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Pharmacological Correction of Microcirculation in Rats Suffering from Traumatic Brain Injury

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Abstract—We investigated the effect of mexicor on functional indices of erythrocytes and the structure of myocardial microcirculation in rats suffering from traumatic brain injury (TBI). At 3, 7, and 12 days after TBI, we measured the concentration of 2,3-diphosphoglycerate (2,3-DPG) and the degree of erythrocyte aggregation and their electrophoretic mobility (EPME) in the blood of rats, as well as analyzing sections of the left ventricular myocardium. The first day after the TBI, we observed a decrease in EPME, an increase of erythrocyte aggregation, and an increase of 2,3-DFG concentration in erythrocytes as compared with intact animals. Intraperitoneal injection of mexicor led to an increase of EPME and 2,3-DPG level and reduced the aggregation of erythrocytes, which was most pronounced during the 3–7 days of the post-traumatic period. Improved functional parameters of erythrocytes were accompanied by the dynamics of regenerative processes in the heart. Intraperitoneal injection of mexicor restrained architectonic damage of microvasculature and cardiomyocytes ultrastructure of the left ventricular myocardium of the heart.

Keywords: mexicor, traumatic brain injury, electrophoretic mobility of erythrocytes, morphology of the heart
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INTRODUCTION

Modern approaches to the treatment of changes occurring in the body during a traumatic brain injury (TBI) are based on the idea that the pathological effects on the brain does not end at the time of injury; but only starts at this time (Tsarenko, 2005). This is because TBI is accompanied not only by structural and functional changes in the central nervous system, but also by a complex of pathophysiological changes appearing in almost all organs and systems, which further bring about recovery or secondary brain injury (Rusakov and Dolgikh, 2007).

Disorders in the microrheology of blood, which determine blood fluidity on the capillary level and depend on the shape, size, and state of erythrocyte membranes, have a significant effect on the perfusion and oxygenation of the brain in the early posttraumatic period (PTP) (Radaev et al., 2004). Oxygenation of tissues and oxygen transport are results of the cardiovascular system as well as the blood system. The pumping function of the heart and the severity of endothelial dysfunction are impaired by TBI autoregulation of cerebral blood flow (Prough, 1998) and result in the development of cerebral perfusion deficiency and, consequently, the formation of hypoxic and free radical injuries of the nervous tissue (Boyarinov et al., 2014; Boyarinova et al., 2014).

Particular attention in the treatment of traumatic brain injury is focused on the use of new drugs, the effect of which is aimed at preventing brain ischemia and hypoxia, as well as improvement of blood supply to the brain (Chikina and Levin, 2005). Currently, derivative of 3-hydroxypyridine mexicor (2-ethyl-6-methyl-3-hydroxypyridine succinate) is widely used as a pharmaceutical substance that combines antihypoxic and antioxidant properties (Boyarinov et al., 2010; Deryugina et al., 2015). The relevance and feasibility of the search for drugs with a corrective effect on the microcirculation of the heart muscle are obvious, since, during TBI, disorders of the cardiovascular system are especially important extracranial disorders.

Therefore, the goal of this study was the investigation of the effect of mexicor on the functional indices of erythrocytes and the structure of myocardial microcirculation in rats suffering from TBI.

Abbreviations: 2,3-DPG—2,3-diphosphoglycerate, PTP—posttraumatic period of TBI, TBI—traumatic brain injury, EPME—electrophoretic mobility of erythrocytes.

MATERIALS AND METHODS

Animals. The study was performed on 36 white outbreed female rats weighing 180–200 g, with 18 rats in each series. The work was performed in accordance with the rules presented in the *Guide to the Care and Use of Laboratory Animals* and requirements of Order of the Ministry of Health of the Russian Federation no. 267 of June 19, 2003, "On the Approval of the Rules of Laboratory Practice in the Russian Federation." The animals were fixed on a plate, and blood was collected from a sublingual vein in an amount of 2.0 mL, which was 8–9% of the circulating blood volume. TBI was modeled by a free-falling weight drop of 100 g from a height of 80 cm on the parietal-occipital region of the head (Cymbalyuk and Kochin, 2008). In the experimental series, the rats after TBI were intraperitoneally injected with mexicor for 12 days (two times per day) in a daily dose of 8.0 mg/kg of animal weight (a solution for intravenous and intramuscular administration, JSC EkoFarmInvest, Russia); in the control series, the rats were injected with the same volume of saline solution. The administration of the drug was started 1 h after the TBI. Blood sampling in a series was carried out from sublingual vein in an amount of 2.0 mL at 1, 3, 7, and 12 days after the alteration. Such blood sampling technology simulates the fractional blood loss, which, during the 12 days of the post-traumatic period, was 32–36% of the volume of circulating blood in the rats. The values of the physiological norm of the studied parameters were determined in intact animals (30 rats).

