Research Article

Pharmacological correction of endothelial dysfunction using ademethionin and taurine

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Abstract

Introduction: Pharmacological correction of endothelial dysfunction is a urgent problem of modern medicine.

Materials and methods: Endothelial dysfunction was simulated in male rats using the e-NOS inhibitor L-NAME (25 mg/kg/day intraperitoneally, for 7 days). Simulation of ADMA-like preeclampsia was performed by intraperitoneal injection of L-NAME to females in the same doses for 7 days (14-20th days of pregnancy). These pathologies were corrected by administering ademethionine in dose 150 mg/kg and taurine at a dose of 260 mg/kg, as well as their combination at the same doses, intragastrically, through an atraumatic probe, once a day.

Results: In the group with use of taurine at a dose of 260 mg/kg the coefficient of endothelial dysfunction decreased to the level of intact animals. Use of ademethionine at a dose of 150 mg/kg and taurine at a dose of 260 mg/kg combined resulted in the most pronounced endothelioprotective effect on the ADMA-like preeclampsia model. The coefficient of endothelial dysfunction decreased more than when using monotherapy of these drugs. Morphological studies of myocardiocytes showed that the combination of ademethionine at a dose of 150 mg/kg and taurine at a dose of 260 mg/kg prevented an increase in the cross-section of cardiomyocytes.

Discussion: Possibly, ademethionine and taurine have an endothelioprotective effect because of their ability to decrease hyperhomocysteinemia.

Conclusion: The investigated drugs showed pronounced endothelioprotective activity and can be recommended for further pre-clinical studies.

Keywords

endothelial dysfunction, preeclampsia, ademethionine, taurine, nitrogen oxide, homocysteine.

Introduction

Endothelial dysfunction (ED) is a pathological state of the endothelium. The basis of its pathogenesis is violation of the synthesis of vasoactive substances. One of the main vasoactive substances secreted by endotheliocytes is nitrogen oxide (NO), an endothelial vasodilator (Félétou and Vanhoutte 2006).

The impaired synthesis of NO results in changes of the vasoregulating function of the endothelium, followed by vasoconstriction.

Oxidative stress leads to ED, as oxygen free radicals are actively involved in reducing nitrogen oxide. Reducing the time of a direct effect of nitric oxide on target cells also leads to the development of endothelial dysfunction (Mason 2016). Due to the main role of oxidative

stress in ED development, LOP products and antioxidant defense indicators can be the markers of ED.

During physiological pregnancy, the balance of production of vasoactive factors is shifted by endothelium towards maintaining vasodilation, due to the constant release of basal nitric oxide (Sharma and Mohan 2011, Sun et al. 2016), which ensures adequate perfusion of placental tissue (Gilbert et al. 2008). Nitrogen oxide, being a potent vasodilator factor, is formed from L-arginine under the action of the endothelial NO synthase enzyme (eNOS). The blood accumulation of methylated L-arginine analogues – ADMA (asymmetric dimethylarginine) and MMA (NG-monomethyl-L-arginine, which are endogenous inhibitors of endothelial NO-synthase (eNOS) – leads to impaired vasodilation (Sibal et al. 2010) and causes preeclampsia (Speer et al. 2008). As known, ADMA is formed as a result of the catabolism of proteins with residues of methylated arginine under the influence of protein arginine methyltransferase (PRMT). Even a slight concentration of ADMA is enough to suppress the activity of NO synthase (NOS) (Dumitrescu et al. 2007).

Increased homocysteine is know to be a predictor of pre-eclampsia in pregnant women and a risk factor for cardiovascular diseases. Hyperhomocysteinemia can both exacerbate existing damage to the endothelium and be an independent factor causing the development of endothelial dysfunction (Antelava et al. 2007, Kemse et al. 2014).

Studies have shown that women are highly likely to develop cardiovascular diseases in future if they have had pre-eclampsia, gestational diabetes and early labor (Hauspurg et al. 2018). These pathophysiological conditions are caused by ED, the ensuing vasoconstriction and a reduced placental, renal and cerebral blood flows. Moreover, impaired blood flow in the uterine arteries can lead to the retarded growth of the fetus, hypamnion and placental abruption.

Due to the involvement of NO in the ED pathogenesis, its reduced synthesis and increased biodegradation resulting from oxidative stress (Sukhovershin et al. 2015), a search for additional pharmacological correction of ED as a predictor of cardiovascular pathology and preeclampsia is viewed as urgent.

