ISSN 1819-7124, Neurochemical Journal, 2017, Vol. 11, No. 4, pp. 325–331. © Pleiades Publishing, Ltd., 2017.
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EXPERIMENTAL ARTICLES

Monoamine Metabolism in the Brain after Disruption of Cerebral Hemodynamics Caused by Acute Blood Loss

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Received January 20, 2017; in final form, March 23, 2017

Abstract—We studied the relationship between neurochemical and functional brain disorders depending on changes in cerebral hemodynamics at different stages of its recovery after acute blood loss. Similar changes in the metabolism of monoamines (MAs) and an increase in seizure susceptibility (SS), which were found at different states of cerebral hemodynamics at 1 hour and 24 hours after hemorrhage, had different causes. In the first case, the changes were mainly due to insufficient cerebral circulation and hypoxia occurring after blood loss, and in the second case, they were due to the prolongation of previous disorders, which continued after the recovery of cerebral hemodynamics. A deficiency of the MA and MA-synthesizing capacity of the brain after acute blood loss extended the duration of functional disorders in the central nervous system, even after the restoration of cerebral circulation.

Keywords: blood loss, brain monoamines, cerebral hemodynamics, autoregulation

DOI: 10.1134/S1819712417030060

INTRODUCTION

The investigation of pathogenic neurochemical mechanisms of functional brain disorders that occur after the impairment of cerebral hemodynamics is one of the most important problems of fundamental and clinical neurology. The high sensitivity of the central nervous system to an oxygen deficiency, as well as a lack of energy and plastic resources, makes it highly susceptible to even short-term cerebral hypoperfusion. Despite the mechanisms that provide autoregulation of the cerebral blood flow in the brain, their compensatory capabilities gradually become exhausted with the exacerbation of hypoperfusion, which leads to the formation of a complex set of neurological disorders [1, 2]. Considering the important role of the neurotransmitter mechanisms of the brain in the pathogenesis of these disorders [3], it may be assumed that the state of monoaminergic (MA-ergic) systems during blood loss may be associated with the state of cerebral hemodynamics and determine the formation of functional disorders of the central nervous system.

Despite numerous studies of different types of blood loss, the effects of cerebral hemodynamic impairments in different periods after the blood loss on changes in the brain MA-ergic systems and associated functional disorders remain poorly studied. Understanding the neurochemical mechanisms in regard to the pathogenesis of cerebral hemodynamics during blood loss is important for both solving fundamental neurochemical and neurophysiological problems and the development of new treatments using transfusion drugs and blood substitutes that are capable of transporting oxygen.

The aim of the study was to investigate monoamine metabolism in the brain during the disruption of cerebral hemodynamics and their autoregulation caused by acute blood loss and their relationship with seizure susceptibility.

MATERIALS AND METHODS

Modeling blood loss. The studies were carried out on male Wistar rats weighing 280–320 g in strict accordance with the Rules of Laboratory Practice in the Russian Federation (Order of the Ministry of Health of the Russian Federation no. 267 of June 19, 2003). Blood sampling was performed without anesthesia through a catheter previously implanted in the internal jugular vein. Implantation of the catheter was performed under general anesthesia with a Zoletil–Rometar mixture (20 and 10 mg/kg, respectively). The blood loss rate was 0.2 mL/100 g of body weight per min. The blood loss was 20 mL/kg of body weight, which was 30% of the total blood volume of the animal and corresponded to moderate blood loss. After blood collection, the volume of fluid was not recovered. Each experimental series described below was per-

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formed on a separate group of animals (no less than eight rats).

Ultrasound Doppler study of blood vessels. The linear velocity of blood flow (LVBF) in the basilar artery was studied by the transcranial Doppler method. The artery was scanned by a 10 MHz sensor (Mindray M5) in the color and pulse-wave Doppler modes. Quantitative evaluation of the Doppler shift spectrum was performed taking the peak systolic, maximum terminal diastolic, and time-averaged maximum blood flow rates into account. In addition, the peripheral resistive index, pulsatility index, and systolodiastolic ratio were calculated. These studies were performed on three groups of animals ($n = 21$) under mild sedation with the inhalation anesthetic isoflurane 1 h, 24 h, and 5 days after the blood loss. Doppler scanning was performed when animals reached stage 4 of sedation on the Ramsay scale (superficial sleep with a response to a loud sound). The anesthetic was dosed with a Drager Vapor 2000 evaporator for isoflurane (Germany).

