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PATHOGENETIC FEATURES OF FORMATION OF EXPERIMENTAL PREECLAMPSIA-LIKE CONDITION

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Objective. To study the pathogenesis of clinical and laboratory syndromes of preeclampsia-like condition and the possibility of influencing them through the introduction of specific antibodies to marinobufagenin. **Materials and methods.** 36 pregnant rats were used in the experiment. 24 rats from 12 to 19 days of pregnancy were prescribed a 1,8% NaCl solution to simulate a preeclampsia-like condition. Subsequently, this sample was divided into 2 groups. In one group (12 animals, the second group), preimmune rabbit serum was administered intraperitoneally as an immune agent. In another group (12 animals, the third group), a single intraperitoneal administration of polyclonal anti-marinobufagenin antibodies was performed. After the antibody injection, a comprehensive clinical and laboratory evaluation was performed. **Results.** Against the background of a hypersol diet, an increase in systolic blood pressure was found, as well as the concentration of marinobufagenin in blood plasma. The introduction of antibodies to marinobufagenin caused a decrease in blood pressure. In addition, the formation of a preeclampsia-like condition showed an increase in endoglin and sFlt1 in the placenta, as well as an increase in sFlt1, collagen-1 and a decrease in Fli-1 in the thoracic aorta. The appointment of antibodies to marinobufagenin led to an increase in the content of Fli-1 to the level in the control group. **Summary.** In the formation of a preeclampsia-like condition, an increase in the level of marinobufagenin in blood plasma leads to an increase in the content of antiangiogenic factors in the placenta and in the thoracic aorta. Intraperitoneal administration of antibodies to marinobufagenin contributes to a significant increase in the content of Fli-1.

Keywords: preeclampsia; marinobufagenin; pregnancy; arterial hypertension.

ПАТОГЕНЕТИЧЕСКИЕ ОСОБЕННОСТИ ФОРМИРОВАНИЯ ЭКСПЕРИМЕНТАЛЬНОГО ПРЕЭКЛАМПСИЯ-ПОДОБНОГО СОСТОЯНИЯ

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Цель исследования – изучить патогенез клинико-лабораторных синдромов преэклампсия-подобного состояния и возможность влияния на них посредством введения специфических антител к маринобуфагенину. **Материалы и методы.** В эксперименте были использованы 36 беременных крыс. 12 из них составили первую контрольную группу. 24 крысам с 12 по 19 дни беременности назначали 1,8 % раствор NaCl для моделирования преэклампсия-подобного состояния. В последующем данную выборку разделили на 2 группы. В одной группе (12 животных, вторая группа) в качестве иммунного средства внутрибрюшинно вводилась преиммунная кроличья сыворотка. В другой группе (12 животных, третья группа) производили однократное внутрибрюшинное введение поликлональных анти-маринобуфагенин антител. После инъекции антител проводили комплексную клинико-лабораторную оценку. **Результаты.** На фоне гиперсолевой диеты установлено увеличение систолического артериального давления, а также концентрации маринобуфагенина в плазме крови. Введение антител к маринобуфагенину вызывало уменьшение артериального давления. Кроме того, при формировании преэклампсия-подобного состояния установлено увеличение содержания эндоглина и sFlt1 в плаценте, а также увеличение sFlt1, коллагена-1 и уменьшение Fli-1 в грудной аорте. Назначение антител к маринобуфагенину приводило к увеличению содержания Fli-1 до уровня в контрольной группе. **Выводы.** При формировании преэклампсия-подобного состояния повышение уровня маринобуфагенина в плазме крови приводит к возрастанию содержания антиангиогенных факторов в плаценте и в грудной аорте. Внутрибрюшинное введение антител к маринобуфагенину способствует значительному повышению содержания Fli-1.

Ключевые слова: преэклампсия; маринобуфагенин; беременность; артериальная гипертензия.

INTRODUCTION

Preeclampsia is one of the most significant current problems in obstetric and gynecological practice. This syndrome is one of the leading causes of prenatal complications and has a significant negative effect on both the mother's body and the fetus. According to the results of previous epidemiological studies, preeclampsia was found to complicate 2%–8% of all pregnancies [14–16]. In general, 10%–15% of maternal mortality in developed countries is due to preeclampsia [3, 10, 11]. Previous studies revealed that endogenous cardiotonic steroids, in particular marinobufagenin (MBG), play a major role in the pathogenesis of preeclampsia [1, 5, 6, 9, 12]. Neutralization of their effect contributes to the regression of pathological symptoms. In previous experiments, we elaborated a model accompanied by the development of clinical and laboratory changes typical of preeclampsia [5]. Its application enables us to perform an in-depth study of the mechanisms of development of this syndrome.