The endothelium protective effects of ademethionine and taurine are being actively studied. Taurine and ademetionin are known to effectively prevent the development of endothelial dysfunction, ischemic damage to organs and systems. Taurine has an antioxidant effect, restores the expression of endothelial NO synthase, which is the main endothelium protective pharmacodynamic effect (Battson et al. 2017, Ito et al. 2012, Rukan et al. 2013). Ademethionine is involved in transmethylation, transsulfurization, and transamination reactions, and by inhibiting the PRMT enzyme and preventing the ADMA formation, leads to an increased expression of the eNOS enzyme (Czarnecka et al. 2017, Kim et al. 2013, Sukhanov et al. 2014, Tang et al. 2018).

Materials and methods

The experiments were performed on male rats (220-265 g) and pregnant Wistar females (170-240 g). The experiments were carried out in compliance with the requirements of the federal law of the Russian Federation *On Protection of Animals against Cruel Treatment* dated June 24, 1998, the rules of laboratory practice in preclinical studies in the Russian Federation (GOST 3 51000.3-96 and GOST R 53434-2009), European Community directives (86/609 EU), the rules and the International Recommendations of the European Convention for the Protection of Vertebrate Animals used in experimental studies (1997) and the Laboratory Practice Rules adopted in the Russian Federation (order of the Ministry of Healthcare of the Russian Federation No. 708 of August 29, 2010).

Simulation of endothelial dysfunction was performed by injections of the NO synthase inhibitor N-nitro-L-arginine methyl ester (L-NAME, Sigma) to males intraperitoneally once a day at a dose of 25 mg/kg for seven days. Animals of the intact group were injected with saline (0.9% NaCl) in the same volume (Pokrovsky 2006).

The following experimental groups of animals were formed of male rats:

– intact – (n=10);
– group of L-NAME-induced deficiency of nitrogen oxide (n=10);
– L-NAME+ademethionine 150 mg/kg (n=10);
– L-NAME+taurine 260 mg/kg (n=10);
– L-NAME+ademethionine 150 mg/kg* + taurine 260 mg/kg (n=10).

Simulation of preeclampsia. L-NAME was injected intraperitoneally to females at a dose of 25 mg/kg/day for 7 days, starting from the 14-20th day of pregnancy.

Then the animals were divided into the following groups:

– intact (n=10);
– Preeclampsia (n=10);
– Preeclampsia+ademethionine 150 mg/kg (n=10);
– Preeclampsia+taurine 260 mg/kg (n=10);
– Preeclampsia+ademethionine 150 mg/kg* + taurine 260 mg/kg (n=10).

Ademethionine and taurine, as well as their combination, were injected to the experimental animals intragastrically daily (through an atraumatic probe) at a dose of 150 mg/kg/day and 260 mg/kg/day against the injection of L-NAME to them. The combination of ademethionine and taurine was injected at the same doses, via the same routes of administration and the same duration of therapy. Taurine was administered one hour after the administration of ademethionine.

Functional Vascular and Cardiac Tests

On the 8th day of the experiment (the 21st day of pregnancy), a catheter was inserted into the left carotid artery of the animals to record hemodynamic parameters. The animals were at that moment under anesthesia. Bolus dosing of vascular and cardiac samples was in the right femoral vein. The hemodynamic parameters, namely, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured continuously by means of a TSD104A sensor and a Biopac MP150 hardware-software complex. Acetylcholine (40 µg/kg) was injected intravenously to determine endothelium-dependent vasodilatation (EDV), and sodium nitroprusside (30 µg/kg) was injected intravenously to determine endothelium-independent vasodilation (ENDV) (Pokrovsky et al. 2006).

The coefficient of endothelial dysfunction (CED) was calculated as the ratio of the area of the triangle above the blood pressure (BP) recovery curve in the endothelium-independent vasodilation reaction to the area of the triangle above the BP recovery curve in the endothelium-dependent vasodilation reaction in terms of mean arterial pressure.

On the model of L-NAME-induced ED after vascular samples, myocardial contractility was studied in anesthetized males in controlled breathing. The left ventricular cavity was accessed with a needle through the apex of the heart, the left ventricular pressure was recorded by means of a TSD104A sensor of ADC L-154 and a Biopac MP150 system; stress tests were performed on adrenaline reactivity (by injecting adrenaline intravenously $1 \cdot 10^{-5}$ mol/L in volume of 0.1 ml/100 g animal body weight) and on load resistance (by compression of the ascending part of the aortic arch for 30 s) (Pokrovsky et al. 2008).

Biochemical assessment of endothelial function

The total nitrates and nitrites were measured in one step by using a modified method (Metelskaya et al. 2004); the concentration of homocysteine (HC) was determined by an enzymatic method using a Pliva-Lachema Diagnostika s.r.o set. The content of lipid peroxidation products (LPP) in the blood plasma was also determined: diene conjugates (DC, relative units/ml), malonic dialdehyde (MDA, µmol/l), oxidized low-density lipoproteins (OxLDLs, µmol/L); the superoxide dismutase level (SOD, relative units/ml) and the total antioxidant activity of blood serum (TAA, %) were also studied.