EPME was determined by microelectrophoresis (Krylov and Deryugina 2011) registering the passage of 100-μm distances by washed erythrocytes in Tris-HCl buffer (pH = 7.4) at a current of 12 mA. The EPME value was calculated according to the formula $U = S/TH$, where S is the distance by which cells moved, T is the time by which cells moved distance S, and H is the potential gradient. The value of the potential gradient was determined according to the formula $H = I/g\chi$, where I is the current, g is the cross section of the chamber, and χ is the electric conductivity of the medium.

The content of 2,3-diphosphoglycerate (2,3-DPG) in erythrocytes was measured by the nonenzymatic method (Vinogradova et al., 1980). Nucleotides (ATP, ADP, AMP) were removed from TCA filtrate of hemolyzed erythrocytes by adsorption on activated charcoal followed by centrifugation (tube 1). Some of the TCA filtrate (0.5 mL) was subjected to cineration by adding 0.5 mL of a 5% magnesium nitrate solution and boiled; after cooling, the tube contents were dissolved in 0.5 mL of 0.36 N H_2SO_4 (tube 2). C_P was determined in each tube by adding 0.5 mL 0.36 N H_2SO_4, 0.25 mL 4.6% ascorbic acid, 0.25 mL 0.9% ammonium molybdate, and 0.5 mL stabilizing solution (9% Na citrate, 9% Na arsenate, and 9% acetic acid in equal amounts). After 15 min, the coloration density was registered using a KFK-3 photoelectric photometer for 12 days daily (two times per day) (Russia) at a wavelength of 660 nm. C_P concentration was determined from a calibration curve using a standard solution of KH_2PO_4. Calculation of the concentration of 2,3-DPG was performed according to the formula (C_P (tube 1) × 100 − C_P (tube 2) × 10)/2.

The degree of erythrocyte aggregation was obtained by counting individual erythrocytes and their aggregates in a Goryaev's chamber (Deryugina et al., 2006). A blue dextran T-2000 solution (20 mg/mL) in Tris-HCl buffer (pH = 7.4) was used as the aggregation stimulator. Washed erythrocytes were diluted with dextran solution (a ratio of 1 : 10), and the number of nonaggregated erythrocytes was counted in the Goryaev's chamber. The total number of erythrocytes in a sample was counted in an isotonic NaCl solution using the same ratio. Level of aggregation A was calculated using the formula

A = 100% − (number of free (not aggregated) erythrocytes × total number of erythrocytes^{-1} × 100%).

At 3, 7, and 12 days after the TBI, against a background of intraperitoneal injection of sodium thiopental (100 mg/kg animal), decapitation of rats, median thoracotomy, and removal of the heart were performed (six animals at each indicated time point). For studies of the light-optical level, the material was placed in 10% buffered neutral formalin solution immediately after the section. Fixation of material was performed for 72–96 h; then, after dehydration, sections of left ventricular myocardial tissue were embedded in paraffin. Staining of sections prepared using an MC-2 sliding microtome (Ukraine) was done using hematoxylin-eosin. The thickness of sections was 7 μm. The investigation and photography of the preparation was carried out by using a Vizo 101 microvisor (LOMO, Russia). For electron microscopy, left ventricular myocardial tissues were placed in a 2.5% glutaraldehyde solution, followed by additional fixation with a 1% osmic acid solution, dehydrating in alcohols of increasing strength, and embedded in a mixture of epoxy resins (Araldite and Epon 812). The structural changes of hemocapillars were studied on ultrathin sections obtained by an ultramicrotome (Leica Microsystems, Austria) using a Morgagni 268D electron microscope (FEI, United States) equipped with a Mega View III video camera (EMSIS, Germany). For analysis of microcirculation, all capillaries were counted and their number was taken as 100%. The proportion of capillaries containing free erythrocytes, erythrocyte aggregates, leukocytes, thrombocytes, and fine and aggregated plasma proteins and the absence of osmiophilic amorphous material were determined based on this number.

