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Molchanova O.V.
Pokrovskaya T.G.
Povetkin S.V.
Reznikov K.M.

ENDOTHELIOPROTECTIVE PROPERTY OF THE COMBINATION OF THE THIOCTIC ACID AND ROSUVASTATIN SHOWN IN THE ENDOTHELIAL DYSFUNCTION MODELS

1) Doctor of the ultrasonic diagnostics. Belgorod Oncological Clinic
1, Kuibisheva St., Belgorod, 308010, Russia. e-mail: terra-98@mail.ru
2) Doctor of Medical Sciences, Professor; Department of pharmacology of Belgorod State National Research University
85, Pobedy St., Belgorod, 308015, Russia. e-mail: pokrovskaia-tg@mail.ru
3) Doctor of Medical Sciences, Professor; Department of Clinical Pharmacology and Pharmacotherapy Kursk State Medical University. 3, K. Marksa St., Kursk, 305040, Russia. e-mail: sv_povetkin@mail.ru
4) Doctor of Medical Sciences, Professor Department of Pharmacology. Voronezh State Medical University named after N.N. Burdenko. *10, Studencheskaya street, Voronezh, 394036, Russia.* e-mail: resnikov_km@mail.ru

Abstract: During the experiment, the modeling of endothelial dysfunction of male rats was performed by intraperitoneal administration of L-NAME at a dose of 25 mg/kg for 7 days, and the same of female rats was performed by bilateral ovarioectomy and further intraperitoneal administration of L-NAME at a dose of 25 mg/kg for 7. The deficiency of nitric oxide as a result of the NO-synthase blockade was accompanied by the impairment of the endothelium-dependent and independent vasodilatation estimated in the pharmacological tests, which was expressed in the increasing coefficient of endothelial dysfunction. As a result of the research it was discovered that the combined application of thioctic acid at a dose of 50 mg/kg/day with antioxidant features and rosuvastatin at a dose of 0.85 mg/kg/day, which is a lipid-lowering drug, has endothelioprotective effect on the models of L-NAME-induced and hypoestrogen-L-NAME-induced deficiency of nitric oxide, which is expressed in prevalence of endothelium-dependent relaxations of vessels and decreasing coefficient of endothelial dysfunction, as well as prevention of increase in nitric oxide production.

Keywords: L-NAME, endothelial dysfunction, thioctic acid, rosuvastatin, nitric oxide, oxidative stress, ovarioectomy.

Introduction: According to statistics, the incidence of and mortality from complications of cardiovascular diseases, particularly arterial hypertension (AH) and coronary heart disease (CHD) has been steadily increasing, which is evidence of the need to study the development mechanisms of this disease and possibilities of its correction capacity exposure to certain pathogenetic links [1]. The role of endothelial cells in the development of cardiovascular diseases was an important discovery for understanding the pathogenesis of hypertension, atherosclerosis, ischemic heart disease, cardiomyopathy, congestive heart failure, and metabolic disorders such as hyperlipidemia, hyperhomocysteinemia, diabetic vascular lesions, and venous transformation [2, 3, 4, 5]. This factor is called endothelial dysfunction (ED).

The endothelium maintains homeostasis by regulating the balance of opposing processes: vascular tone, responsible for vasodilation and vasoconstriction; vascular anatomical structure, by regulating the synthesis and the inhibition of cell proliferation factors; hemostasis, by participating in the synthesis and the inhibition of fibrinolysis factors and platelet aggregation; and local inflammation, by producing pro- and anti-inflammatory cytokines [6, 7, 8, 9, 10]. The endothelium lines all vessels, regardless of their organ localization, therefore endothelial dysfunction, which is based on the decrease in nitric oxide (NO) synthesis by endothelial cells, is a predictor of both arterial and venous diseases, and diseases of the microvasculature components [11, 12, 13].

Therefore one of the main current tasks of pharmacology is the search for drugs and their combinations capable of correcting the endothelial dysfunction and having endothelioprotective effect.

According to the literature, one of the chemical compounds having this effect is lipoic acid ([alpha]-LA) [14], which is a coenzyme in the oxidative decarboxylation of pyruvate acid to acetyl-CoA, and a-ketoglutaric acid to succinyl-CoA (in Krebs cycle). Facilitating thus the conversion of lactic acid into pyruvic acid with further decarboxylation of the latter, [alpha]-LA promotes elimination of metabolic acidosis.