The heart was fixed in a 10% solution of neutral formalin. The sections were stained with hematoxylin and eosin. Heart morphometry was performed using an ocular micrometer.

The data obtained were statistically processed using Statistica 10.0 software. Descriptive statistics applied to all data. The normality of distribution was assessed by means of Shapiro-Wilk and Kolmagorov-Smirnov tests. Statistical significance depending on the particular data was assessed by using the criteria of Student and Mann-Whitney tests with the Bonferroni amendment. Differences at p<0.05 were recognized as statistically significant.

Results

Model of L-NAME-induced endothelial dysfunction

Simulation of L-NAME-induced ED in male rats led to changes in their hemodynamic parameters, vascular functional tests for endothelium-dependent and endothelium-independent vasodilation, and was significantly different from the group of the intact animals.

When L-NAME was injected to male rats, an increase in blood pressure to 188.3±6.7/140.0±3.9 mmHg was recorded. The studied drugs prevented the development of severe hypertension. The values of SBP and DBP were significantly lower than the corresponding values of animals with L-NAME-modeled pathology, but the differences in these indicators among themselves in the monotherapy groups and in the combination are insignificant (Fig. 1).

CED in the group of intact males was 1.2±0.1, while with ED, the index increased 5 times and amounted to 5.2±0.5. Ademethionine (150 mg/kg) reduced CED to 2.4±0.4. Against the background of Taurine (260 mg/kg), CED was 1.3±0.1, which was close to the level of that in intact animals; with the combined use of ademethionine (150 mg/kg) and taurine (260 mg/kg), CED was 1.6±0.2 (Fig. 2).

Conducting functional stress tests on the model of L-NAME-induced NO deficiency registered an increase in the absolute values of left ventricular pressure in the adrenoreactivity test to 245.3±5.7 mm Hg, which is 19% higher than the values of intact animals. The use of a com-
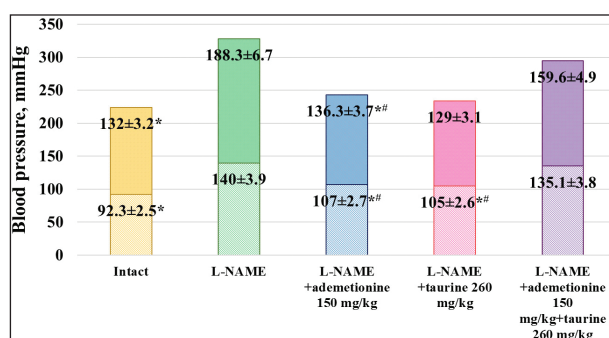

Figure 1. Model of L-NAME-induced NO deficiency. Effect of ademethionine, taurine on the blood pressure of male rats (M±m). *Note*: * – p<0.05 compared with the L-NAME group of animals; # – p<0.05 compared with L-NAME + ademethionine 150 mg/kg + taurine 260 mg/kg

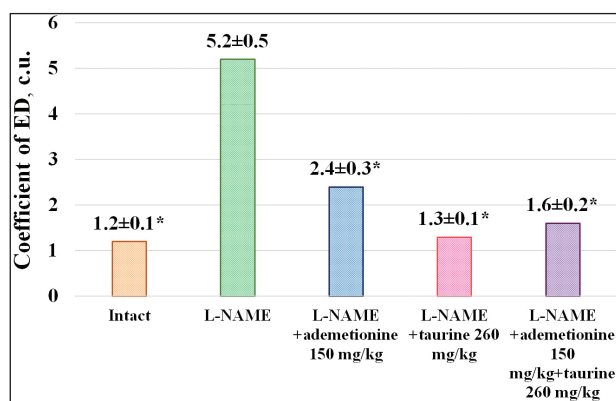**Figure 2.** Effect of ademethionine, taurine on CED of male rats in the simulation of L-NAME-induced NO deficiency (M±m). *Note*: * – p<0.05 compared to the L-NAME group of animals; CED – coefficient of endothelial dysfunction
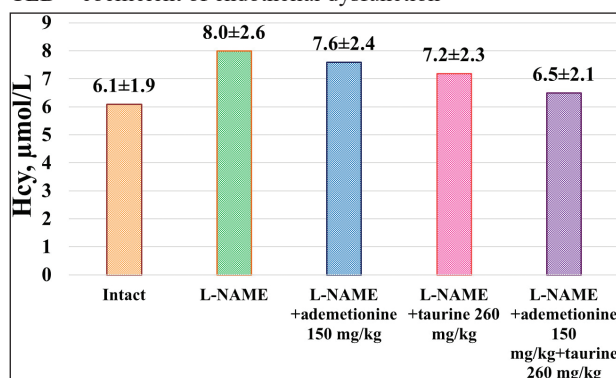

Figure 3. Effect of ademethionine and taurine on the level of homocysteine in the blood of male rats when simulating L-NAME-induced NO deficiency (M±m). *Note*: Hcy – homocysteine

bination of ademethionine (150 mg/kg) and taurine (260 mg/kg) contributed to the prevention of an increase in adrenoreactivity caused by L-NAME-induced pathology (Table 1).

