

The Effect of Arginase II Selective Inhibitors on the Functional Parameters of Experimental Animals in ADMA-Like Preeclampsia

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Abstract

Introduction: Perinatal mortality rate and the rate of preterm birth (10-12%) in pregnant women with hypertensive disorders far outweigh the corresponding values in women with physiological pregnancy. Despite such close attention worldwide to this problem, today the number of this complication has no tendency to decrease.

Objective of the study: To study the protective effect of arginase II selective inhibitors KUD-974, KUD-975, KUD-259 on functional parameters in rats with ADMA-like preeclampsia.

Methods: The study was conducted in 140 female Wistar rats weighing 250-300 g.

Results: The analysis of the obtained in this experimental study results showed that a decrease in the activity of arginase leads to an increase in the production of nitric oxide, which has a beneficial effect on vascular function.

Conclusion: Arginase II inhibitors are currently a promising group of drugs for the treatment of hypertensive conditions in pregnant women.

Key words: Preeclampsia, Arginase Inhibitors, Endothelial Dysfunction.

Introduction

Over the past decade, preeclampsia, which is a special case of hypertensive disorders during pregnancy, has been the object of increased attention, as this complication causes every 3rd case of obstetric morbidity and annually takes up to 50,000 lives of young women around the world and is the most common cause in the structure of maternal mortality [1-3,]. Perinatal mortality rates and the rate of preterm birth (10-12%) in pregnant women with hypertensive disorders far outweigh the corresponding values in the women with normal pregnancy. The incidence of preeclampsia during pregnancy ranges from 2 to 8% [4-6]. Despite such close attention to this problem all over the world, today the number of cases of this complication does not tend to decrease [7, 8].

In recent years, the number of studies indicating that the main role in the development of preeclampsia plays a disorders of the endothelial function, which lead to development of generalized spasm, increase in blood pressure and, as a consequence, ischemic disorders in organs [9, 10, 24]. Endothelium is a powerful endocrine organ involved in the regulation of vascular tone and maintenance of their normal structure, control of blood rheology and processes of local inflammation. Normally, anticoagulant and

antithrombotic activity of the endothelium prevail over procoagulant activity, but in the conditions of damage this balance is shifted towards procoagulation.

One of the factors in the development of endothelial dysfunction is a deficiency of nitric oxide (NO), which is the main vasodilating factor produced by the endothelium. In the physiological pregnancy, one of the adaptive mechanisms of the cardiovascular system of a woman is to increase the endogenous production of NO and increase the sensitivity of smooth muscle vascular cells to it.

No synthesis is carried out under the action of the enzyme endothelial NO-synthase (eNOS) from the amino acid L-arginine. Arginase inhibitors are substances of natural origin, the mechanism of action of which is to block the enzyme arginase, and, consequently, in prevention of the metabolism of L-arginine into ornithine and urea [11, 12, 22, 23]. As a result, a greater amount of L-arginine is metabolized to nitric oxide under the action of NO-synthase [13-15, 21]. Reduced arginase activity leads to increased production of nitric oxide, which has a positive effect on the endothelial function. Thus, the administration of arginase inhibitors to increase the synthesis of NO is one of the methodological approaches to prevent

the development of endothelial dysfunction [16-18, 20, 25].

Objective of the Study

To study the protective effect of arginase II selective inhibitors KUD-974, KUD-975, KUD-259 on functional parameters in rats with ADMA-like preeclampsia.

Methods

The study was performed on 140 female Wistar rats weighing 250-300 g. ADMA-like preeclampsia in the studied animals was simulated by the administration of a non-selective NOS inhibitor L-Nitro-Arginine Methyl Ester (L-NAME) (25 mg/kg/day) intraperitoneally from the 14th to the 20th day of the pregnancy. Arginase II selective inhibitors KUD 259, KUD 974, KUD 975 were administered to the experimental animals at the dose of 1 mg/kg/day per os from the 14th to the 20th day of the pregnancy. Methyldopa, which was administered at the dose of 0.043 g/kg twice a day per os from the 14th to the 20th day of the pregnancy, and L-Norvaline 10 mg/kg/day per os from the 14th to the 20th day of pregnancy, were selected as drugs for animal control groups.