The obtained data were proceeded using the BIOSTAT (Analystsoft, United States) and Excel (Microsoft, United States) applications. Results are presented as $M \pm m$, where M is the arithmetic mean and m is the

The effect of mexicor on the concentration of 2,3-DPG in the erythrocytes, their electrophoretic mobility, and aggregation during PTP of TBI

TBI, os	2,3-DPG, μmol /mL		EPME, μm cm V^{-1} s^{-1}		The fraction of aggregated erythrocytes, %	
	C	Mexicor	C	Mexicor	C	Mexicor
Without TBI	3.30 ± 0.09		0.91 ± 0.01		37.10 ± 1.70	
1	6.22 ± 0.62[a]	5.16 ± 0.67[a]	0.70 ± 0.02[a]	0.77 ± 0.02[a, b]	94.92 ± 0.55[a]	88.43 ± 3.79[a, b]
3	6.12 ± 0.65[a]	6.68 ± 0.43[a]	0.68 ± 0.01[a]	0.82 ± 0.03[a, b]	84.83 ± 1.76[a]	53.88 ± 5.81[a, b]
7	4.60 ± 0.41[a]	5.68 ± 0.51[a, b]	0.74 ± 0.03[a]	0.83 ± 0.03[a, b]	82.79 ± 1.62[a]	67.08 ± 2.51[a, b]
12	4.15 ± 0.52[a]	4.46 ± 0.68[a]	0.76 ± 0.02[a]	0.84 ± 0.02[a, b]	78.09 ± 0.77[a]	68.21 ± 1.18[a, b]

C—control group of animals, intraperitoneally administered with saline solution after TBI; [a, b]—adequacy of difference from the index in intact animals and animals of the control group ($P < 0.05$).

standard error of the mean. The significance of differences was determined according to Student's *t*-test. Differences were considered significant at a significance level of $P < 0.05$.

RESULTS AND DISCUSSION

The functional performance of erythrocytes was assessed by EPME, characterizing the net surface charge. The net surface charge depends on the structural state of the cell membranes and determines the aggregation properties of erythrocytes and the content of 2,3-DPG, a metabolite, affecting the donation of oxygen by tissues and contributing to maintenance of oxygen tension (pO_2) in blood plasma and cells of organs at an adequate level. A decrease in EPME and increased aggregation of erythrocytes were observed 24 h after TBI. These changes were accompanied by an increase in the concentration of 2,3-DPG in the erythrocytes as compared with the intact animals. Three days after TBI, with administration of mexicor, EPME increased by 20%, the degree of erythrocyte aggregation decreased by 36% and increased the concentration of 2,3-DPG by 29% relative to the values that were observed on the first day, while EPME and the concentration of 2,3-DPG did not change in the control group, while erythrocyte aggregation decreased only by 11% (table). The same dynamics of the studied parameters remained after 7 days in the experimental group in comparison with the controls, where the levels of erythrocyte aggregation and EPME remain unchanged relative to the third day of the experiment, while the concentration of 2,3-DPG in the erythrocytes decreased. By the 12th day of the PTP, alignment of the studied parameters in groups was observed.

Thus, the rats of the control series in the PTP caused by TBI had already in the first 24 h developed changes in the functional state of erythrocyte membranes, causing microcirculatory disorders, which were found also over the next 12 days of observation. Intraperitoneal administration of mexicor initially reduced the manifestations of microcirculatory disorders and then caused an increase in EPME, reduction of the aggregation of erythrocytes, and increase of 2,3-DPG concentration in erythrocytes, which improved tissue perfusion and activated the compensation of oxygen debt, which was especially intensely realized from the third to seventh days of the PTP.