A decrease in myocardial reserve was recorded in the test for load resistance. In intact males, the left ventricular pressure decreased to 79.4±2.1% by the 25th second of the aortic compression, and in animals with L-NAME-induced ED – to 64.5±3.2% (Table 1).

The concentration of nitrite ions (NOx) in male rats that received L-NAME was 60.4±2.5; in intact animals, it was 116.2±3.9 mkmol. The combination of ademethionine (150 mg/kg) and taurine (260 mg/kg) increased the concentration of nitrite ions in the plasma of laboratory animals under L-NAME-induced NO deficiency to 92.1±3.8 mkmol (Table 2).

The use of ademethionine and taurine on models of L-NAME-induced endothelial dysfunction also lead to the correction of indicators of lipid peroxidation and antioxidant defense system (Table 2).

The level of homocysteine decreased with the correction by means of these substances, but the differences in the studied groups were not significant (Fig. 3).

The functional and biochemical parameters, reflecting the development of L-NAME-ED, were confirmed by the results of morphological studies. The morphometric studies showed that in intact animals the cross section of cardiomyocytes was 8.3±1.1, and in male rats treated with L-NAME – 19.2±1.1 mkm (Fig. 4).

Thus, the injection of L-NAME at a dose of 25 mg/kg intraperitoneally in male rats daily during 7 days lead to the development of ED, characterized by a sharp increase

Table 1. Effect of use of ademetionine and taurine on functional parameters in male rats when modeling L-NAME-induced NO deficiency (M±m)

Indicator	Intact	L-NAME	L-NAME+ ademethionine 150 mg/kg	L-NAME+ taurine 260 mg/kg	L-NAME+ ademethionine 150 mg/kg +taurine 260 mg/kg
ADR, mmHg	197.1±3.1*	245.3±5.7	233.1±2.1*#	212.1±2.2*#	147.6±1.8*#
LR, %	79.4±2.1	64.5±3.2	47.3±1.1*	52.4±1.3	65.7±3.5*

Note: ADR – adrenoreactivity, LR – load resistance. * – p<0.05 compared with the L-NAME group of animals; # – p<0.05 compared with L-NAME + ademethionine 150 mg/kg + taurine 260 mg/kg

Table 2. Simulation of L-NAME-induced ED. Effect of Ademethionine, Taurine, and Their Combination on Lipid Peroxidation, Antioxidant System in Male Rats (M±m)

Indicator	Intact	L-NAME	L-NAME+ ademethionine 150 mg/kg	L-NAME+ taurine 260 mg/kg	L-NAME+ ademethionine 150 mg/kg + taurine 260 mg/kg
NOx, mkmol/L	116.2±3.9*	60.4±2.5	85.6±3.3*	79.2±3.1*	92.1±3.8*
DC (relative units/ml)	0.12±0.02*	0.39±0.03	0.28±0.03*	0.21 ±0.02*	0.19±0.01*
MDA (mkmol/l)	0.33±0.03*	1.59±0.01	1.29±0.15*	1.10 ±0.01*	0.89±0.02*
OxLDL (mkmol/l)	0.04±0.01*	0.18±0.01	0.14±0.02*	0.12 ±0.02*	0.10±0.01*
SOD (relative units/ml)	15.45±0.40*	12.89±0.28	14.50±0.23*	14.60 ±0.30*	15.20±0.18*
TAA (%)	40.90±0.89*	36.43±0.95	36.78±1.40#	38.42 ±0.47#	39.32±0.41*

Note: NOx – nitrogen oxide, DC – diene conjugates, MDA – malonic dialdehyde, OxLDL – low density oxidized lipoproteins, SOD – superoxide dismutase, TAA – total antioxidant activity of blood serum. * – p<0.05 compared with L-NAME; # – p<0.05 compared with the combination of ademethionine 150 mg/kg and taurine 260 mg/kg.

in CED, BP, adrenoreactivity and along with the development of latent heart failure, characteristic biochemical changes and histological pattern of myocardial hypertrophy and hyperplasia of the vascular wall.