This study aimed to investigate the pathogenesis of clinical and laboratory syndromes of preeclampsia-like conditions and the possibility of influencing them by administering specific antibodies to MBG.

MATERIALS AND METHODS

In the experiment, 36 pregnant Sprague-Dawley rats were used, weighing 225–250 g, under standard vivarium conditions. The animals were divided into three groups. Twelve animals received a normal diet (control, group 1), and 24 rats received a 1.8% NaCl solution from days 12 to 19 of gestation to simulate a preeclampsia-like condition. Subsequently, this sample was divided into two groups: in one group, pre-immune rabbit serum was administered intraperitoneally at a dose of 50 μg/kg to 12 animals as an immune agent (group 2); in the other group, 12 rats received a single intraperitoneal administration of polyclonal anti-MBG antibodies, also at a dose of 50 μg/kg (group 3). The antibody dosage was sufficient for *in vitro* reversal of 75% of the activity of renal Na^+/K^+-ATPase reduced by MBG, and amounted to 50 μg/kg [4, 9]. After antibody injection, systolic blood pressure was assessed in all groups using the tail cuff, blood plasma MBG levels were studied, animal weights were measured, the amount of consumed fluid and excreted urine was examined for 1 day, and the level of proteinuria, as well as 24-hour kidney excretion of Na^+, were determined. After euthanasia, the number of fetuses and their average weights were estimated, the placenta was weighed, and the level of endoglin in the placenta was estimated. In addition, the level of sFlt1 in the placenta and rings of the thoracic aorta were estimated, and the amounts of Fli1, collagen-1, transforming growth factor beta (TGF-beta), and collagen-4 in the rings of the thoracic aorta was measured. The tissue samples of the placenta and the rings of the thoracic aorta were prepared according to a previously developed technique [7]. To assess the plasma MBG level, monoclonal anti-MBG antibodies 4G4 were used. Western blotting using commercial sets of specific antibodies was used on the prepared tissue samples to establish the levels of endoglin, sFlt1, Fli-1, procollagen 1 and collagen-1, collagen-4, and TGF-beta. GraphPad Instat and GraphPad Prism (GraphPad Software Inc., USA) and MS Office 2007 were used as software packages for statistical analysis of the data obtained.

RESULTS AND DISCUSSION

The parameters were evaluated on day 20 of pregnancy in rats. A statistically significant increase in systolic blood pressure was registered in rats during administration of a 1.8% sodium chloride solution (1.0 ml). Moreover, in group 1 (control), systolic blood pressure was 107 ± 2 mm Hg. At the same time, in group 2, this value increased sharply to 117 ± 2 mm Hg ($p < 0.05$). Furthermore, when antibodies to MBG were administered (group 3), a significant decrease in this indicator to 93 ± 3 mm Hg occurred, which was significantly different from the values in groups 1 ($p < 0.05$) and 2 ($p < 0.01$). These data are presented in Fig. 1.

A study of the level of proteinuria established that the lowest daily urinary protein excretion rate was characteristic of animals fed with a normal diet (group 1, control), in which it was 15 ± 2 mg/24 h. In the case of a high-salt diet, the level of proteinuria increased significantly to 24 ± 1.5 mg/24 h ($p < 0.05$). Moreover, the administration of antibodies to MBG did not contribute to a significant change in proteinuria, which corresponded in this group to 27 ± 2 mg/24 h ($p < 0.05$).

With the formation of a preeclampsia-like condition, in the blood plasma, a significant increase in the MBG level was noted. In particular, in animals that received the usual amount of salt, its concentration was 0.49 ± 0.11 nmol/L. At the same time, in the group receiving a 1.8% sodium chloride solution, it increased to 1.54 ± 0.34 nmol/L ($p < 0.05$).