Electron microscopic study of the microcirculatory bloodstream of the left ventricular myocardium showed that, on the third day of the PTP, in the rats of the experimental series, erythrocytes and fine amorphous osmiophil material (plasma proteins) were found in 38% of capillaries (Fig. 1a). A decrease of amorphous osmiophil material was noted in 41% of microcirculatory vessels. Microaggregates of erythrocytes (Fig. 1b), reticulocytes (Fig. 1c), and thrombocytes (Fig. 1d), as well as individual neutrophils, were identified in some vessels.

In the animals of the control series, recovery of microcirculation was observed in 40% of the capillaries of the left ventricle; in 28% of the capillaries, decrease of osmiophil material was detected; and the lumen of the capillaries did not contain osmiophil material in 20%. The last fact indicates a lack of circulation in microvessels (no-reflow phenomenon). Membrane structure and bubbles (Figs. 2a, 2d); thrombus of erythrocytes and thrombocytes (Fig. 2b); and microaggregates of erythrocytes, reticulocytes, and neutrophils (Fig. 2c), which significantly complicate microcirculation, were found in the lumen of a number of capillaries. The endothelium in a number of capillaries was swollen, sometimes being edematous (Fig. 2a). In some cases, the passage of erythrocytes outside the vascular bed, probably of diapedetic nature, was observed (Fig. 2d).

On the seventh day of the PTP in the group of animals that had been administered with mexicor, the positive dynamics of the recovery of the microcirculatory bloodstream of the left ventricular myocardium was noted: a large part of the microvessels (65%) con-

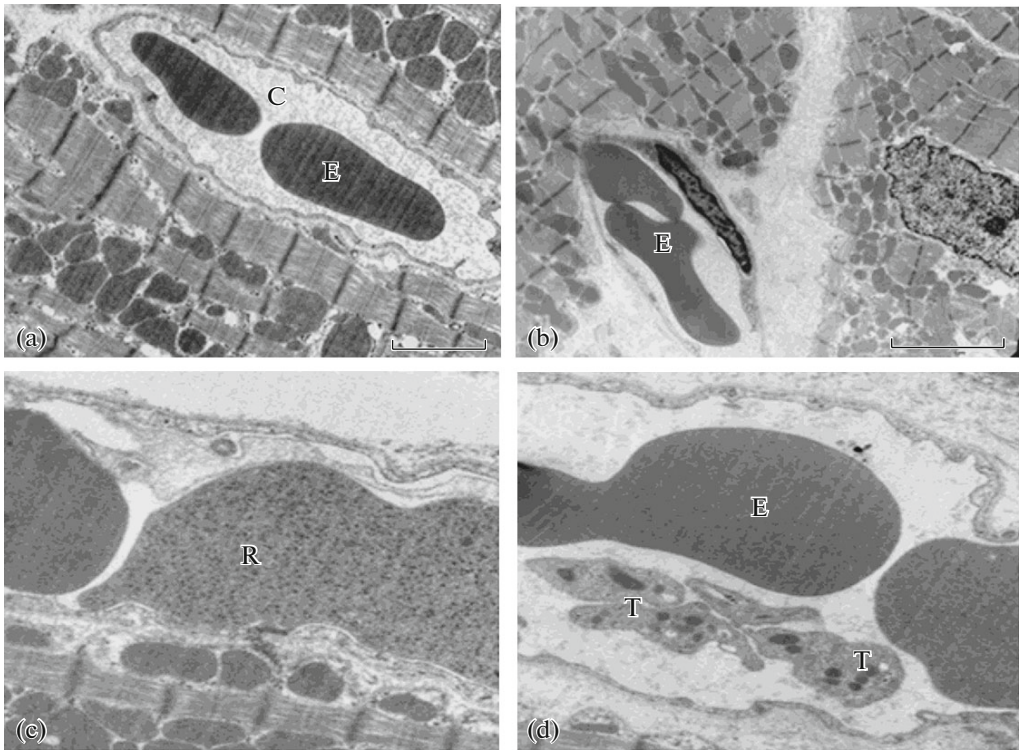

Fig. 1. The blood capillaries of the left ventricular myocardium of rats administered with mexicor in the third day of the post-traumatic period after traumatic brain injury (hereinafter in Figs. 2–5, TBI) at different magnifications. C—capillary lumen, E—erythrocyte, R—reticulocyte, and T—thrombocyte. Magnification: 8900× (a), 4400× (b), 15000× (c), 12600× (d).

