

UDC: 618.3-06-08:577.112.385.2

DOI: 10.18413/2313-8955-2015-1-4-66-68

**Gureev V.V.¹
Martynova O.V.²
Anciferova O.E.³
Martynov M.A.⁴
Pokrovskaja T.G.⁵
Malorodova T.N.⁶
Lokteva T. I.⁷**

**CORRECTION OF ADMA-INDUCED PREECLAMPSIA
WITH THE USE OF PHOSPHODIESTERASE 5 AND SELECTIVE
INHIBITOR OF ARGINASE II ZB49-0010**

- 1) PhD in Medicine, Associate Professor. Department of Pharmacology. Belgorod State National Research University. 85 Pobedy St., Belgorod, 308015, Russia. E-mail: gureev@bsu.edu.ru
- 2) Graduate Student. Department of Pharmacology. Belgorod State National Research University. 85 Pobedy St., Belgorod, 308015, Russia. E-mail: m.olga91@mail.ru
- 3) Graduate Student. Department of Pharmacology. Belgorod State National Research University. 85 Pobedy St., Belgorod, 308015, Russia
- 4) Attending Physician in the Department of Hospital Surgery. Department of Pharmacology. Belgorod State National Research University. 85 Pobedy St., Belgorod, 308015, Russia
- 5) MD, Professor of Pharmacology. Department of Pharmacology. Belgorod State National Research University. 85 Pobedy St., Belgorod, 308015, Russia
- 6) PhD in Medicine, Associate Professor. Department of Pharmacology. Belgorod State National Research University. 85 Pobedy St., Belgorod, 308015, Russia
- 7) Graduate Student. Department of Pharmacology. Belgorod State National Research University. 85 Pobedy St., Belgorod, 308015, Russia

ABSTRACT. Simulation experimental ADMA-like preeclampsia was carried out by administering the rats with L-NAME during 14-20 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. The use of phosphodiesterase 5 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; phosphodiesterase 5; a selective inhibitor of arginase II.

**Гуреев В.В.¹
Мартынова О.В.²
Анциферова О.Е.³
Мартынов М.А.⁴
Покровская Т.Г.⁵
Малородова Т.Н.⁶
Локтева Т.И.⁷**

**КОРРЕКЦИЯ ЭКСПЕРИМЕНТАЛЬНОГО АДМА-ПОДОБНОГО
ГЕСТОЗА ФОСФОДИЭСТЕРАЗОЙ 5 И СЕЛЕКТИВНЫМ
ИНГИБИТОРОМ АРГИНАЗЫ II ZB49-0010**

- 1) к.м.н., доцент кафедры фармакологии Медицинского института НИУ «БелГУ», 308015, Белгород, ул. Победы, 85, Россия E-mail: gureev@bsu.edu.ru
- 2) аспирант кафедры фармакологии Медицинского института НИУ «БелГУ», 308015, Белгород, ул. Победы, 85, Россия; E-mail: m.olga91@mail.ru
- 3) аспирант кафедры фармакологии Медицинского института НИУ «БелГУ», 308015, Белгород, ул. Победы, 85, Россия
- 4) ординатор кафедры госпитальной хирургии Медицинского института НИУ «БелГУ», 308015, Белгород, ул. Победы, 85, Россия
- 5) д.м.н., профессор кафедры фармакологии Медицинского института НИУ «БелГУ», 308015, Белгород, ул. Победы, 85, Россия
- 6) к.м.н., доцент кафедры фармакологии Медицинского института НИУ «БелГУ», 308015, Белгород, ул. Победы, 85, Россия

7) аспирант кафедры фармакологии Медицинского института НИУ «БелГУ»,
308015, Белгород, ул. Победы, 85, Россия

Аннотация: Моделирование экспериментального АДМА-подобного гестоза осуществляли путем введения крысам L-NAME с 14 по 20 сутки беременности. У животных наблюдалось повышение артериального давления, протеинурия, нарушение микроциркуляции в плаценте, нарушение регуляции сосудистого тонуса и деструктивные изменения в плаценте ишемического генеза. Использование тетрагидробиоптерина и селективного ингибитора аргиназы II ZB49-0010 приводило к выраженной коррекции морфофункциональных нарушений возникающих при моделировании экспериментального гестоза. Таким образом, результаты проведенного эксперимента дают основания для продолжения поиска препаратов с эндотелеопротестивными свойствами с целью коррекции гестоза.

Ключевые слова: крысы, N-нитро-L-аргинин-метилловый эфир, дисфункция эндотелия, экспериментальный гестоз, тетрагидробиоптерин, селективный ингибитор аргиназы II.

INTRODUCTION. Preeclampsia is the most common disease of pregnant women and ranks first in causes of maternal and perinatal mortality. Recently, many authors have played a significant role in the pathogenesis of the disease is removed endothelial dysfunction [1, 2]. The 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 monomethylarginine (L-NMMA), which are predictors of preeclampsia [3, 4, 5].

MAIN PART. In this regard, the current research seems to influence phosphodiesterase 5 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 with a ADMA-similar agent – a 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). The 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, 9]. 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 + phosphodiesterase 5 (0,9 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.