All of the above reactions underlie the protective effect of dihydrolipoic acid, provide its therapeutic effect and cause a wide nosological range of use of the [alpha]-lipoic acid-based drugs [15, 16].

Main part: Subject to the above, the objective of this study was to investigate endothelioprotective properties of α-lipoic acid in the form of pellets Thioctacid BV (600 mg) at a dose of 50 mg/kg/day together with statin hypolipidemic drug Rosuvastatin (10 mg) at a dose of 0.85 mg/kg/day as one of the possible effective combinations used in case of endothelial dysfunction, with the help of models of L-NAME-induced and [17, 18, 19] hypoestrogen-L-NAME-induced nitric oxide deficiency.

Materials and research methods. Experiments were conducted in two animal models of endothelial dysfunction. The L-NAME-induced nitrogen deficiency was modeled in nonlinear white male rats weighing 250-300 g, the NO-synthase inhibitor N-nitro-L-arginine methyl ester (L-NAME, Sigma) was aministrated intraperitoneally once a day at a dose of 25 mg/kg in the volume of 1 ml/kg for 7 days (n=10 animals) [20, 21]. Intact animals were administered physiological NaCl solution in the same volume (n=10 animals). Thioctic acid and rosuvastatin, as well as their combination were administered intragastrically daily in fasting state (gavage) at doses of 50 mg/kg/day and 0.85 mg/kg/day, respectively, for 7 days.

The hypoestrogen-L-NAME-induced nitrogen deficiency was modeled in white female Wistar rats weighing 200-250 g. To simulate the endothelial dysfunction, the 3.5-month-old rats were anesthetized with chloral hydrate (300 mg/kg) with further bilateral ovariectomy. On day 43 (6 weeks after surgery) the NO-synthase inhibitor N-nitro-L-arginine methyl ester (L-NAME, Sigma) was administrated intraperitoneally once a day at a dose of 25 mg/kg in the volume of 1 ml/kg for 7 days (n=10 animals) [17, 18, 19]. Intact animals were administered physiological NaCl solution in the same volume (n=10 animals). Thioctic acid and rosuvastatin, as well as their combination were administered intragastrically daily in fasting state (gavage) at doses of 50 mg/kg/day and 0.85 mg/kg/day, respectively, for 7 days, simultaneously with L-NAME.

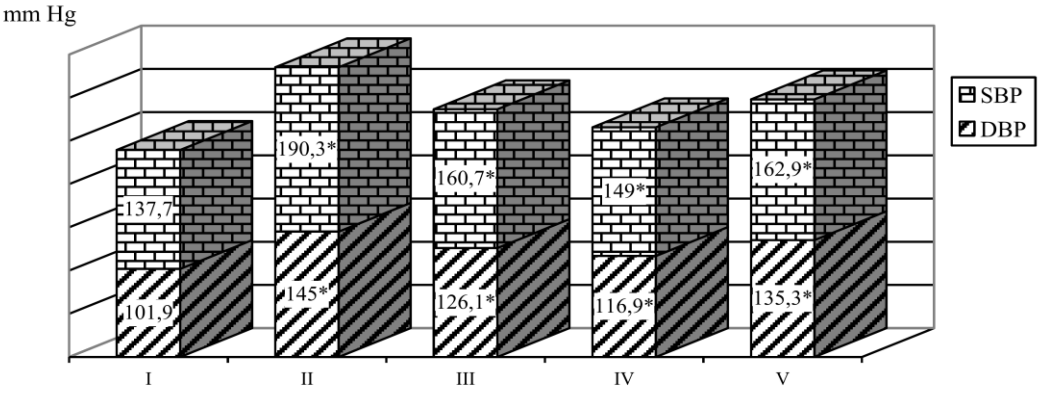
In both methods of modeling the anestetized (chloral hydrate 300 mg/kg and zoletil 150 m/kg, intraperitoneally) animals were taken to the experiment on day 8 after administration of L-NAME and drugs both in monotherapy and in their combination and their blood pressure (BP) and BP reaction on endothelium-dependent (acetylcholine at a dose of 40 mg/g) and endothelium-independent (nitroprusside in a dose of 30 mg/kg) vasodilation were assessed by inserting a catheter in the carotid artery. Pharmacological agents were administered by bolus injection into the right femoral vein.

The systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were recorded with the use of the TSD104A sensor and the MP150 hardware and software system (Biopac System, Inc., USA).

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) [17, 18, 19, 22].

The level of total nitrite in rats serum was taken for a biochemical marker of endothelial dysfunction [15, 23]. Statistical processing of data involved calculation of the average value and standard deviation. Differences were considered significant at $p<0.05$.

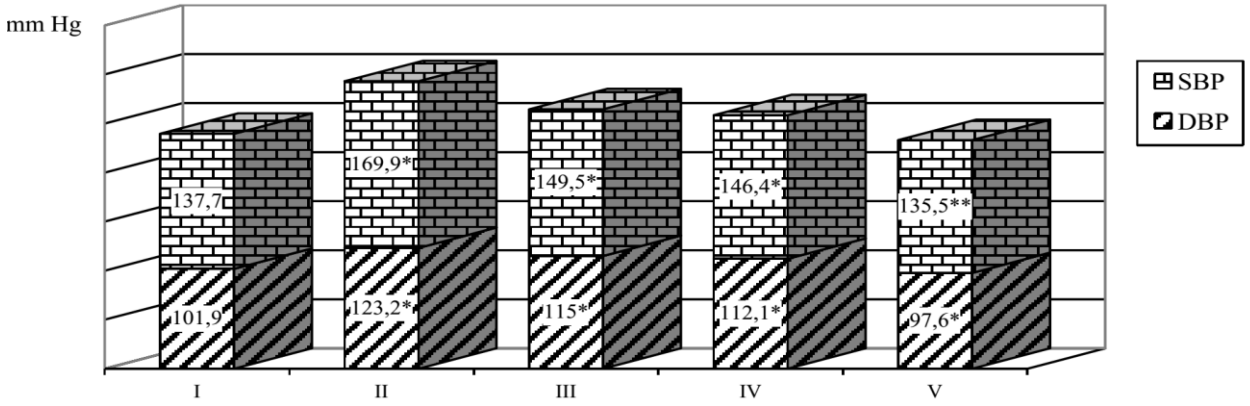
Results and discussion: Blood pressure in intact male rats: systolic (SBP) – 125.0±6.3 mm Hg., diastolic (DBP) – 82.0±5.8 mm Hg. Administration of NO-synthase blocker, an L-arginine analogue, L-NAME, led to severe arterial hypertension (AH) (SBP – 190.3±6.7, DBP – 145.0±3.9 mm Hg.) (Fig. 1).



I - Intact;
II-L-NAME 25mg/kg;
III-L-NAME 25 mg/kg+rosuvastatin 0.85 mg/kg;
IV-L-NAME 25 mg/kg+thioctic acid 50 mg/kg;
V-L-NAME 25 mg/kg+rosuvastatin 0.85 mg/kg+thioctic acid 50 mg/kg

Figure 1. The influence of the thioctic acid (50 mg/kg) and rosuvastatin (0.85 mg/kg) on the blood pressure by the modeling of L-NAME (intraperitoneal administration of L-NAME at a dose of 25 mg/kg for 7 days)-induced deficiency of nitric oxide
Note: * – $p<0.05$ – as compared to intact group

Blood pressure in intact female rats: systolic (SBP) – 128.1±6.0 mm Hg, diastolic (DBP) – 95.7±4.0 mm Hg. Modeling of pathology with the use of NO-synthase blockade, L-NAME on the background of hypoestrogen-induced nitric oxide deficiency led to arterial hypertension (SBP – 169.9±7.3, DBP – 123.2±7.5 mm Hg) (Fig. 2). Thus, both models showed a significant increase in blood pressure, which indicates the role of nitric oxide in the development of hypertension.



I - Intact;
II-Ovarioectomy+L-NAME 25 mg/kg;
III-Ovarioectomy+L-NAME 25 mg/kg+rosuvastatin 0.85 mg/kg;
IV-Ovarioectomy+L-NAME 25 mg/kg+thioctic acid 50 mg/kg;
V-Ovarioectomy L-NAME 25 mg/kg+rosuvastatin 0.85 mg/kg + thioctic acid 50 mg/kg

Figure 2. The influence of the thioctic acid (50 mg/kg) and rosuvastatin (0.85 mg/kg) on the blood pressure by the modeling of hypoestrogen-L-NAME (intraperitoneal administration of L-NAME at a dose of 25 mg/kg for 7 days)-induced deficiency of nitric oxide.