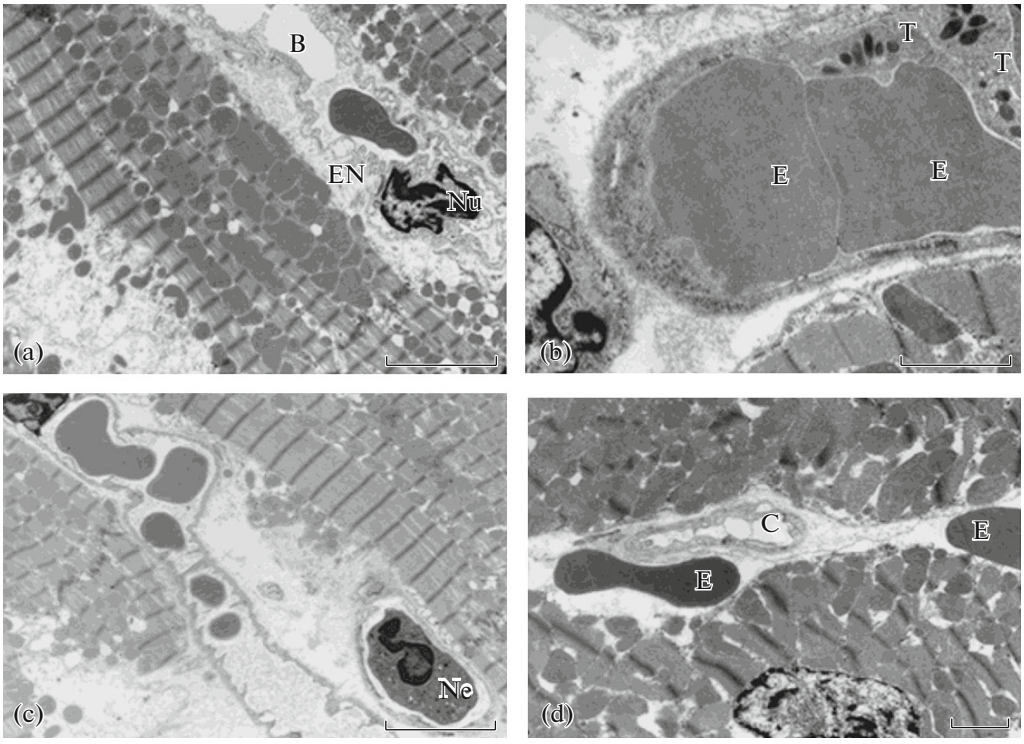

Fig. 2. The blood capillaries of the left ventricular myocardium of rats of the control group on the third day of the post-traumatic period of TBI at different magnifications. B—bubble, EN—endothelium, Nu—endothelial nucleus, E—erythrocyte, T—thrombocyte, Ne—neutrophil, and C—capillary lumen. Magnification: (a) 4400×, (b) 22000×, (c) 4400×, and (d) 5600×.