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 of the vasoconstrictor and vasodilating mechanisms of regulation of vascular tone, as evidenced by the increase in QED with $1,1 \pm 0,11$ intact pregnant animals to $3,12 \pm 0,17$ ($p < 0.05$). In addition, there was a significant rise in systolic and diastolic blood pressure $134,5 \pm 2,3$ and $92,0 \pm 2,1$ to $186,3 \pm 6,9$ and $143,1 \pm 4,2$ mm Hg. Art. respectively. The introduction of the blocker NO-synthase resulted in a significant reduction in the microcirculation of the placenta index with 446.3 ± 27.5 to $218.3 \pm 13,67$ ($p < 0.05$), as well as in the reduction of the NOx content of the stable metabolite in serum $2,28 \pm 0,11$ mmol / dL to $1,28 \pm 0,08$ / dl ($p < 0.05$).

Application of phosphodiesterase 5 and selective inhibitor of arginase II ZB49 = 0010 led to the normalization of relations between the 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 of 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±2,3y	92,0±2,1y	1,10±0,11y	446,3±27,46y	2,28±0,11y
L-NAME	186,3±6,9*	143,1±4,2*	3,12±0,17*	218,3±13,67*	1,28±0,08y
L-NAME + FDE 5	149,7±2,2*	97,6±3,2*	1,85±0,08 y	398,7±24,84 y	1,36±0,1y
L-NAME + ZB49-0010	162,5±8,7*	130,2±6,7*	1,49±0,14y	435,4±27,35y	1,95±0,06y

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.

The efficiency of use of FDE 5 can be explained by the inhibition of phosphodiesterase 5 in the endothelia and an increase by the maintenance of cyclic adenosine monophosphate.

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 [10, 11, 12, 13].

Ultimately, the mechanism of action of both drugs is reduced to restore the NO-synthesis function and to reduce the endothelial dysfunction. The differences in their endothelioprotective effects explain 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 endoteleoprotectivnoy correction of preeclampsia.

ACKNOWLEDGEMENTS. Research was partially supported by fund of assistance to development of small forms of the enterprises in the scientific and technical sphere (No. 5233GU1/2014 of 24.03.2015)

REFERENCES

1. Adu-Bonsaffoh. Nitric oxide dysregulation in the pathogenesis of preeclampsia among Ghanaian women. / Adu-Bonsaffoh [et al.] Integr Blood Press Control. . – 2015. Vol. 19;8. P. 1-6.
2. Brandão A.H. Prediction of early and late preeclampsia by flow-mediated dilation of the brachial artery / A.H. Brandão [et al.] Radiol Bras. – 2014. – Vol. 47(4). P. 206-9.
3. Fei X. Maternal plasma levels of endothelial dysfunction mediators including AM, CGRP, sICAM-1 and tHcy in pre-eclampsia. / X. Fei [et al.] Adv Clin Exp Med. 2012. Vol. 21(5). P. 573-579.
4. Groesch K.A. Nitric oxide generation affects pro-

and anti-angiogenic growth factor expression in primary human trophoblast. Placenta. / K.A. Groesch [et al.] – 2011. Vol. 32(12). P. 926-931.

5. Wang A. Preeclampsia: the role of angiogenic factors in its pathogenesis. / A. Wang [et al.] Physiology (Bethesda). 2014. 24: 147–158.

6. Gureev V.V. Remote Ischemic Preconditioning Correction in Adma-Like Gestosis Model./ V.V. Gureev [et al.] Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2014. №5. Vol. 1095-1098.

7. Korokin M.V. Effect of L-arginine, vitamin B6 and folic acid on parameters of endothelial dysfunction and microcirculation in the placenta in modeling of L-NAME-induced NO deficiency./ M.V. Korokin [et al.] Bulletin of Experimental Biology and Medicine. -2011.- 152(1): 70–72. doi: 10.1007/s10517-011-1456-z.

8. Pokrovsky M.V. Pharmacological correction of ADMA-eNOS-associated target in preeclampsia. / M.V. Pokrovsky[et al.] Obstetrics and Gynecology.2011. 2: 16-20.

9. Pokrovsky M.V. USE OF L-ARGININE IN CORRECTION OF ENDOTELIALNY DYSFUNCTION AT EXPERIMENTAL PREEKLAMPSIYA./ M.V. Pokrovsky [et al.] Experimental and clinical pharmacology. 2012. T. 75. No. 2. P. 14-16.

10. Gureev V. V. CORRECTION ADMA-LIKE GESTOZ IN EXPERIMENT./ V. V. Gureev [et al.] Bridge Ampere-second.Kursk scientific and practical bulletin «Chelovek I Ego Zdorovye». 2012. No. 1. P. 14-19.

11. Pokrovsky M.V. REALITIES AND PROSPECTS OF PHARMACOLOGICAL ORRECTION «ADMA-ENOS» – THE ASSOCIATED WAYS AT PREEKLAMPSIYA/ M.V. Pokrovsky [et al.] Rational pharmacotherapy in cardiology. 2010. T. 6. No. 6. P. 882-887.

12. Gureev V. V. INOS ROLE IN CORRECTION OF ENDOTELIALNY DYSFUNCTION AT ADMA-LIKE GESTOZ SHORT EPISODES OF ISHEMIL-REPERFUZII IN EXPERIMENT/ V. V. Gureev [et al.] Basic researches. 2012. No. 8-2. P. 298-301

13. Gureev V.V. Correction of ADMA-like preeclampsia in an experiment using arginase inhibitor L-norvaline and preparations included in the standard treatment regimen./V. V. Gureev [et al.] Kursk scientific-practical herald «Man and his health».2012. № 2. P. 14-20.