The use of taurine at a dose of 60 mg/kg showed a more pronounced endothelioprotective effect in comparison with the use of ademethionine (150 mg/kg) and a combination of these drugs for the correction of ED, which was expressed in the prevalence of endothelium-dependent vascular relaxation and reduction in CED to the level of intact animals, but the differences in the studied groups were insignificant. Simultaneously, the results of stress tests revealed a cardioprotective effect, which showed in preventing an increase in adrenoreactivity, as well as in preventing a decrease in the content of nitrite ions (NOx) in the group treated with the combination of ademethionine 150 mg/kg and taurine 260 mg/kg. The morphological studies of cardiomyocytes found the prevention of an increase in the cross-section of cardiomyocytes in animals with L-NAME-induced pathology, under the influence of a combination of these drugs.

ADMA-like preeclampsia model

In the simulation of ADMA-like preeclampsia, the use of ademethionine 150 mg/kg and taurine 260 mg/kg in monotherapy, unlikethe combined use, was found to restore BP to the baseline values that did not significantly differ from those in intact animals (Fig. 5).

The combined use of ademethionine (150 mg/kg) and taurine (260 mg/kg) had a pronounced endothelioprotective effect, with CED decreasing to 1.4±0.2. These indicators were better than when using the monotherapy with ademethionine (1.8±0.2) or taurine (1.5±0.4) (Fig. 6).

The microcirculation rate in the placenta in the intact pregnant females on the 21st day was 450.7±25.8 PU (perfusion units). When simulating ADMA-like preeclampsia – 215.3±12.7 PU. In the monotherapy with taurine, a pronounced improvement in the microcirculation in the placenta was observed – 477.2±31.0 PU; when using ademethionine – 416.4±39.0 PU; when using the combinations of these drugs – 459.5±56.9 PU (Fig. 7).

The concentration of nitrite ions (NOx) in pregnant female rats with PE is 48.2±4.0 μM, and in intact animals – 118.3±4.0 μM. The combined use of ademethionine 150 mg/kg with taurine 260 mg/kg increases the content of nitrite ions to 80±4.2 (Table 3).

The use of ademethionine and taurine at the these doses also had a positive effect on the indices of lipid peroxidation and the antioxidant system (Table 3).

When simulating ADMA-like preeclampsia, a significant increase in the level of homocysteine in the blood of pregnant females was observed, compared to that in the intact ones – 6.5±1.4 and 5.0±1.2 μmol/l, respectively. When correcting PE with the combination of ademethionine 150 mg/kg and taurine 260 mg/kg, a significant
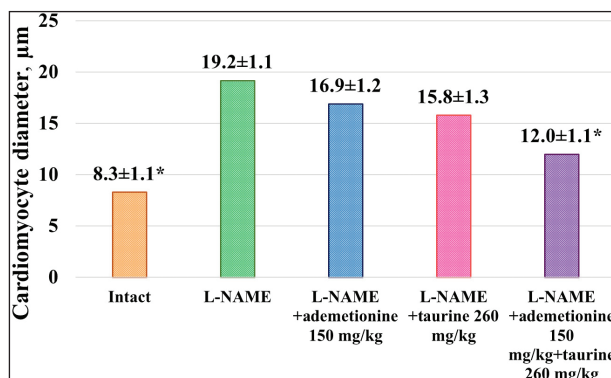

Figure 4. Effect of ademethionine, taurine on the diameter of the cardiomyocytes of male rats when simulating L-NAME-induced NO deficiency (M±m). Note: * – p<0.05 compared with the L-NAME group of animals; # – p<0.05 compared with L-NAME + ademethionine 150 mg/kg + taurine 260 mg/kg.
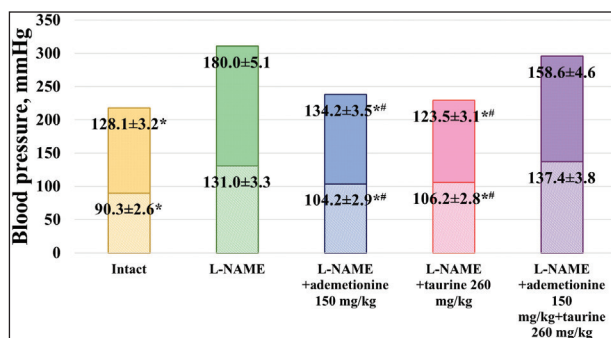

