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Endothelium-Protective Action of Thioctic Acid and Rosuvastatin Combination at Concomitant Hypoestrogen and L-Name-Induced Deficit of Nitric Oxide.

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ABSTRACT

In the result of the performed research, it was discovered that concomitant use of thioctic acid with antioxidant properties and Rosuvastatin (from the class of anticholesterol drugs) had endothelium protective action at the model hypestrogen-L-NAME-induced deficit of nitric oxide consisting in predomination of endothelium-dependent vasodilation and decreasing of endothelial dysfunction factor, as well as in preventing decreasing of nitric oxide production.

Keywords: ovariectomy, L-NAME, endothelial dysfunction, thioctic acid, Rosuvastatin, nitric oxide

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INTRODUCTION

Annual increase of case rate and death rate because of complications of arterial hypertension (AH) and coronary heart disease (CHD) requires study of mechanisms of this disorder developing and possible ways of its correction by affecting some pathogenic elements [1]. One of a breakthrough in this field was an evidence of endothelial cells role in cardio-vascular disease developing: AH, atherosclerosis, CHD, cardiomyopathy, chronic cardiac insufficiency, metabolic disturbances: hyperlipemia, hyperhomocisteinemia, as well as pathogenesis of diabetic vascular disturbance, venous conversion, limphangion dysfunction as predictor for lymphedema developing [2, 3]. This factor was called endothelial dysfunction (ED).

Endothelium supports homeostasis by regulation of contrary processes balance: vascular tone by taking care of vasodilation and vasoconstriction, anatomical organization of vessels by regulating synthesis and inhibition of proliferation factors, hemostasis by participating in synthesis and inhibition of fibrinolysis factors and thrombocyte aggregation, local inflammation by producing anti-inflammatory cytokines [4, 5, 6]. Endothelium covers all the vessels not depending on their organ location; hence, endothelial dysfunction (which development basis is decreasing of endothelial cells synthesis by nitric oxide (NO)) is predictor of arteries, veins and microcirculatory bloodstream elements disorders [7, 8].

Hence, one of the pharmacology main tasks at the present stage is search of agents and their combinations able to correct endothelial dysfunction having endothelial protective action.

According to literature data, one of chemical compounds with this action is lipoic acide ([alpha]-LA) [9] being a cofactor in oxidative decarboxylation of pyroracemic acid to acetyl-coenzyme A and of a-ketoglutaric acid to succinyl-coenzyme A (Krebs cycle). Thus, facilitating lactic acid transformation to pyroracemic one with the following oxidative decarboxylation of the last one, [alpha]-LA tends to metabolic acidosis elimination [10].

All above-mentioned reactions are the basis of protective action of disodium lipoic acid, assure its curative action and provide wide nosological range of use of [alpha]-lipoic acid agents [11].

Regards to the above mentioned, this investigation goal is study of endothelium protective properties of α-lipoic acid in tablets Thioctacid HR (600 mg) and its combinations with hypolipidemic preparation from statins group – Rosuvastatin (10 mg), as one of possible effective combination at endothelial dysfunction, at model of hypoestrogen-L-NAME of nitric oxide induced deficit.

METHOD

Investigation is performed at white rat females of 200-250 g weight, Wistar line. To simulate endothelial dysfunction, 3.5 months old rats were anesthetized with chloral hydrate (300 mg/kg) and were made bilateral ovariectomy. At the 43rd day (6 weeks after operation) inhibitor NO-synthase N-nitro-L-arginine methyl ether (L-NAME, Sigma) was injected abdominally once a day in a dose 25 mg/kg in volume of 1 ml/kg within 7 days (n = 10 animals) [12, 13]. Animals of intact group were injected with normal saline solution NaCl in the same volume (n = 10 animals). Thioctic acid and Rosuvastatin, as well as their combination, are injected abdominaly every day (through the proof stick) in doses of 50 mg/kg/day and 0.85 mg/kg/day respectively within 7 days together with L-NAME.

At the 8th day, the animal under anesthesia (300 mg/kg chloral hydrate and 150 mg/kg Zoletil, abdominaly) was taken to the experiment, and, at the first stage, it was evaluated arterial pressure (AP) and AT reactions to endothelium-dependent (40 mkg/kg acetylcholine) and endothelium-independent (30 mkg/kg nitroprusside) vasodilation by introducing catheter to arteria carotis. Pharmacological agents were injected bolusly to right femoral vein.

There was registered systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and cardiac rate (CC) by TSD104A sensor and MP150 hardware and software system manufactured by Biopac System, Inc., USA).