Results

The administration of the arginase II selective inhibitors in the animals with ADMA-like preeclampsia led to a statistically significant ($p < 0.05$) decrease in blood pressure levels in comparison with the group of untreated animals (Fig. 1).

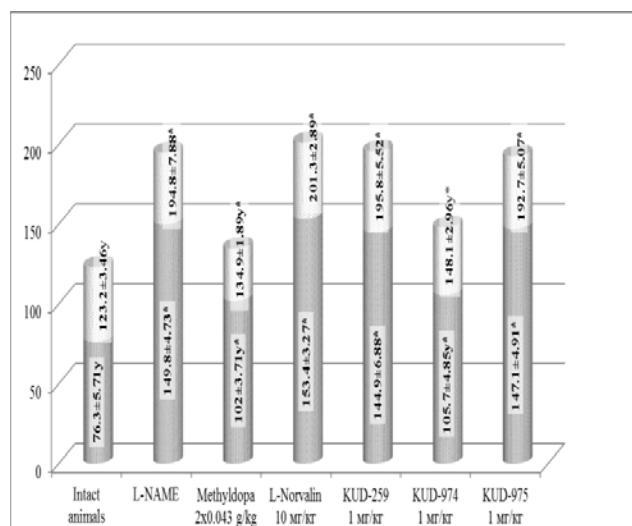


Figure -1: The effect of the arginase II selective inhibitors on the blood pressure of rats with ADMA-like preeclampsia

Note: * - $p < 0.05$ in comparison with the group of intact animals; y - $p < 0.05$ in comparison with L-

NAME group; *y - $p < 0.05$ the comparison of the intact animals group with L-NAME group.

The evaluation of the endothelial function revealed a statistically significant ($p < 0.05$) improvement in the endothelial dysfunction coefficient in animals with ADMA-like preeclampsia which were administered by the arginase II selective inhibitors in comparison with the group of untreated animals (Fig. 2).

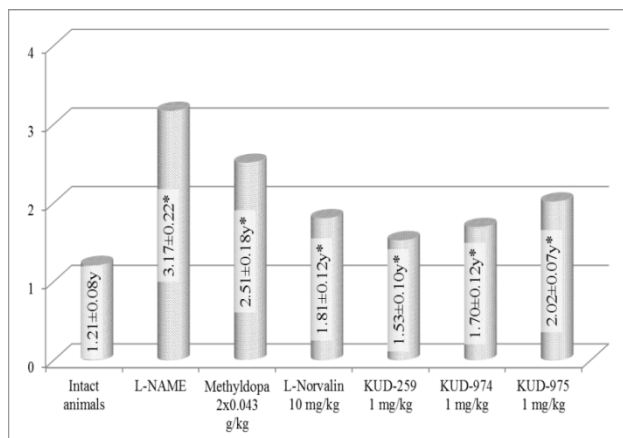


Figure-2: The effect of the arginase II selective inhibitors on the endothelial dysfunction coefficient in rats with ADMA-like preeclampsia

Note: * - $p < 0.05$ in comparison with the group of intact animals; y - $p < 0.05$ in comparison with L-NAME group; *y - $p < 0.05$ the comparison of the intact animals group with L-NAME group.

The analysis of the concentration level of nitric oxide terminal metabolites in the plasma of rats with ADMA-like preeclampsia showed a statistically significant ($p < 0.05$) increase in the groups of animals with ADMA-like preeclampsia, which were administered by the arginase II selective inhibitors in comparison with the group of untreated animals (Fig. 3).