Note: * – at $p<0.05$ as compared to intact animals; ** – at $p<0.05$ as compared to L-NAME

The results of vascular tests for endothelium-dependent (acetylcholine) and endothelium-independent (sodium nitroprusside) relaxation of blood vessels and increase in EDC from 1.1±0.1 in intact animals to 5.4 ± 0.6 ($p<0.05$) in animals with L-NAME-induced nitrogen deficiency indicate the impaired relationship of vasoconstriction and vasodilation mechanisms of vascular tone regulation. The group with ovarioectomy+L-NAME showed increase in EDC from c 0.8±0.11 in intact animals up to 4.6±0.6 ($p<0.05$).

The group of male rats, where only rosuvastatin was administered on the background of L-NAME administration, had EDC equal to 3.1±0.3 ($p<0.05$), while the group with administration of thioctic acid in addition to rosuvastatin had EDC equal to 1.9±0.2, which was significantly less than in L-NAME-administered animals ($p<0.05$) (Fig. 3).

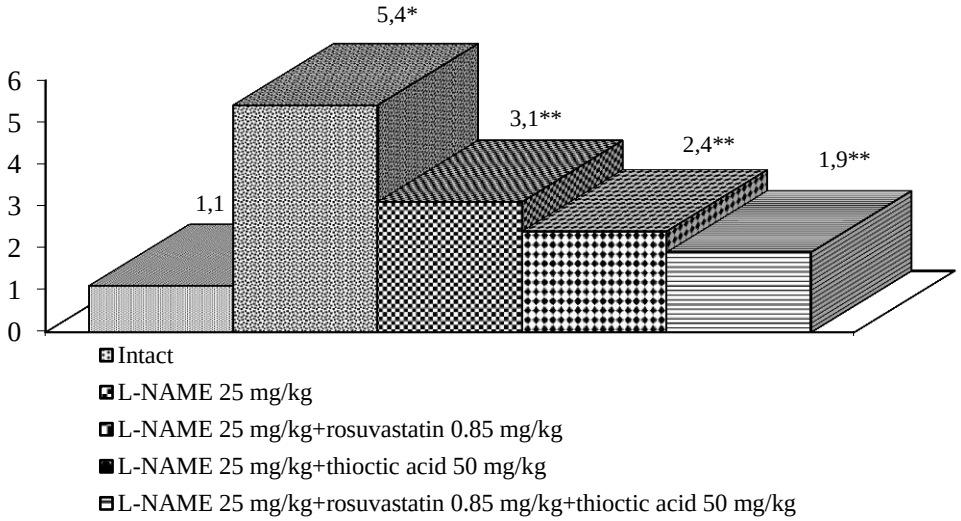


Figure 3. The influence of the thioctic acid (50 mg/kg) and rosuvastatin (0.85 mg/kg) on the endothelial dysfunction coefficient by the modeling of L-NAME (intraperitoneal administration of L-NAME at a dose of 25 mg/kg for 7 days)-induced deficiency of nitric oxide.

Note: *– at $p<0.05$ as compared to intact animals; **– at $p<0.05$ as compared to L-NAME

The group of rats with ovarioectomy, where only rosuvastatin was administered on the background of L-NAME NO-synthase inhibitor, had EDC equal to 1.7±0.2 ($p<0.05$), while the group with administration of thioctic acid in addition to rosuvastatin had EDC equal to 1.4±0.3, which was less than in L-NAME-administered animals ($p<0.05$) (Fig. 4).

