Experimental Study of Taurine Antitoxic Activity in the Model of Chronic Epinephrine Intoxication

O.N. Oleynikova, L.M. Makarova, V.E. Pogoreliy, and N.A. Novikova

1 Introduction

Numerous clinical studies have revealed a negative influence of acute stress in human's and animal's organs (Wurtman 2002), while only fragmentary experimental data exist on the effects of chronic stress on the body. Chronic stress leads to attenuation of body resources and development of cardio-vascular, endocrine, nervous, pulmonary and gastro-intestinal diseases, amongst others. The problem of development of new chronic stress correctors exists; therefore investigation of taurine activity during this pathology is perspective line of research. Taurine demonstrates multiple cellular functions including a central role in neurotransmission, as a trophic factor in CNS development, in maintaining the structural integrity of the membrane, in regulating calcium transport and homeostasis, as an osmolyte, as a neuromodulator and as a neuroprotectant (Wu and Prentice 2010). Our previous experiments have demonstrated neuroprotective and antihypoxic activity of taurine administered in vivo at a dose of 50 mg/kg in different models of brain ischemia (Oleynikova et al. 2009; Makarova et al. 2014). Therefore, we decided to investigate taurine at the above-mentioned dose on the metabolism in rats in a model of chronic epinephrine intoxication. In this work we concentrated our attention on brain metabolism and brain lipid peroxidation as the main pathway of oxidative stress.

O.N. Oleynikova • L.M. Makarova • V.E. Pogoreliy • N.A. Novikova (✉)
Pharmacology with Course of Clinical Pharmacology Department, Pyatigorsk Medical-Pharmaceutical Institute, Branch of the Volgograd State Medical University, Volgograd, Russia
e-mail: novikova.83@bk.ru

J. Marcinkiewicz, S.W. Schaffer (eds.), *Taurine 9*, Advances in Experimental Medicine and Biology 803, DOI 10.1007/978-3-319-15126-7_44

2 Methods

2.1 Experimental Materials and Methods

Experiments were done on male outbred rats (250–300 g). To develop chronic epinephrine intoxication adrenalin hydrochloride was administered intraperitoneally at a dose of 500 mg/kg once daily for a 6 week duration. Two weeks from the experiment start taurine was administered intraperitoneally in a dose of 50 mg/kg in normal saline once daily to the experimental group (n = 8). The control group was treated with the same volume of the normal saline (n = 8). After 28 days of treatment, arterial blood was taken from the right common carotid artery and venous blood was taken from the sagittal sinus under chloral hydrate general anesthesia (300 mg/kg). The following biochemical parameters were assessed to evaluate metabolic changes: total lipids, total cholesterol, total albumin, calcium, medium-sized peptides. To evaluate cerebral lipid peroxidation animals were decapitated under chloral hydrate general anesthesia (300 mg/kg) and brains were extracted. Brains were rapidly bathed in the normal saline; hemispheres were split along the midline. Amounts of malondialdehyde and diene conjugates were measured in the left and right hemispheres.

Total lipid plus total cholesterol concentrations in the blood serum were measured by colorimetric method (reaction with acetic oxide and sulfuric acid for cholesterol; and reaction with vanillin and phosphoric acid for total lipids). Total albumin was measured by biuret method. Ca^{2+} concentration in the blood serum was measured by colorimetric method (reaction with cresol phthalein). Medium-sized peptides were measured by high molecular weight protein settling method (with perchloric acid and ethanol). Diene conjugates concentration was measured in the complex "heptane-isopropyl alcohol." To evaluate amounts of malondialdehyde, the reaction with thiobarbituric acid was used.

2.2 Statistic Analysis

Statistical significance was determined by Student's t-test. Each value was expressed as the mean ± SEM. Differences were considered statistically significant when the calculated P value was less than 0.05.