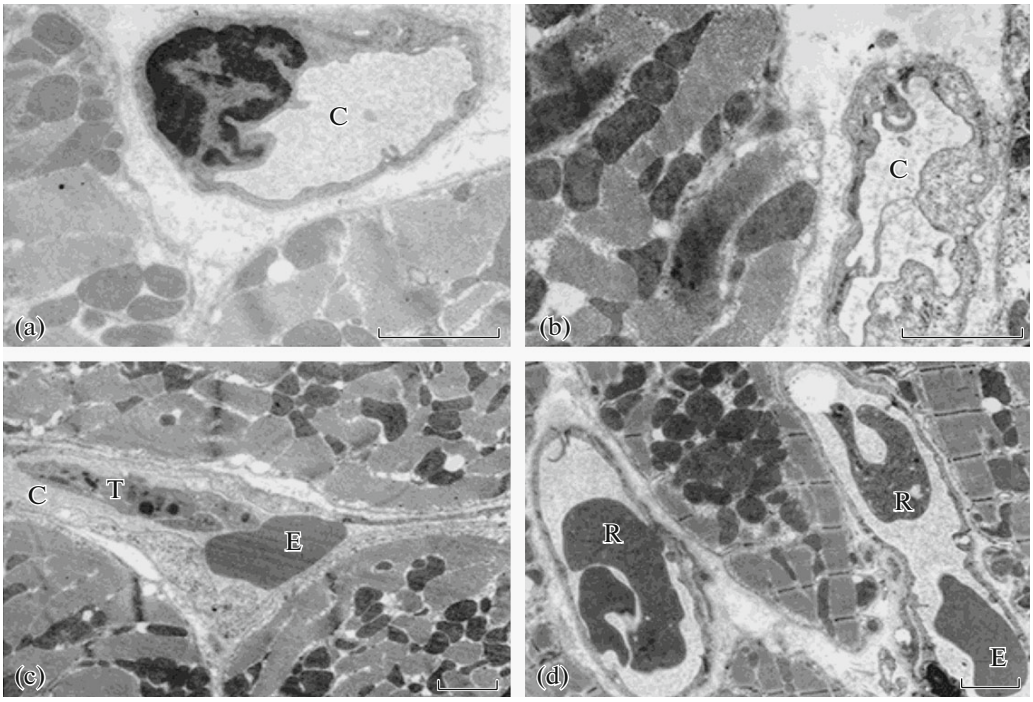

Fig. 3. The blood capillaries of the left ventricular myocardium of rats administered with mexicor on the seventh day of the post-traumatic period of TBI at different magnifications. C—capillary lumen, E—erythrocyte, T—thrombocyte, and R—reticulocyte. Magnification: (a, b) 11000×, (c, d) 7100×.

tained erythrocytes and amorphous fine osmiophil material (Fig. 3a). The number of capillaries containing a small amount of the particulate osmiophil amorphous material halved relative to the third day (Fig. 3b). In 6% of the capillaries (versus 13% on the third day), aggregates of thrombocytes and erythrocytes (Fig. 3c), microaggregates of erythrocytes and reticulocytes, and individual thrombocytes and reticulocytes were found (Fig. 3d).

In the animals of the control series, 7 days after the TBI, recovery of the microcirculatory bloodstream was detected in only 45% of capillaries (Fig. 4a). Membrane structures, aggregation of erythrocytes, endothelial outgrowths into the lumen of the vessel, microclasmatosis, and a decrease of amorphous osmiophil material (Fig. 4b) were found in some capillaries; in a few cases, thrombocyte stasis was detected (Fig. 4c). The number of vessels that did not contain amorphous osmiophil material and blood cells (no reflow) slightly decreased in comparison with the third day, but was higher than in the animals of the experimental series for the same period (Fig. 4d).

The restoration of architectonic of the microcirculatory bloodstream was determined over the 12 days of the PTP in animals of both series in the left ventricular myocardium. Individual thrombocytes and reticulocytes were detected only in individual capillaries (Fig. 5).

Assessing the ultrastructure of the microcirculatory bloodstream of the left ventricular myocardium in the control series of rats, we can conclude that, at the third and seventh days of the PTP, significant changes of both the capillaries, as well as abnormalities within and outside the blood vessels, were determined. These abnormalities were manifested as the formation of endothelial outgrowths in the vascular lumen; swelling, edema and thinning of the endothelium; impaired vascular permeability with the release of erythrocytes outside the blood flow; the detection of membrane structures, bubbles, microaggregates, and thrombus of erythrocytes and thrombocytes in vascular lumen; and even complete absence of circulation in some capillaries (no-reflow phenomenon). This impairs the functioning of the microcirculatory bloodstream. Intraperitoneal administration of mexicor prevents damage to the architectonic of the microcirculatory bloodstream in the left ventricular myocardium. Thus, in animals of the experimental series, in the same periods, only intravascular changes that were less pronounced were determined. At 12 days of PTP in both series, in comparison with the previous stages of the study, a gradual recovery of the structure of the microcirculatory bloodstream was observed, but changes were still more pronounced in the control series.