Studying the weights of rats enabled us to establish that upon induction of a preeclampsia-like condition, this indicator decreased sharply. Thus, in the control group, which received the normal diet, its average value was 346 ± 7 g, while in rats treated with the high-salt diet, it decreased to 240 ± 8 g ($p < 0.01$). At the same time, the administration of antibodies to MBG has practically no effect on this indicator,

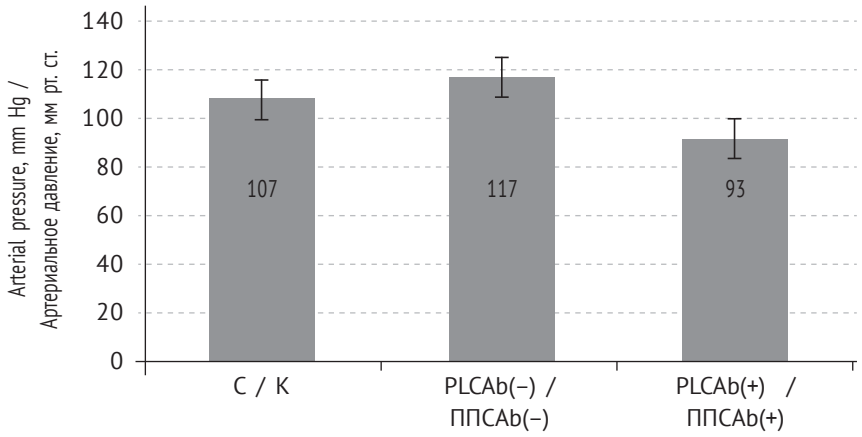

Fig. 1. The level of systolic blood pressure in the experimental groups. C — the first group of rats with a normal diet (control), PLCAb(–) – the second group of rats with preeclampsia-like condition, which were not injected with antibodies to MBG, PLCAb(+) – the third group of rats with preeclampsia-like condition, which were injected with antibodies to MBG

Рис. 1. Уровень систолического артериального давления в экспериментальных группах. К — первая группа крыс с обычной диетой (контроль), ППСАb(–) — вторая группа крыс с преэклампсия-подобным состоянием, которым не вводились антитела к МБГ, ППСАb(+) — третья группа крыс с преэклампсия-подобным состоянием, которым вводились антитела к МБГ

contributing only to a tendency toward an insignificant increase to 247 ± 9 g ($p < 0.01$).

The amount of fluid absorbed increased sharply with the formation of a preeclampsia-like condition and did not depend on the administration of antibodies to MBG. In the control group fed with the normal diet, animals consumed 49 ± 3 ml of water during the day. In the case of a diet with a high-salt content, this indicator was 83 ± 8 ml in group 2, which did not receive antibodies to MBG ($p < 0.01$), and 81 ± 9 ml in group 3, where they were administered ($p < 0.01$).

The level of daily diuresis was also largely dependent on the diet. Thus, in group 1 (the control), which consumed the normal diet, the average volume of urine excreted per day was 22 ± 2 ml; in group 2, which received a high-salt diet but did not receive antibodies, it was 65 ± 2 ml ($p < 0.01$), and in the sample of animals given antibodies to MBG (group 3), it reached 55 ± 5 ml ($p < 0.01$).

A similar dynamic of changes was recorded in the study of kidney excretion of Na^+. Its value in the control group corresponded to 24 ± 9 ml/day, in the case of administration of a 1.8% sodium chloride solution (group 2), it reached 104 ± 12 ml/day ($p < 0.01$), and when antibodies were administered (group 3), it was 99 ± 7 ml/day ($p < 0.01$).

The formation of a preeclampsia-like condition naturally resulted in a decrease in the average weight of the placenta and fetus. Thus, in animals with normal pregnancies, which received normal amounts of salt, the average placental weight was 6.2 ± 0.4 g. In rats that received a high-salt diet (group 2), it was 4.7 ± 0.5 g ($p < 0.05$), and in the case of administration of antibodies to MBG (group 3), it was 4.4 ± 0.3 g ($p < 0.05$). The mean weights of the fetuses in these groups reached 33 ± 5 g, 22 ± 3 g ($p < 0.05$), and 21 ± 2 g ($p < 0.05$), respectively. We also noted a significant decrease in the number of fetuses during the development of a preeclampsia-like condition. In particular, in the control group (group 1), the average value of this indicator corresponded to 12.4 ± 0.3, in the sample receiving an increased salt amount (group 2), it was 8.5 ± 1.2 ($p < 0.05$), and with the administration of antibodies to MBG (group 3), it was 9.0 ± 1.08 ($p < 0.05$). The general data on the parameters studied are presented in Table 1.