3 Results

Concentrations of total lipids in the control group of animals was elevated up to 31.5 % in the arterial blood and was decreased up to 49.2 % in the venous blood compared to intact animals (Fig. 1). Concentration of total cholesterol was

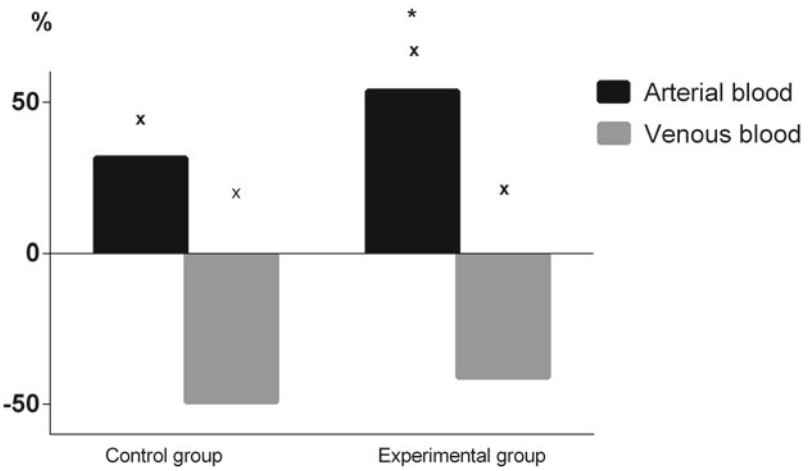

Fig. 1 Taurine administrartion influence on the concentration of total lipids in serum during chronic epinephrine intoxication (% compared with intact animals). $p<0.05$ compared to: * - Control group, x - Intact animals

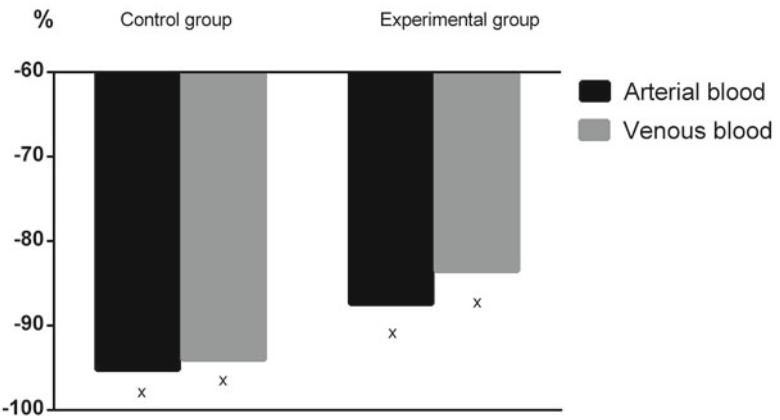

Fig. 2 Taurine administrartion influence on the cholesterol concentration in serum during chronic epinephrine intoxication (% compared with intact animals). $p<0.05$ compared to: * - Control group, x - Intact animals

significantly decreased both in the venous and arterial blood up to 90.2 % and 94 % respectively (Fig. 2).

Taurine treatment elevated concentration of total lipids up to 53.7 % in the arterial blood and decreased up to 41 % in the venous blood compared to intact animals. Concentration of total cholesterol did not differ significantly compared to control group.

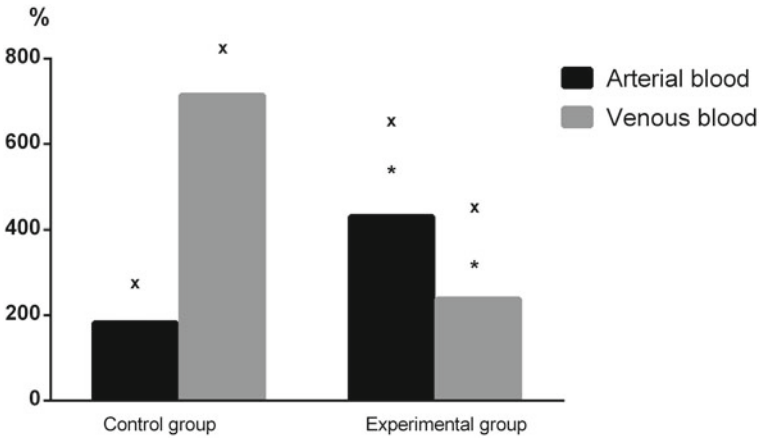

Fig. 3 Taurine administrartion influence on the Ca2+ concentration in serum during chronic epinephrine intoxication (% compared with intact animals). $p<0.05$ compared to: * - Control group, x - Intact animals