Thus, in the PTP caused by TBI, the formation of disorders of architectonic of the microcirculatory bloodstream of the left ventricle in conjunction with reduced EPME and increased aggregation of erythro-

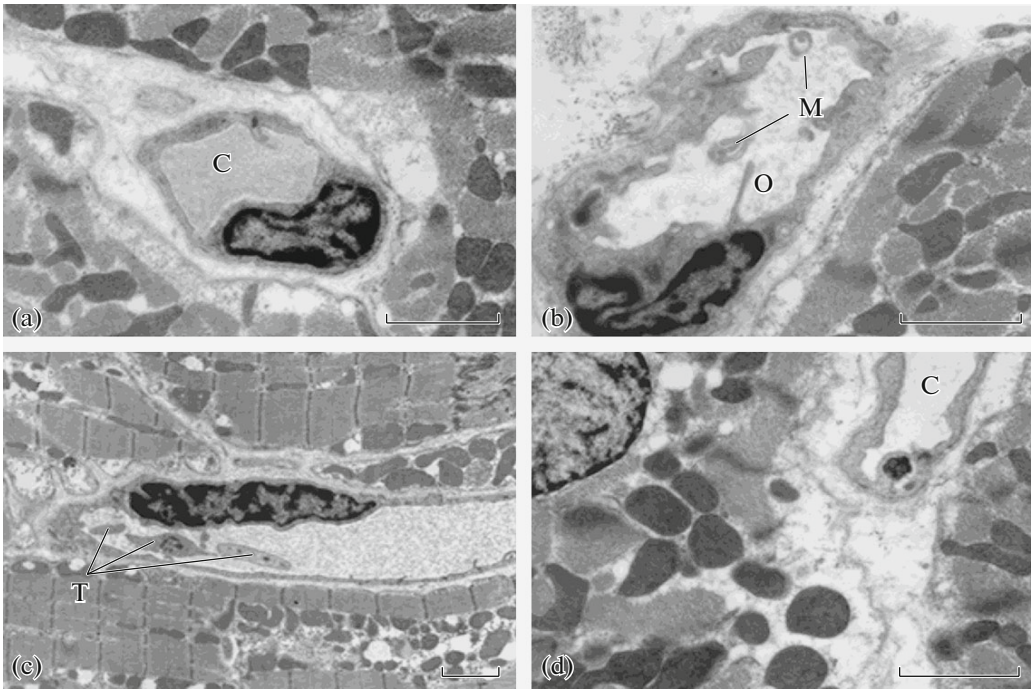

Fig. 4. The blood capillaries of the left ventricular myocardium of rats of the control group on the seventh day of the post-traumatic period of TBI at different magnifications. C—capillary lumen, O—outgrowth of endothelium, M—microclasmatosis, and T—thrombocyte. Magnification: (a, b, d) 11000×, (c) 5600×.

cytes and thrombocytes and activation of the thrombotic process led to capillary occlusion and impaired the blood flow in coronary vessels and the transport of glucose, free fatty acids and oxygen required for the synthesis of ATP into the mitochondria of cardiomyocytes. A lack of energy substrates and oxygen appearing in cells is a major cause of cardiac function in patients with concomitant TBI (Boyarinov et al., 2014). The detected disorders of the cardiovascular system were already progressing during the first day of PTP and they important extracranial factors of secondary brain injury in TBI.