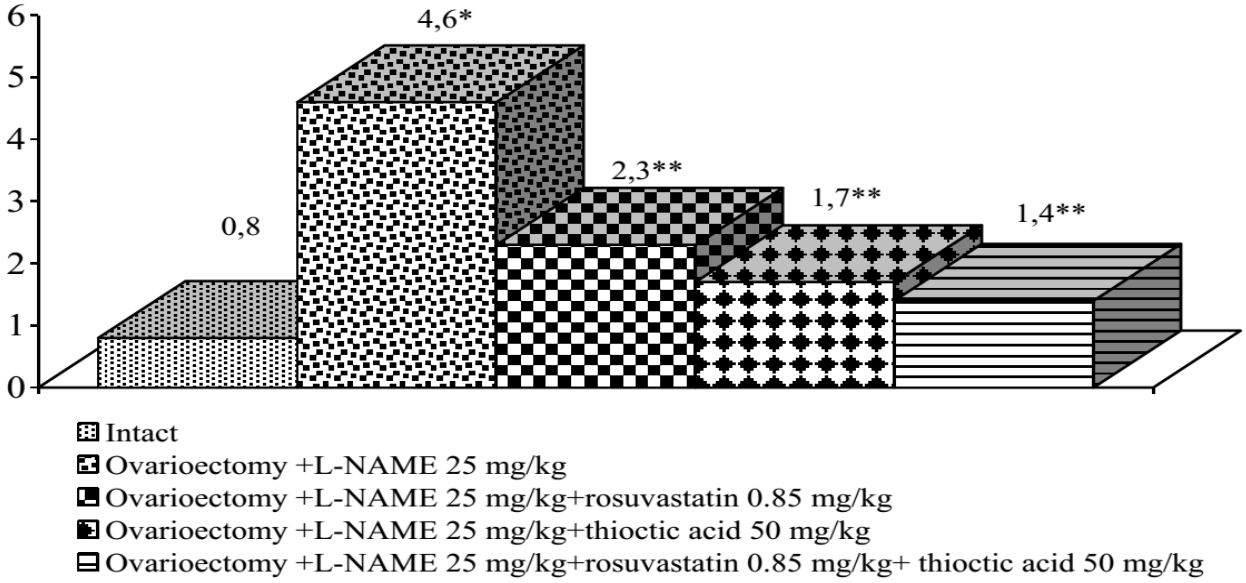


Figure 4. The influence of the thioctic acid (50 mg/kg) and rosuvastatin (0.85 mg/kg) on the endothelial dysfunction coefficient by the modeling of hypoestrogen-L-NAME (intraperitoneal administration of L-NAME at a dose of 25 mg/kg for 7 days)-induced deficiency of nitric oxide.

Note: * – at $p<0.05$ as compared to intact animals; ** – at $p<0.05$ as compared to L-NAME

At the same time, we have also noted the antihypertensive effect of these drugs both in monotherapy and in combined application in both models, which was expressed in the decreasing blood pressure, which was: SBP – 162.9±7.6 mm Hg, DBP – 135.1±5.2 mm Hg ($p<0.05$) in the group of animals with L-NAME-induced nitric oxide deficiency, and SBP – 135.5±2.9 mm Hg, DBP – 97.6±7.1 mm Hg in a group of animals with hypoestrogen-L-NAME-induced nitrogen oxide deficiency, respectively ($p<0.05$). Thus, we can state that the studied drugs prevented the development of severe hypertension, and SBP and DBP values were significantly lower than the corresponding values in animals with endothelial dysfunction. However, the model of L-NAME-induced nitrogen oxide deficiency showed unreliable to each other differences of these parameters between the groups of animals treated with rosuvastatin and thioctic acid as monotherapy and in their combination (Fig. 1) Though, it was found that upon modeling of hypoestrogen-L-NAME -induced hypertension, a combined use of rosuvastatin 0.85 mg/kg and thioctic acid 50 mg/kg, as opposed to monotherapy, normalized blood pressure to the target values not significantly different from those of intact animals (Fig. 2).

Investigations of biochemical markers in a series of experimental animals confirmed an increasing endothelioprotective activity of drugs under combined use of thioctic acid and rosuvastatin in both models, which was expressed in the increasing content of nitrite ions (NOx) (μmol) [15, 23]. It was found that rosuvastatin and thioctic acid applied as monotherapy in the model of L-NAME-induced nitrogen oxide deficiency increased the concentration of nitrite ions in the plasma of laboratory animals, but these differences were not statistically significant. Thus, the combined use of these drugs has allowed to achieve a significant increase in the content of nitrite ions (Fig. 5).