Ca^{2+} concentration in blood serum is a well-known biomarker of body metabolism and plays an important role in the cell injury. Significant hypercalcemia was found in the control group of animals. Ca^{2+} concentration in the venous blood was four times higher than in the arterial blood. Animals in the control group had several neurological signs due to this hypercalcemia: weakness and stupor. Taurine treatment blocked development of hypercalcemia: Ca^{2+} concentration was two times higher in the arterial blood and significantly lower (three times lower) in the venous blood (Fig. 3).

Total albumin in the arterial blood was elevated up to 21.8 % in the control group compared to intact animals. Concentration in the venous blood did not differ significantly from the intact group. Taurine administration did not considerably influence this parameter (Fig. 4).

Medium-sized peptides concentration (markers of endogenous epinephrine intoxication) was significantly increased in the venous blood—up to 185.3 % compared to intact group. It was found out that therapeutic administration of taurine reduced medium-sized peptides concentration in the venous blood. Taurine also reduced medium-sized peptides concentration in the arterial blood compared to intact group (Fig. 5).

Next, we investigated taurine's influence on the peroxide oxidation products concentration in the brains. In the control group peroxide oxidation primary products (diene conjugates) were significantly elevated—up to 195.8 % in the right hemisphere and up to 60 % in the left hemisphere. Whereas peroxide oxidation secondary products concentration was decreased up to 38.3 % and 16 % in

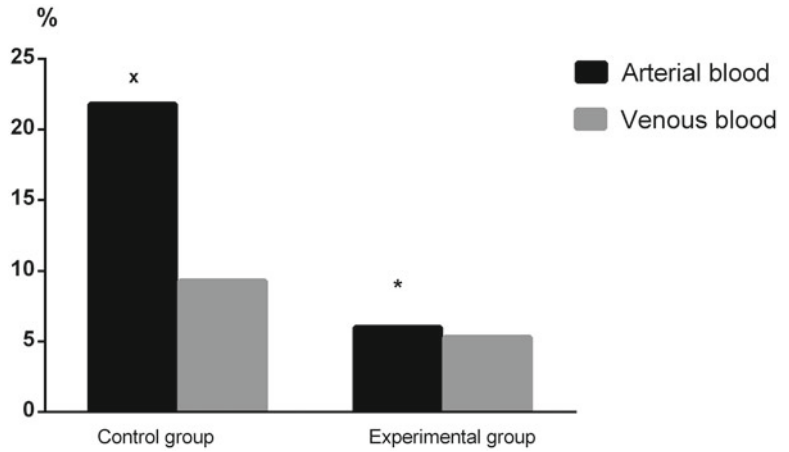

Fig. 4 Taurine administrartion influence on the concentration of total albumin in serum during chronic epinephrine intoxication (% compared with intact animals). $p<0.05$ compared to: * - Control group, x - Intact animals

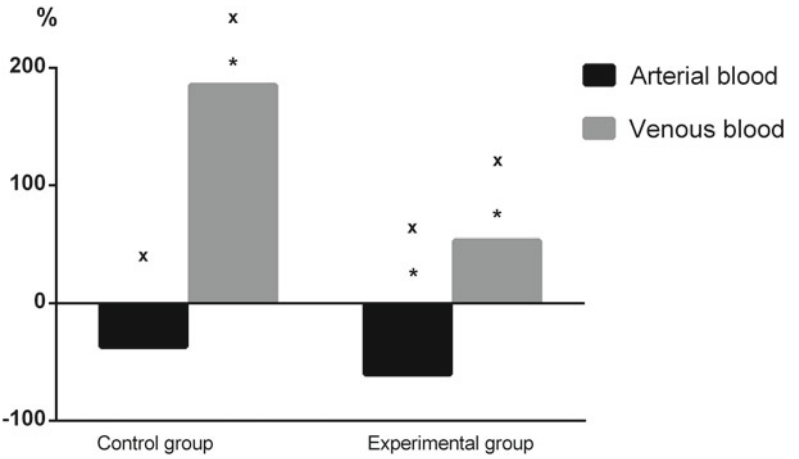

Fig. 5 Taurine administrartion influence on the medium-sized peptides concentration in serum during chronic epinephrine intoxication (% compared with intact animals). $p<0.05$ compared to: * - Control group, x - Intact animals

the right and left hemispheres respectively compared to intact group. Taurine reduced amount of diene conjugates (2–3 times) and significantly reduced amount of peroxide oxidation secondary products in the both hemispheres compared to control group (Figs. 6 and 7).