Functional tests. After carrying out triplex scanning of the basilar artery of the brain and determining the main indices of intracranial circulation in the control and experimental animals, the reserve capacities of the metabolic and myogenic autoregulation units were evaluated 1 h, 24 h, and 5 days after the blood loss. The studies were performed under mild sedation with the inhalation anesthetic isoflurane as described above. An important advantage of functional tests is that they allow one to minimize individual differences and assess the direction of changes.

However, to obtain and correctly interpret the functional reserve parameters, it is necessary to use the effects that are inherent to the cerebral autoregulation system [4]. For this purpose, a hypercapnic test is used for an objective evaluation of the metabolic link of autoregulation [4]. A mixture of 5–7% carbon dioxide and air was inhaled for 1–2 minutes. To monitor CO_2 and O_2 in the inhaled air, a KARDEKS MAR-02 capnograph (KARDEKS, Russia) and OxiQuant S Plus oxygen monitor were used. An increase in the peak systolic velocity by 40–60% was considered relevant.

To assess the reserve capacity of myogenic regulation, a short-term compression of the common carotid artery was performed [4]. Compression within 5–6 s causes an acute decrease in pressure in the intracranial vessels and a reflex compensatory vasodilation. When the blood flow in the basilar artery is restored, a significant increase in all velocity parameters of the blood flow is recorded. According to the degree of increase in velocity parameters, it is possible to assess the reserve capacities of the myogenic regulation link.

Activation of MA-ergic systems. In a separate experimental series, the animals were injected intraperitoneally with dopamine or serotonin synthesis precursors (Madopar-125 or 5-hydroxytryptophan) 1 h, 24 h, and 5 days after the blood loss. Madopar-125 (Hoffmann-La Roche, Switzerland) contains L-DOPA, a precursor of DA synthesis, and benserazide, which is an inhibitor of peripheral decarboxylation of L-DOPA. Benserazide is nontoxic and does not pass the BBB even at high doses. Madopar-125 was administered at a dose of 25 mg/kg (L-DOPA) 1.5 h before the sacrifice of the animals. 5-hydroxytryptophan (5-HTP, Serva, Germany) was administered at a dose of 20 mg/kg 2 hours before the sacrifice. The maximum increase in MA takes place in this period [5]. Control animals received equivalent volumes of saline.

Evaluation of seizure susceptibility. In a separate experimental series, the seizure threshold in animals was evaluated at different time points after AI. For these purposes, a 1% pentylenetetrazole solution (PTZ, Sigma, United States) was injected into the tail vein of the rats using a infusomat (Braun Perfusor Compact, Germany) at a rate of 0.1 mL/min. The threshold dose of PTZ that induced clonic–tonic convulsions was determined individually for each animal and expressed in mg/kg of body weight.