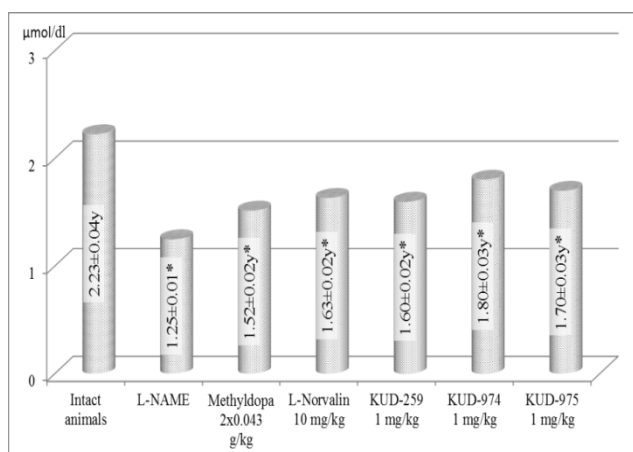


Figure -3: The effect of the arginase II selective inhibitors on the concentration of the nitric oxide terminal metabolites in the plasma of rats with ADMA-like preeclampsia.

Note: *- p <0.05 in comparison with the group of intact animals; y - p <0.05 in comparison with L-NAME group; *y - p <0.05 the comparison of the intact animals group with L-NAME group.

The evaluation of a placental microcirculation in the in experimental animals revealed a statistically significant (p <0.05) increase of the microcirculation values in comparison with the group of untreated animals (Fig. 4).

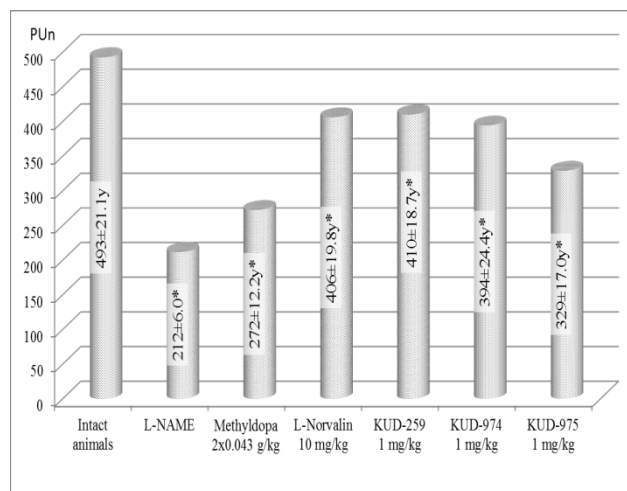


Figure-4: The effect of the arginase II selective inhibitors on the placental microcirculation in rats with ADMA-like preeclampsia

Note: *- p <0.05 in comparison with the group of intact animals; y - p <0.05 in comparison with L-NAME group; *y - p <0.05 the comparison of the intact animals group with L-NAME group.

Conclusion

The performed study revealed a pronounced protective effect of the arginase II selective inhibitors KUD-974, KUD-975, KUD-259 on the functional parameters in rats with ADMA-like pre-eclampsia.

In this study, endothelial dysfunction was chosen as a target for the search for new drugs for the prevention and treatment of preeclampsia, as a dysfunction of small arterial vessels leads to disorders of the blood pressure regulation and microcirculation in tissues, which lead to a dysfunction of organs and systems, and in some cases to multiorgan failure.

The evaluation the results obtained in this experimental study, found that a decrease in the arginase activity leads to an increase in the production of nitric oxide, which has a beneficial effect on vascular function. Thus, the application of arginase inhibitors to increase the NO synthesis is one of the methodological approaches to prevent the endothelial dysfunction.

Treatment used by modern obstetrics and gynecology doctors in daily practice, focused on

reducing the dominant syndromes underestimation of the pathogenetic components. Modern knowledge of the preeclampsia pathogenesis and the accumulated experimental data justify the foreseeable prospects for the development of drugs for the preeclampsia treatment and prevention and reveal new opportunities for further research. Therefore, today it is important to search for new pharmacological agents that can stop this complication of pregnancy, affecting the development and course of preeclampsia. Thus, it can be assumed that arginase inhibitors are currently a promising group of drugs for the treatment of hypertensive conditions in pregnant women. Arginase II inhibitors are of particular interest, given their selectivity.

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