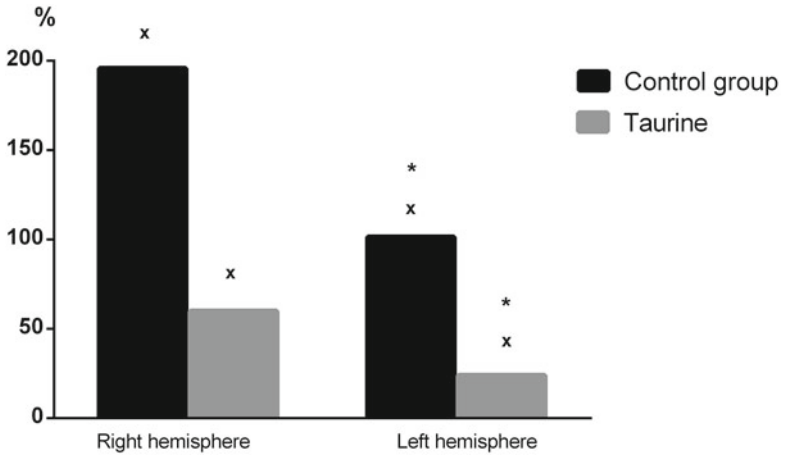

Fig. 6 Taurine administrartion influence on the diene conjugates concentration in the left and right hemispheres during chronic epinephrine intoxication (% compared with intact animals). $p < 0.05$ compared to: * - Control group, x - Intact animals

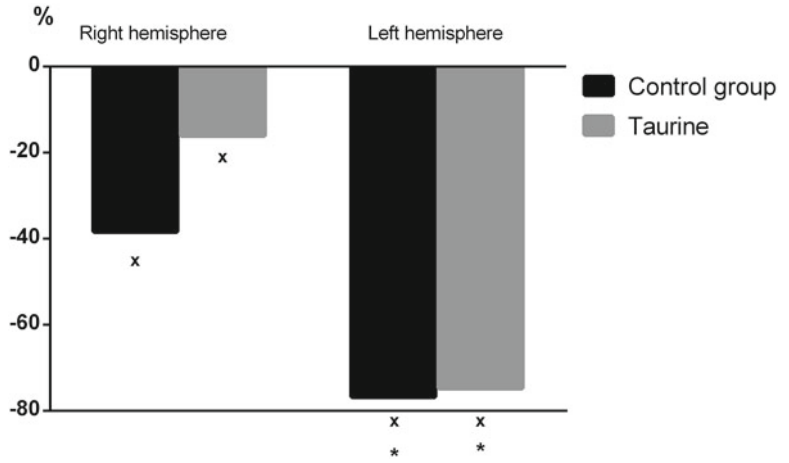

Fig. 7 Taurine administrartion influence on the peroxide oxidation secondary products concentration in the left and right hemispheres during chronic epinephrine intoxication (% compared with intact animals). $p < 0.05$ compared to: * - Control group, x - Intact animals

4 Discussion

According to literature data, emotional stress is the main reason of many human diseases such as cardio-vascular diseases, endocrine, nervous, pulmonary and gastro-intestinal disorders, immune system deteriorations etc. (Loucks et al. 2003; Norberg et al. 2007). During emotional stress epinephrine in the blood vessels

oxidizes to adrenochrome with formation of superoxide radical which is very active and can cause cell apoptosis (Troshin et al. 2006). Cardiotoxicity and neurotoxicity of products of adrenaline oxidation are widely described in the literature (Kolpakov 1974; Rump et al. 2001).