In the process of studying placental tissue samples, we found that the development of a preeclampsia-like condition was accompanied by a significant increase in the level of antiangiogenic factors, such as endoglin and sFlt1. Moreover, in group 1, which received the normal diet, the endoglin value corresponded to 1.0 ± 0.15 RU. In group 2, which did not receive antibodies to MBG, when prescribing a high-salt diet, this indicator increased to 6.1 ± 0.4 RU ($p < 0.01$), and in group 3, after administration of antibodies to MBG, its amount corresponded to 6.4 ± 0.3 RU ($p < 0.01$). When studying the level of sFlt1, similar results were obtained. Thus, it was revealed that in the control group, which received the normal diet, its level was 1.0 ± 0.15 RU. Under conditions of modeling a preeclampsia-like condition (group 2), its value increased to 2.8 ± 0.3 RU ($p < 0.05$). The use of antibodies to MBG also does not contribute to a

Table 1 / Таблица 1

General data on changes in clinical and laboratory parameters in the examined experimental groups of animals ($M \pm S$)
Общие данные изменения клинико-лабораторных показателей в обследованных экспериментальных группах животных ($M \pm S$)

Indication / Показатель	Pregnant rats ($n = 12$) / Беременные крысы ($n = 12$)	Pregnant rats + 1.8 % NaCl ($n = 12$) / Беременные крысы + + 1,8 % NaCl ($n = 12$)	Pregnant rats + 1.8 % NaCl + + antibodies MBG ($n = 12$) / Беременные крысы + + 1,8 % NaCl + антитела к МБГ ($n = 12$)
Body weight, g / Вес тела, г	346 ± 7	240 ± 8**	247 ± 9**
Volume of absorbed liquid, ml/24 h / Объем поглощенной жидкости, мл/24 ч	49 ± 3	83 ± 8**	81 ± 9**
Daily diuresis, ml/24 h / Суточный диурез, мл/24 ч	22 ± 2	65 ± 2**	55 ± 5**
The excretion of Na^+, ml/24 h / Экскреция Na^+, мл/24 ч	24 ± 9	104 ± 12**	99 ± 7**
Plasma MBG, nmol/l / Маринобуфагенин плазмы, нмоль/л	0.49 ± 0.11	1.54 ± 0.34*	–
Weight placenta, g / Вес плаценты, г	6.2 ± 0.4	4.7 ± 0.5*	4.4 ± 0.3*
Weight fetus, g / Вес плодов, г	33 ± 5	22 ± 3*	21 ± 2*
Quantity fetus, un. / Количество плодов, шт.	12.4 ± 0.3	8.5 ± 1.2*	9.0 ± 1.08*

Note. Significant differences between the group without preeclampsia-like condition and other animal groups: *$p < 0.05$, **$p < 0.01$.
Примечание. Достоверные различия между группой без преэклампсия-подобного состояния и иными группами животных: *$p < 0,05$, **$p < 0,01$.

significant change in this indicator, which reached 2.7 ± 0.3 RU after their administration in the group 3 ($p < 0.05$).

When studying samples of the thoracic aortic rings, we revealed that the level of sFlt1 factor in them also increased significantly in case of the formation of a preeclampsia-like condition. Thus, if in group 1, it was 1.0 ± 0.15 RU, then when using a diet with a high-salt content (group 2), its amount increased to 3.5 ± 0.3 RU ($p < 0.05$). The use of antibodies to MBG did not affect this indicator, which amounted to 3.6 ± 0.4 RU ($p < 0.05$).

The subsequent research steps revealed that development of a preeclampsia-like condition contributes to a significant decrease in the level of factor Fli 1 in tissue samples of the thoracic aortic rings. Moreover, in the animals of group 1, which received the normal diet, the amount of this substance in the samples under study was 1.0 ± 0.1 RU. In group 2, when 1.8% sodium chloride was administered, this indicator decreased sharply to 0.2 ± 0.05 RU ($p < 0.01$). It is very important to note that administration of antibodies to MBG resulted in a significant increase in the Fli 1 concentration. Thus, its value in group 3 reached 0.9 ± 0.1 RU. This value did not differ significantly from the indicators obtained in the control group ($p > 0.05$). General information is presented in Fig. 2.