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To estimate developing degree of endothelial dysfunction in experimental animals and its correction by agents under study, we have calculated endothelial dysfunction factor (EDF) [8].

As biochemical markers of endothelial dysfunction, we determined NO-synthase level (eNOS) in the rat's aorta and level of total nitrite in the rats' blood serum [14, 15]. At statistical processing of data, we calculated the average value, standard deviation value. Differences were considered as authentic at $p<0.05$.

INVESTIGATION RESULTS

Arterial pressure in intact animals was the following: systolic (SAP) – 128.1±6.0 mm Hg, diastolic (DAP) – 95.7±4.0 mm Hg. Disturbance simulation by blocking NO-synthase associated with hypostrogen induced nitric oxide deficit resulted in arterial hypertension (AH) (SAP – 169.9±7.3, DAP – 123.2±7.5 mm Hg). Rosuvastatin injection associated with L-NAME decreased arterial pressure up to 151.2±6.2 mm Hg and 113.8±3.3 mm Hg respectively ($p<0.05$), and injection of Rosuvastatin together with thioctic acid resulted in more decreasing of arterial pressure that made 135.5±2.9 mm Hg, DAP – 97.6±7.1 mm Hg respectively ($p<0.05$).

Results of vascular batches for endothelium-dependent (acetylcholine) and endothelium-independent (sodium nitroprusside) relaxation of vessels and EDF increasing from c 0.8±0.11 in intact animals to 4.6±0.6 ($p<0.05$) in group ovariectomy+ L-NAME testify about disturbance of interrelations of vasodilation and vasoconstrictive mechanisms of vascular tone regulation.

In the group of animals with ovariectomy, where there was injected NO-synthase inhibitor L-NAME associated only with Rosuvastatin, this ratio was 1.7±0.2 ($p<0.05$), and in the group with injection of Rosuvastatin together with thioctic acid, this ratio was 1.4±0.3 what is less than in the animals group with L-NAME ($p<0.05$) injection.

Table 1: Dynamics of factors of systolic (SAP), diastolic (DAP) arterial pressure, endothelial dysfunction factor, biochemical factors in the experimental groups of animals (M±m, n=10).

Factor / Group	SAP, mm Hg	DAP, mm Hg	EDF, relative units.	eNOS, in % from control	NO_x total, mc mole
Intact	128.1±6.0	95.7±4.0	0.8±0.1	80.1±3,8	122.8±9.6
Ovariectomy+L-NAME	169.9±7.3*	123.2±7.5*	4.6±0.7*	23.6±3.4*	53.4±6.1*
Ovariectomy+L-NAME+ Rosuvastatin	151.2±6.2*	113.8±3.3*	1.7±0.2**	44.8±4.3**	78.1±5.1**
Ovariectomy+L-NAME+ Rosuvastatin + thioctic acid	135.5±2.9*	97.6±7.1*	1.4±0.3**	64.7±5.3**	88.6±8.2**

Note: EDF – endothelial dysfunction factor; * - $p < 0.05$ compared to intact animals group; ** - $p < 0.05$ compare to L-NAME group.

Investigation of biochemical markers in series of experimental animals have confirmed increasing of endothelium protective activity of agents at concomitant use of thioctic acid and Rosuvastatin.

Thus, expression factor eNOS under the influence of agents has authentically increased (42.2±3.6), to the fullest extent at the combined administration of thioctic acid and Rosuvastatin. Nitrite-ions (NO_X total) concentration has also considerably increased (67.8±7.3) in the group, where there was pharmacological correction by combining thioctic acid and Rosuvastatin associated with pathology simulation.

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CONCLUSIONS

Thus, is the result of the performed investigation, it was determined that combined administration of 0.85 mg/kg/day Rosuvastatin and 50 mg/kg/day thioctic acid had more endothelium protective action on the simulations of hypoestrogen-L-NAME-induced NO deficit compared to Rosuvastatin monotherapy; it was expressed by decreasing of endothelial dysfunction factor (EDF) up to the level close to the intact animals level, as well as by preventing decrease of NOx nitrite-ions contents. Besides, there was considerable prevention of hypertension developing what was not reached by monotherapy, at which narrow pathogenetic direction of Rosuvastatin action at endothelial dysfunction is connected with its pleiotropic action, notable with decreasing of anti-inflammation cytokine-interleukin-6 level that is associated with developing of endothelial dysfunction; at this, one reason consisting in high biodegradation of nitric oxide as a result of peroxidation remains uncompensated. Hence, endothelial dysfunction monotherapy with Rosuvastatin is considered as to be insufficient, and conditions the further search of more effective means in pharmacotherapy; one of these means is concomitant use of Rosuvastatin and thioctic acid.

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