Figure 5. Effect of ademethionine, taurine on blood pressure of female rats against the background of ADMA-like preeclampsia simulation (M±m). Note:* – p<0.05 compared with pregnant rats against the background of ADMA-like preeclampsia; # – p<0.05 compared with L-NAME + ademethionine 150 mg/kg + taurine 260 mg/kg.
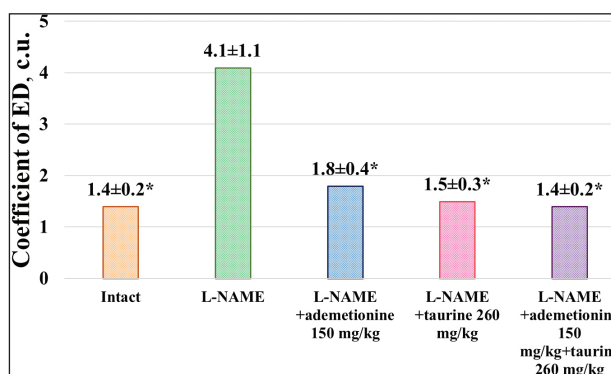

Figure 6. Effect of ademethionine and taurine on CED in female rats against the background of ADMA-like preeclampsia simulation (M±m). Note: CED –coefficient of endothelial dysfunction; * –p<0.05 compared with pregnant rats against the background of ADMA-like preeclampsia.

Table 3. Effect of Ademethionine, Taurine, and Their Combination on Lipid Peroxidation, Antioxidant System in Pregnant Rats when Simulating L-NAME-induced Preeclampsia (M±m).

Indicator	Intact	L-NAME-preeclampsia	L-NAME- preeclampsia + ademethionine 150 mg/kg	L-NAME-preeclampsia + taurine 260 mg/kg	L-NAME- preeclampsia + ademethionine 150 mg/kg + taurine 260 mg/kg
NOx, mkmol/l	118.3±4.0*	48.2±4.0	67.1±3.8*	72.5±3.7*	80±4.2*
DC (relative units/ml)	0.11±0.01*	0.38±0.02	0.25±0.02*	0.20 ±0.01*	0.18±0.01*
MDA (mkmol/l)	0.34±0.02*	1.63±0.02	1.30±0.16*	1.02 ±0,02*	0.90±0.02*
OxLDL (mkmol/l)	0.03±0.01*	0.16±0.02	0.15±0.02*	0.10 ±0.01*	0.08±0.01*
SOD (relative units/ml)	15.20±0.38*	13.00±0.29	14.35±0.19*	14.61 ±0.22*	15.18±0.19*
TAA (%)	41.62±0.80*	35.40±0.80	38.62±1.30	40.01 ±0.39	40.10±0.40*

Note: NOx – nitrogen oxide, DC – diene conjugates, MDA – malonic dialdehyde, OxLDL – low density oxidized lipoproteins, SOD – superoxide dismutase, TAA – total antioxidant activity of blood serum. * – p<0.05 compared with L-NAME-PE; # – p<0.05 compared with the combination of ademethionine 150 mg/kg and taurine 260 mg/kg.

decrease in the level of homocysteine was observed to 4.9±1.3 μmol/l (Fig. 8).

Thus, the most pronounced endothelioprotective effect on the model of ADMA-like preeclampsia was observed with the combined use of ademethionine and taurine, which was reflected in a decreased CED.

Therefore, the combination of ademethionine with taurine on the model of ADMA-like preeclampsia can be one of the rational approaches for correcting endothelial dysfunction during pregnancy in clinical practice, since the effect of this combination on the nitroergic and neurohumoral systems is pathogenetically justified, and these drugs are approved for use in pregnant women.

Discussion

The way of how damage to the system is caused by L-NAME, as well as points of application of ademethionine, which increases the amount of NO, and taurine, which simulates the synthesis of NO, due to capturing reactive oxygen species.

Fig. 9 presents a hypothesis about the mechanism of endothelium protective effects of ademethionine and taurine on the L-NAME-model-induced endothelial dysfunction, with L-NAME inhibiting eNOS.

From the literature it is known that ademethionine has an endothelioprotective effect by blocking the protein arginine methyltransferase (PAMT) enzyme – an enzyme that participates in the synthesis of asymmetric dimethylarginine (ADMA), and taurine, in turn, is a powerful antioxidant: it inhibits the production of superoxide radicals, decreases the production of the factor, and decreases the tumor necrosis factor, which is a marker of placenta inflammation, and restores the expression of endothelial NO synthase.

