity is fully justified.

Subject to the above, the therapeutic effect of the use of investigated derivatives of 3-(2,2,2-trimethylhydrazinium) propionate, which is higher as compared to the basic molecule, according to the obtained data, could be due to either addiction or potentiation of properties being a part of the active components of the molecule.

Furthermore, pharmacological composition that throughout the entire study showed endothelio- and cardioprotective effects contains a hydroxyl group, which enhances the antioxidant properties of a molecule, which in combination with the activation of the ATP-dependent potassium channels and stress exposure leads to realization of the effects of ischemic preconditioning, normalization of the energy balance in the cell, and the maximum anti-ischemic, and endotelio- and cardioprotective effects in the range of investigated 3-(2,2,2-trimethylhydrazinium) propionate.

Conclusions.

1. (3-(2,2,2-trimethylhydrazinium) propionate (Mildronate®) and its derivatives (nicotinate, 5-bromonicotinate, 5-hydroxinicotinate, glycinate) 3-(2,2,2-trimethylhydrazinium) propionate potassium) have expressed endotelio- and cardioprotective effect on the model of L-NAME-induced nitrogen oxide deficiency, which indicates their contribution to NO-ergic system.

2. All of the derivatives in the range of 3-(2,2,2-trimethylhydrazinium) propionate have the most pronounced endothelio- and cardioprotective effect on the model of L-NAME induced nitrogen oxide deficiency as compared to the reference drug (Mildronate®), which confirms the feasibility of their further enhanced study.

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