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Correction of ADMA-Induced Preeclampsia with Use of Tetrahydrobiopterin and Selective Inhibitor of Arginase II ZB49-0010.

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ABSTRACT

Simulation experimental ADMA-like preeclampsia was carried out by administering the rats L-NAME 14 to 20 days of pregnancy. In animals, there was an increase in blood pressure, proteinuria, impaired microcirculation in the placenta, the violation of the regulation of vascular tone and destructive changes in the ischemic placenta. Use of tetrahydrobiopterin and selective inhibitor of arginase II ZB49-0010 leads to the expression of morphological and functional correction of violations occurring in modeling of experimental preeclampsia.

Keywords: rats, N-nitro-L-arginine methyl ester, endothelial dysfunction, preeclampsia, tetrahydrobiopterin, a selective inhibitor of arginase II.

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INTRODUCTION

Preeclampsia is the most common disease of pregnant women and ranks first in causes of maternal and perinatal mortality. Recently, many authors have a significant role in the pathogenesis of the disease is removed endothelial dysfunction [1, 2]. Increased levels of free radicals, hormones, growth factors, pro-inflammatory cytokines, antigens of the fetus and other humoral factors causing increase of cell adhesion molecules, and the accumulation of endogenous inhibitors of eNOS - methylated analogs of L-arginine asymmetric dimethylarginine (ADMA) and monometilarginina (L-NMMA), which are predictors of preeclampsia [3, 4, 5]. In this regard, current research seems to influence tetrahydrobiopterin and selective inhibitor of arginase II ZB49-0010, on for ADMA-like experimental preeclampsia.

PROCEDURE

The experiment was performed on 40 female white rats of Wistar strain weighing 250-300 g ADMA-similar agent - non-selective NO-synthase blocker of N-nitro-L-arginine methyl ester (L-NAME) was administered intraperitoneally in a dose of 25 mg / kg / daily for seven days (day 14-20 of pregnancy). Endothelial dysfunction was assessed by the ratio of endothelium and vascular endothelium reactions to the calculation of the coefficient of endothelial dysfunction (CED) [6, 7, 8]. Pregnant females were divided into groups (n = 10): I - intact; II - with L-NAME administration daily from the 14th to the 21st day of pregnancy; III - the introduction of L-NAME + tetrahydrobiopterin (10 mg / kg); IV - with the introduction of L-NAME + selective inhibitor of arginase II ZB49-0010. Microcirculation Research carried on the outer surface of the uterine horn at a distance of 1 mm from the visible edge of the placental disc.

A morphological study of placentas with the implantation site of the uterine horn with the staining with hematoxylin and eosin.

FINDINGS OF THE STUDY

The blockade of NO-synthase caused by the seven-day administration of L-NAME, led to a breach of the relationship vasoconstrictor and vasodilating mechanisms of regulation of vascular tone, as evidenced by the increase in QED with 1,1 ± 0,11 intact pregnant animals to 3,12 ± 0,17 (p <0.05). In addition, there was a significant rise in systolic and diastolic blood pressure 134,5 ± 2,3 and 92,0 ± 2,1 to 186,3 ± 6,9 and 143,1 ± 4,2 mm Hg. Art. respectively. Introduction blocker NO-synthase resulted in a significant reduction in the microcirculation of the placenta index with 446.3 ± 27.5 to 218.3 ± 13,67 (p <0.05), as well as to reduce the NOx content of the stable metabolite in serum 2 28 ± 0,11 mmol / dL to mmol 1,28 ± 0,08 / dl (p <0.05). Microscopic examination of the placenta observed uneven blood filling spongy layer, vacuolar degeneration of the trophoblast giant, foci of necrosis on the border of the giant trophoblast and decidual tissue, degenerative changes and anemia decidual layer.

Application of tetrahydrobiopterin and selective inhibitor of arginase II ZB49 = 0010 led to the normalization of relations between vasodilating and vasoconstrictor response in experimental pre-eclampsia, as evidenced by the decline and statistically significant (p <0.05) decrease in blood pressure (Table. 1). In addition, there was an improvement of microcirculation in the placenta.

Table 1: Results of correction ADMA-like preeclampsia in rats (M ± m)

Index / Group of animals	SBP, mmHg.	DBP, mmHg.	CED, conv.	Microcirculation PU	Concentration of nitrite ions (NOx), µmol/l
Intact animals	134,5±2,3^{y}	92,0±2,1^{y}	1,10±0,11^{y}	446,3±27,46^{y}	2,28±0,11^{y}
L-NAME	186,3±6,9*	143,1±4,2*	3,12±0,17*	218,3±13,67*	1,28±0,08^{y}
L-NAME + BH4	157,4±7,9^{*y}	116,7±8,8^{*y}	1,73±0,24^{*y}	402,0±26,20^{y}	1,86±0,07^{y}
L-NAME + ZB49-0010	162,5±8,7*	130,2±6,7*	1,49±0,14^{y}	435,4±27,35^{y}	1,95±0,06^{y}

Note: SBP, DBP - systolic and diastolic blood pressure (mmHg.); CED - the coefficient of endothelial dysfunction (conv.); microcirculation in the placenta (PU); the concentration of nitrite ion (NOx); * - P <0.05 compared to the group of intact animals; y- P <0.05 compared with the group of L-NAME.

When blood serum biochemical study found a statistically significant reduction of the prevention of stable metabolites of NO, the level of which amounted to 1,86 ± 0,07 mmol / dl and 1,95 ± 0,06 mmol / dL, respectively.

Microscopic examination of the placenta revealed positive dynamics histology under the influence of both drugs, which resulted in a uniform layer of spongy blood filling, no damage layer of the giant trophoblast and decidua.

Efficiency tetrahydrobiopterin, eNOS is a cofactor, can be explained by increased eNOS activity [9, 10, 11]. This restored NO-synthesizing function of the endothelium, and the ratio of vasodilating and vasoconstrictor effects of coming to a better balance.

The mechanism of action of the selective inhibitor of arginase II ZB49-0010 its inhibitory effects on arginase 2. Given that eNOS and arginase compete for common substrate, increases the possibility of using L-arginine for NO synthesis [12, 13].

Ultimately, the mechanism of action of both drugs is reduced to restore NO-synthesis function and reduce endothelial dysfunction. The differences in their endothelioprotective effects explains the different points of application in the pathway L-Arginine - NO.

CONCLUSION

Thus, the results of this experiment provide a basis for further research in order to find drugs with activity endoteleoprotestivnoy correction of preeclampsia.

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