The level of collagen-1 in the tissues of the thoracic aorta also varied significantly in separate groups of laboratory animals. In particular, in group 1, during physiological pregnancy, its concentration was 1.0 ± 0.1 RU. In group 2, when a preeclampsia-like condition formed, the value of collagen-1 increased significantly and reached 2.4 ± 0.3 RU ($p < 0.01$ with respect to the control group). The administration of antibodies to MBG did not change this indicator significantly, and in group 3 it was 2.2 ± 0.4 ($p < 0.01$ with respect to the control group). The relevant data are presented in Fig. 2.

We also investigated the likelihood of the formation of vascular fibrosis with the activation of growth factors. For this purpose, the levels of transforming growth factor beta (TGF-beta) and collagen-4 in the tissues of the thoracic aorta were examined. It was found that in the case of the formation of a preeclampsia-like condition when hypertonic saline was administered, the concentration of these compounds was not increased significantly. Thus, TGF-beta in group 1, which received a normal diet, was found at a concentration

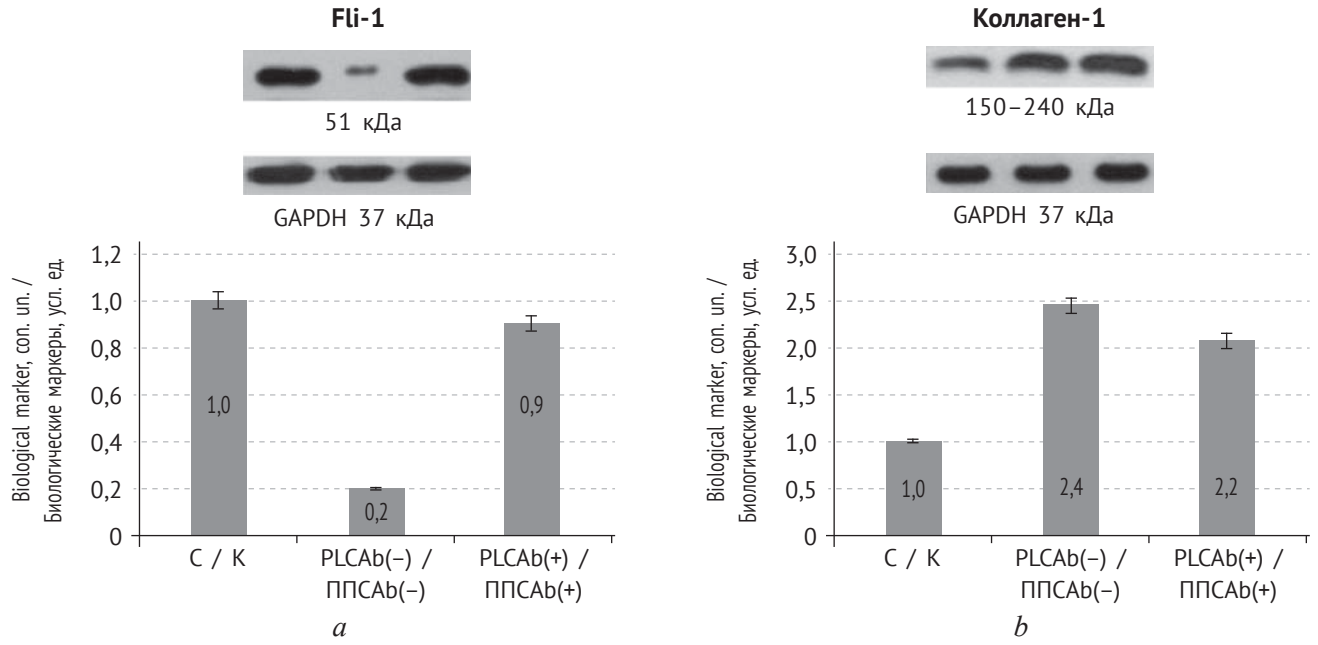

Fig. 2. The level of systolic blood pressure in the experimental groups. C – the first group of rats with a normal diet (control), PLCAb(–) – the second group of rats with preeclampsia-like condition, which were not injected with antibodies to MBG, PLCAb(+) – the third group of rats with preeclampsia-like condition, which were injected with antibodies to MBG

Рис. 2. Уровень биологических факторов в грудной аорте: Fli-1 (*a*), коллагена-1 (*b*). К — группа крыс с обычной диетой (контроль), ППСAb(–) — группа крыс с преэклампсия-подобным состоянием, которым не вводились антитела к МБГ, ППСAb(+) — группа крыс с преэклампсия-подобным состоянием, которым вводились антитела к МБГ