SAM or ademethionine is formed endogenously from methionine amino acid using the methionine adenosyl transferase enzyme. Further, S-adenosylhomocysteine is
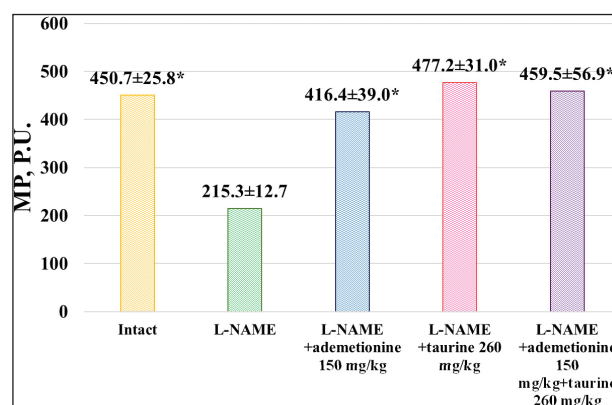

Figure 7. Effect of ademethionine and taurine on the microcirculation in the placenta in pregnant rats against the background of simulated ADMA-like preeclampsia (M±m). *Note*: MP – microcirculation in the placenta, PU – perfusion units. * – p<0.05 compared with pregnant rats against the background of ADMA-like preeclampsia; # – p<0.05 compared with L-NAME + ademethionine 150 mg/kg + taurine 260 mg/kg
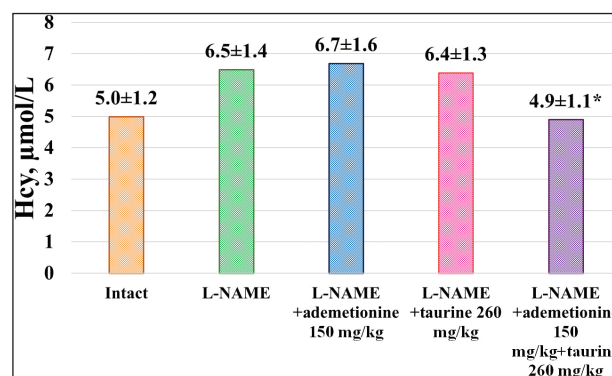

Figure 8. Effect of ademethionine, taurine on the level of homocysteine in the blood of pregnant rats against the background of simulated ADMA-like preeclampsia (M±m). *Note*: Hcy – homocysteine. * – p<0.05 compared with pregnant rats against the background of ADMA-like preeclampsia.
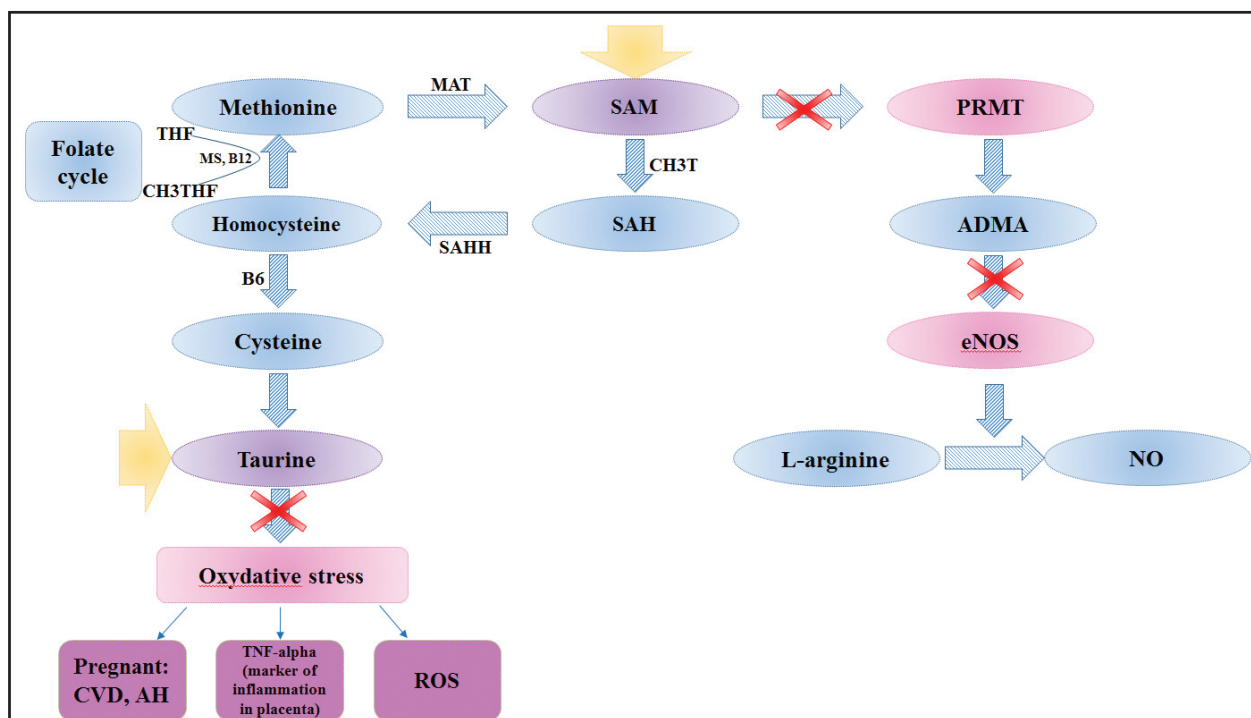
Figure 9. The hypothetical mechanism of the action of ademethionine and taurine on the model of L-NAME-induced endothelial dysfunction. Note: SAM – ademethionine (S-adenosylmethionine), SAH – S-adenosylhomocysteine, PAMT – proteinmethyltransferase, ADMA – asymmetric dimethylarginine, eNOS – endothelial NO-synthase, CVD –cardiovascular diseases, AH – arterial hypertension, TNF-alpha - tumor necrosis factor alpha, ROS-reactive oxygen species, CH3THF-methyltetrahydrofolate, THF tetrahydrofolate, MS methionine synthase, B12-cyanocobalamin, B6-pyridoxine, MAT-methionine-adosyltransferase, CH3T-methyltransferase, SAHH - S-adenosyl-homocysteine hydrolase.