Mexicor is a cytoprotector that is produced in Russia and contains succinate and emoxypine. Due to its high penetrative properties, emoxypine penetrates rapidly into cells, and, in the cytoplasm, it is separated into two components, each of which has a positive effect under the conditions of hypoxia. Emoxypine promotes the inhibition of free radical processes, and succinic acid supports the processes of the formation of high-energy compounds. Therefore, intraperitoneal administration of mexicor to rats during the PTP has a significant impact on the recovery of the rheological parameters of the blood and microcirculation already in the first day after TBI. After 3 and 7 days, it significantly prevents the impairment of the structural and functional integrity of the vascular endothelium, which is the main cellular component of the regulation system of blood aggregation. Oxidative stress caused by an increased level of free radicals in blood is known to be one of the main mechanisms leading to endothelial damage to microcirculatory vessels and disorders of endothelial function (Semchenko et al., 2003; Schulz et al., 2004.). The results of previously published studies (Boyarinova et al., 2014) demonstrated that, in patients with concomitant TBI, the processes of free radical oxidation were activated, and long-term and continuous intravenous infusions of mexicor significantly reduced the content of free radicals in the blood of these patients as early as in early PTP. Considering the above facts, we can suggest that, during the PTP in rats, mexicor, due to its antiradical properties, has a stabilizing effect on the membranes of erythrocytes and endotheliocytes and, thereby, restores their functional activity. The energy-synthesizing action of mexicor also played an important role in the maintenance of vital activity of cells in rats after TBI. This action is associated not only with increased delivery and consumption of succinate by cells, the implementation of the phenomenon of fast oxidation of succinate by succinate dehydrogenase and activation of the mitochondrial respiratory chain (Mihin et al., 2008), but also with improved oxygen delivery to endotheliocytes and erythrocytes, due to the increased synthesis of 2,3-DPG in these cells, as was shown by the results of this study. Along with the favorable effect of mexicor on microcirculation in rats that have undergone TBI, its positive effect on cardiac hemody-

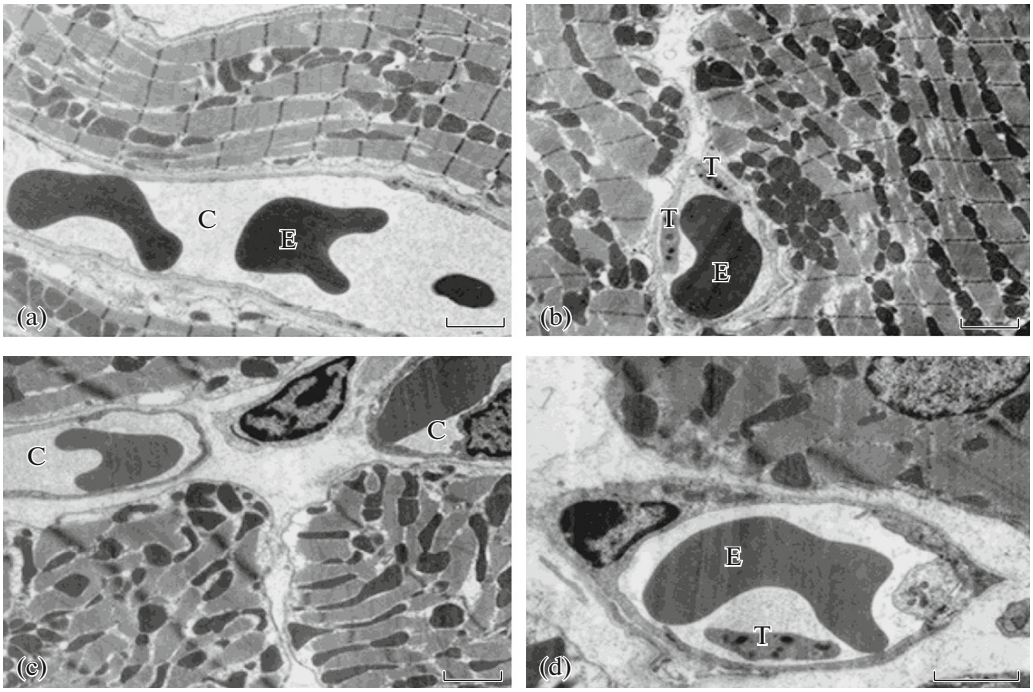

Fig. 5. The ultrastructure of capillaries of the left ventricular myocardium of (a, b) rats administered with mexicor and (c, d) control animals on the 12th days of the post-traumatic period of TBI. C—capillary lumen, E—erythrocyte, and T—thrombocyte. Magnification: (a, b, c) 5600×, (d) 8900×.

namics in patients with concomitant TBI at the early stages of formation of traumatic disease has been established (Boyarinov et al., 2014).

Thus, mexicor has energy-synthesizing, antiradical, and oxygen-suppling effects during the PTP caused by TBI. This drug has a corrective effect not only on microcirculation, but on the entire cardiovascular system, which largely should prevent secondary brain damage.

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