Table 2 / Таблица 2

General data on changes in biological markers in the examined experimental groups of animals (*M* ± *S*)
Общие данные изменения биологических маркеров в обследованных экспериментальных группах животных (*M* ± *S*)

Biological marker, con. un. / Биологические маркеры, усл. ед.	Pregnant rats (*n* = 12) / Беременные крысы (*n* = 12)	Pregnant rats + 1.8 % NaCl (*n* = 12) / Беременные крысы + + 1,8 % NaCl (*n* = 12)	Pregnant rats + 1.8 % NaCl + + antibodies MBG (*n* = 12) / Беременные крысы + 1,8 % NaCl + + антитела к МБГ (*n* = 12)
Endoglin in the placenta / Эндоглин в плаценте	1.0 ± 0.15	6.1 ± 0.4**	6.4 ± 0.3**
sFlt1 in the placenta / sFlt1 в плаценте	1.0 ± 0.15	2.8 ± 0.3*	2.7 ± 0.3*
sFlt1 in the thoracic aorta / sFlt1 в грудной аорте	1.0 ± 0.15	3.5 ± 0.3*	3.6 ± 0.4*
Fli-1 in the thoracic aorta / Fli-1 в грудной аорте	1.0 ± 0.1	0.2 ± 0.05**	0.9 ± 0.1
Collagen-1 in the thoracic aorta / Коллаген-1 в грудной аорте	1.0 ± 0.1	2.4 ± 0.3**	2.2 ± 0.4**
TGF-beta in the thoracic aorta / ТФР-бета в грудной аорте	1.0 ± 0.2	1.1 ± 0.1	1.2 ± 0.1
Collagen-4 in the thoracic aorta / Коллаген-4 в грудной аорте	1.0 ± 0.1	1.2 ± 0.1	1.1 ± 0.15

Note. Significant differences between the group without preeclampsia-like condition and other animal groups: **p* < 0.05, ***p* < 0.01.
Примечание. Достоверные различия между группой без преэклампсия-подобного состояния и иными группами животных: **p* < 0,05, ***p* < 0,01.

of 1.0 ± 0.2 RU, and in the groups that received a high-salt diet, its amount was 1.1 ± 0.1 RU (group 2, without the use of antibodies to MBG, $p > 0.05$) and 1.2 ± 0.1 RU (group 3, with the administration of antibodies to MBG, $p > 0.05$). Similar results were also obtained when studying the level of collagen-4. Thus, its amount in the control group (group 1) was 1.0 ± 0.1 RU; in group 2 during the formation of a preeclampsia-like condition, without the administration of antibodies to MBG, it was 1.2 ± 0.1 RU; and in group 3 when additional of antibodies to MBG were administered, it was 1.1 ± 0.15 RU. General information on the level of the biomarkers studied in the thoracic aorta is presented in Table 2.

DISCUSSION

In our study, it was revealed that, in the formation of a preeclampsia-like condition in laboratory rats that consumed an excess of 1.8% sodium chloride solution, a significant increase in the MBG level in blood plasma resulted in a significant increase in the level of antiangiogenic factors of endoglin and sFlt1 in the placenta, as well as in the thoracic aorta. Such changes may indicate the development of endothelial dysfunction, through a chain of interconnected biochemical reactions, and impaired vasorelaxation processes [13]. Also, a significant decrease in the Fli 1 level was revealed in aortic tissue samples, which naturally results in an increase in the level of collagen-1 and the development of vascular fibrosis [8]. A similar mechanism becomes possible, given the fact that factor Fli 1 has a negative effect on the formation of procollagen-1 [2]. In fact, intraperitoneal administration of antibodies to MBG contributes to a significant increase in the level of Fli 1, which may indicate the possibility of preventing the formation of vascular fibrosis through immunotherapy. Our study also found that the levels of collagen-4 and TGF-beta were not increased under these conditions. This fact indicates that activation of the signaling pathway with the participation of TGF-beta under the conditions studied does not play a significant role and does not enable us to consider it one of the factors resulting in the formation of vascular fibrosis.

CONCLUSION

The formation of symptoms of a preeclampsia-like condition is based on two mechanisms: the first is represented by a significant increase in the level of antiangiogenic factors in the placental tissues and blood vessels along with an increase in the MBG level in blood plasma, and the second is associated with a decrease in the level of Fli 1 in blood vessels and an increase in the level of collagen-1. The use of specific antibodies to MBG contributes to regression of the pathological symptoms observed.

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