formed from SAM under the action of SAM-dependent methyltransferase enzyme, and it is hydrolyzed to homocysteine by S-adenosylhomocysteine hydrolase. Homocysteine, completing the sycle, is converted to methionine in the transfer reaction of the methyl group from 5-methyltetrahydrofolate, one of the two classes of methionine synthases. With a hereditary defect of enzymes involved in the SAM cycle and with an excessive intake of ademethionine, remethylation processes can be disturbed, which leads to an accumulation of homocysteine in the blood, i.e. hyperhomocysteinemia, which results in oxidative stress and ED.

However, in this L-NAME model of induced endothelial dysfunction, the administration of ademethionine had endothelium protective effects and reduced oxidative stress. This may have happened because most of the administered ademethionine inhibited PRMT, which contributed to an increase in NO. And as known, one of the main vasoactive substances secreted by endotheliocytes is nitric oxide (NO) – an endothelial vasodilator.

Taurine is a sulfur-containing amino acid, which is synthesized in the body from cysteine, which is formed from homocysteine with the participation of pyridoxal phosphate. Thus, therapy with ademethionine can be used in case of pathologies with pronounced oxidative stress. It can also be combined with a drug with antioxidant properties – taurine.

Conclusion

Summing up, it should be noted that the proposed methodological complex of functional, biochemical and morphological changes linked with the development of NO deficiency due to the blockade of NO-synthase in male rats and pregnant female rats against the background of preeclampsia makes it possible to quite objectively detect and evaluate the endotheliotropic effect of pharmacological agents.

These facts were confirmed by the results of the present research. Thus, ademethionine at a dose of 150 mg/kg and taurine at a dose of 260 mg/kg showed an endothelium protective effect on L-NAME-induced NO deficiency both in monotherapy and in combination, which showed in the prevalence of endothelial-dependent vascular relaxation and a decreased CED at the same time, with taurine in the combined use showing additive endothelioprotective effects.

The maximum reduction in CED to the level of that in the intact animals, against the background of simulated L-NAME-induced NO deficiency in male rats, was recorded when using taurine 260 mg/kg and amounted to 1.3 ± 0.1.

According to the results of stress tests in the model of L-NAME-induced NO deficiency in male rats, the combination of ademethionine 150 mg/kg and taurine 260 mg/kg had a more pronounced cardioprotective activity, which showed in preventing the development of latent heart failure, which, in turn, showed in increased reserve of myocardial contractility and the ability to prevent an increase in adrenoreactivity against the background of a decreased reaction to reoxygenation.

In the same model, morphological studies of myocardiocytes found that the use of ademethionine 150 mg/kg and taurine 260 mg/kg prevented an increase in cross-section of cardiomyocytes in the animals with L-NAME-induced pathology.

It should be noted that the introduction of the studied drugs at the studied doses showed their endothelium and cardioprotective activity, but was not accompanied by reaching the target blood pressure indicators. This, on the one hand, indicates that CED has independent significance, and, on the other hand, that L-NAME-induced arterial hypertension on the 7th day involves into the pathogenic process not only the nitroergic system, but also all the elements of the humoral and neurogenic regulation contours of the circulatory system.

The study of the NO-producing function of the endothelium confirms the endothelioprotective effects of ademethionine, taurine, and their combination, which shows in preventing the reduction of stable metabolites of nitric oxide under conditions of endothelial dysfunction.

On the model of ADMA-like preeclampsia in pregnant rats, the maximum reduction in CED was observed when using ademethionine 150 mg/kg and taurine 260 mg/kg.

The level of homocysteine, which is a marker of preeclampsia, also decreased to the level of that in the intact animals with the combined use of ademethionine 150 mg/kg and taurine 260 mg/kg in the ADMA-like preeclampsia model.

Conflict of interests

The authors state no conflict of interest concerning with the present submitted manuscript.

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