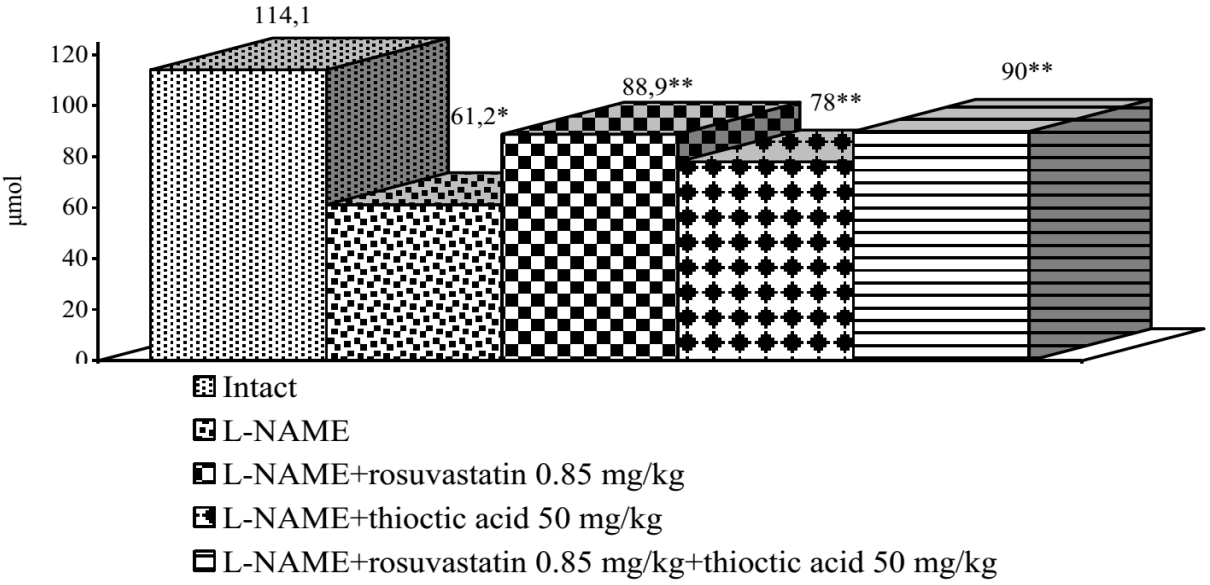


Figure 5. The influence of the thioctic acid (50 mg/kg) and rosuvastatin (0.85 mg/kg) on the concentration of nitric ions (NOx) in rat serum with the modeling of nitric deficiency by intraperitoneal administration of L-NAME at a dose of 25 mg/kg.

Note: *– at p<0.05 as compared to L-NAME; **– at p<0.05 as compared to intact animals

Upon modeling the hypoestrogen-L-NAME-induced nitrogen oxide deficiency, the combined use of rosuvastatin 0.85 mg/kg with thioctic acid 50 mg/kg increased the content of nitrite ions up to 85 µmol. In this case, monotherapy with rosuvastatin 0.85 mg/kg and thioctic acid 50 mg/kg also had a significant effect on the studied parameter, however, to a lesser extent (Fig. 6).