Taurine is one of the most abundant free amino acids in the mammalian body. A number of experimental studies have proved positive antioxidant effect of taurine in the animals (Makarova et al. 2014). Our studies revealed evident antioxidant and antitoxic effects of taurine during excessive adrenochrome formation. We determined that therapeutic administration of taurine dose of 50 mg/kg in the model of chronic epinephrine intoxication reduced medium-sized peptides concentration in the venous blood. Taurine reduced amount of diene conjugates and significantly reduced amount of peroxide oxidation secondary products in the both hemispheres compared to control group. Taurine also blocked development of hypercalcemia and reduced concentration of total lipids in the cerebral venous outflow blood. Taurine did not significantly influence other experimental metabolic parameters.

The antioxidant activity of taurine could be explained by several sites of activity. It is known that taurine reduced oxidative stress in the neutrophiles culture due to neutralization of hypochlorus acid and formation of N-chlortaurine (Nefedov 1999). Moreover, taurine effectively attenuated the hyperhomocysteinemia-induced ROS production and inhibition of Mn-superoxide dismutase and catalase activities in the myocardial mitochondria (Chang et al. 2004). It was shown also that taurine can protect against H_2O_2-induced cell injury in PC12 cell cultures by reducing H_2O_2 -induced endoplasmatic reticulum stress (Pan et al. 2010). In addition, taurine plays an important role in reducing endoplasmatic reticulum stress in C2C12 and 3T3L1 cells (Song et al. 2009).

5 Conclusion

Therapeutic administration of taurine in the dose of 50 mg/kg reduced cerebral metabolic disorders and prevented cerebral lipid peroxidation during chronic epinephrine intoxication.

References

Chang L, Xu J, Yu F, Zhao J, Tang X, Tang C (2004) Taurine protected myocardial mitochondria injury induced by hyperhomocysteinemia in rats. Amino Acids 27:37–48

Kolpakov VG (1974) Monoamine oxidase insufficiency – possible underlying condition of schizophrenia. J Neuropathol Psychiatr 74(8):1254–1263, Russian title

Loucks EB, Soobader M, Fay M, Kawachi I, Berkman LF (2003) Association of social integration with cardiovascular disease risk factors in the elderly. Can J Cardiol 19b(Suppl A):179A

Makarova LM, Pogoreliy VE, Voronkov AV, Mirzoyan RS, Novikova NA (2014) Modern notions about the role of taurine in the central nervous system. Exp Clin Pharmacol 77:38–44

Nefedov LI (1999) Taurine – Grodno: Grodno printing office. 159 p. (Russian title)
Norberg M, Stenlund H, Lindahl B, Andersson C, Eriksson JW, Weinehall L (2007) Work stress and low emotional support is associated with increased risk of future type 2 diabetes in women. Diabetes Res Clin Pract 76:368–377
Oleynikova ON, Makarova LM, Pogoreliy VY, Skachilova SY, Sernov LN, Kesarev OG (2009) Comparative assessment of the influence of taurine, its magnesium salt derivative and magnesium sulfate on the resistance to hypoxia of different etiology. Toxicol Rev 4:19–22
Pan C, Giraldo G, Prentice H, Wu J-Y (2010) Taurine protection of PC12 cells against endoplasmic reticulum stress induced by oxidative stress. J Biomed Sci 17:S17
Rump AF, Schierholz J, Rösen R, Güttler K, Klaus W (2001) Studies on the role of superoxide anion radicals for the cardiotoxicity of adrenochrome. Arzneimittelforschung 51:964–970
Song H, Kim H, Park T, Lee DH (2009) Characterization of myogenic differentiation under endoplasmic reticulum stress and taurine treatment. Adv Exp Med Biol 643:253–261
Troshin VD, Gustov AV, Smirnov AA (2006) Vascular disorders of the neural system. Nizhny Novgorod: Nizhny Novgorod Medical Academy printing office. 538 p. (Russian title)
Wu JY, Prentice H (2010) Role of taurine in the central nervous system. J Biomed Sci 17:S1
Wurtman RJ (2002) Stress and the adrenocortical control of epinephrine synthesis. Metabolism 51:11–14