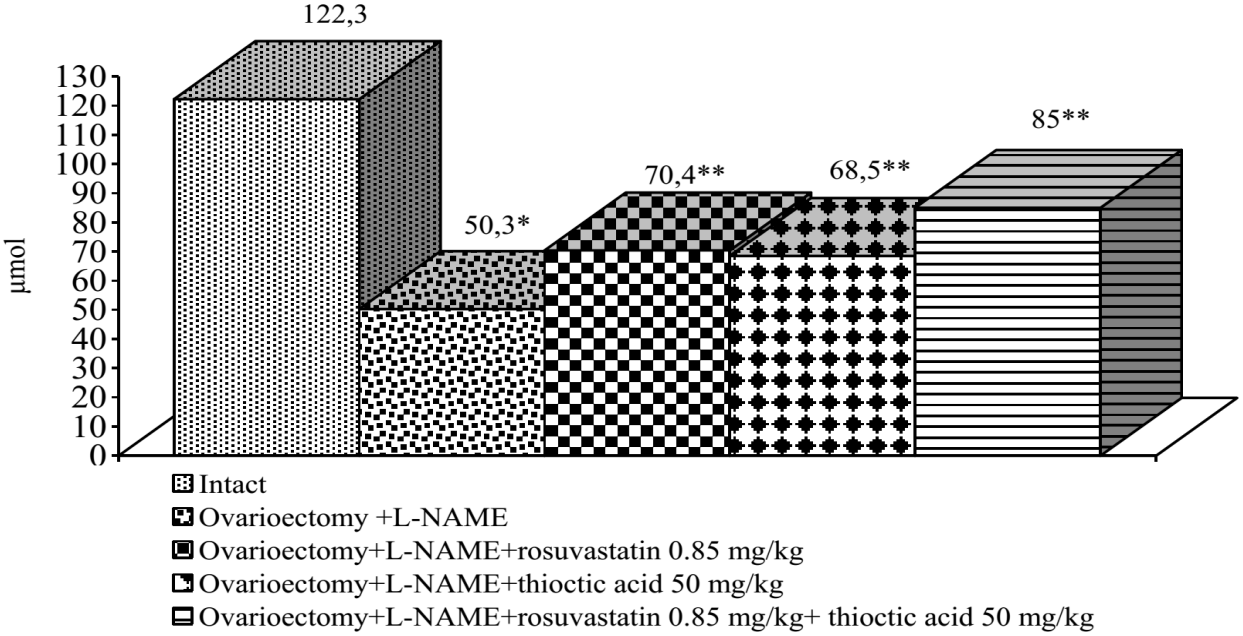


Figure 6. The influence of the thioctic acid (50 mg/kg) and rosuvastatin (0.85 mg/kg) on the concentration of nitric ions (NOx) in rat serum by the modeling of hypoestrogen-L-NAME (intraperitoneal administration of L-NAME at a dose of 25 mg/kg for 7 days)-induced deficiency of nitric oxide.

Note: *– at p<0.05 as compared to L-NAME; **– at p<0.05 as compared to intact animals

Conclusion: Models of L-NAME- and hypoestrogen-L-NAME-induced nitrogen oxide deficiency realize the antioxidant properties of thioctic acid, as according to the literature, inhibition of nitrogen oxide production upon L-NAME use is accompanied by a significant increase in the spontaneous production of a superoxide-anion radical [5, 16, 20]. Hyperproduction of a superoxide radical and its derivatives such as oxygen radicals is a mechanism of the development of oxidative stress (OS) resulting in suppression of

antioxidant protection and increased formation of oxidation products, which is a factor for the formation of endothelial dysfunction [20, 21, 24]. At the same time this link in the pathogenesis of endothelial dysfunction is one of the application points for use of antioxidants as agents in addition to drugs with proven endothelioprotective effect, such as rosuvastatin, for ED correction [26, 27, 28]. As a result of the research it was found that the combined application of rosuvastatin at a dose of 0,85 mg/kg/day and thioctic acid at a dose of 50 mg/kg/day, had greater endothelioprotective effect on the L-NAME- and hypoestrogen-L-NAME-induced nitric oxide deficiency models as compared to monotherapy with rosuvastatin, which was expressed in the reduction of the coefficient of endothelial dysfunction (EDC) to a level close to that of intact animals, as well as in the prevention of reduced content of nitrite ions NO_x. In addition, there was a significant prevention of hypertension development, that could not be achieved with rosuvastatin-based monotherapy, whereby narrow pathogenetic orientation of rosuvastatin on the background of endothelial dysfunction is associated with its pleiotropic effects, in particular, reduced level of proinflammatory cytokines - interleukin-6, which is associated with the development of endothelial dysfunction, whereas one of the reasons such as increased biodegradation of nitrogen oxide resulting from peroxidation remains uncompensated [25, 28, 29, 30]. Therefore, rosuvastatin-based monotherapy of endothelial dysfunction is considered insufficient, and causes further the search for more effective ways of pharmacotherapy, one of which is the combined use of rosuvastatin with thioctic acid. In our view, the combination of rosuvastatin with thioctic acid is justified not only for studying its endothelio- and cardioprotective effect associated with the prevention of indirect inhibition of NO-synthase by correction of oxidative stress, improvement of blood circulation and endoneural neurotrophism through the prevention of ischemic damage to the nervous tissue, acceleration of the pulse conduction along the nerve [16, 31], but also due to the possibility of justifying its use for leveling the side effects of statins associated with a reduction of one of the most important antioxidants – glutathione, since restoration of glutathione [32] through activation of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) is one of the most important properties of thioctic acid [26, 30, 33].

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