Chromatography. The concentrations of monoamines (MA) including noradrenaline (NA), dopamine (DA), serotonin (ST), and their deamination products, that is, dioxyphenylacetic acid (DOPAC) and 5-hydroxyindolylacetic acid (5-HIAA), were determined using high-performance liquid chromatography (HPLC) with electrochemical detection. The analysis was performed in the middle brain, where the bodies of MA-ergic neurons are mainly localized, and the brain structures that receive this innervation (in the ventral hypothalamus and hippocampus). The extracted brain regions were weighed and frozen in liquid nitrogen. They were homogenized in a 20-fold volume of 0.1 N $HClO_4$ containing 0.1% potassium metabisulphite and an internal standard of 3,4-dihydroxybenzylamine (DHBA) (Sigma, United States); its final concentration was 20 ng/mL. The homogenates were centrifuged for 10 minutes at 4°C and 14000 *g* (Biofuge Stratos centrifuge, Germany), and the resulting supernatant was centrifuged (microcentrifuge Micro CA-II, United States) through Nylon-66 microfilters (pore diameter 0.2 μm, United States) for 5 min at room temperature at 3000 g. The filtrate (20 μL) was injected into the HPLC system through an injector (Rheodyne 7725i) equipped with a 20 μL loop. A reversed-phase SiO_2–C18 chromatography column (150 × 4.6 mm, particle size 3 μm) (Beckman, United States) without a precolumn was used. The mobile phase contained 0.1 M citrate-phosphate buffer (pH 3.2) with 0.3 mM sodium octyl sulfate, 0.1 mM EDTA, and 8% acetonitrile. Working solutions of monoamine standards (HA, DA, ST, DOPAC, and 5-HIAA) were prepared at a concentration of 100 ng/mL. Elution of the analyzed solutions was carried out at the rate of 0.7 mL/min using a HPP-5001 high-pressure pump (Laboratorni pristroje, Czech Republic). An electrochemical detector (BAS LC-4b, United States) was used to quantitatively

Table 1. The threshold doses of pentylenetetrazole inducing clonic–tonic convulsions at different times after a blood loss

Time after blood loss	PTZ, mg/kg	Seizure duration, s			*n*
		total	clonic phase	tonic phase	
Control	29.6 ± 2.22	11.1 ± 0.65	6.2 ± 0.38	4.9 ± 0.28	15
1 h	18.5 ± 1.55**	16.7 ± 1.34**	9.8 ± 0.73**	6.9 ± 0.56**	12
1 day	22.7 ± 1.74**	14.9 ± 0.81**	8.7 ± 0.59**	6.2 ± 0.52	10
5 days	31.7 ± 2.71	13.9 ± 0.75*	8.2 ± 0.63*	5.7 ± 0.4	10

* Significant differences in comparison with the control group; * $p < 0.05$, ** $p < 0.01$.

assess the studied substances. Immediately before the analysis and after every 15th test, a mixture of standards was administered into the system. The concentration of endogenous substances was calculated in comparison with the standards and represented as ng/mg of tissue. Collection and processing of chromatographic data was carried out using MultiChrome 1.5 x software.

The statistical processing of data was carried out using the Statistica 6.0 program. The analysis of the differences between the experimental and control groups was carried out using the one-way analysis of the variance followed by evaluation of the differences between groups using the Newman–Keuls and Dunn criteria. The verification of the normal distribution of the samples was carried out using the Kolmogorov–Smirnov test. Statistically significant differences were considered at $p < 0.05$.

RESULTS

Changes in cerebral hemodynamics and their autoregulation after the acute blood loss. At 1 hour after the acute blood loss, disruption of cerebral hemodynamics and their autoregulation was detected. Thus, a statistically significant decrease in the peak systolic (PS), diastolic (PD), and time-averaged blood flow velocity (TAMAX) occurred in the basilar artery of the brain (Fig. 1). At the same time, the indices of vascular resistance did not change and the metabolic and myogenic reserves of cerebral autoregulation significantly decreased. A low capacity of cerebral autoregulation during a decrease in cerebral blood flow may be a pathogenetic basis for the occurrence of foci of increased seizure susceptibility.

At 24 hours after the acute blood loss, the linear blood flow in the basilar artery reached the control level, but the reserves of autoregulation tended toward a decrease. Both cerebral hemodynamics and the cerebral autoregulation recovered on the fifth day after the blood loss.

Seizure susceptibility at different periods after the blood loss. The results of the studies presented in Table 1 show changes in the SS of animals at different periods after the acute blood loss. Thus, 1 hour after the blood loss, SS increased significantly, which occurred as a reduction by 37% (in comparison with the control) of the threshold dose of pentylenetrazole inducing clonic-tonic convulsions. In this case, the total duration of the convulsive seizure, as well as its clonic and tonic phases, increased by 49, 57, and 40%, respectively. Similar results were obtained 24 hours after the blood loss. After 5 days, the threshold dose of the convulsant inducing convulsions did not differ from the control, but the total duration of seizures increased by 24% due to an increase in the duration of the clonic phase by 30% ($p < 0.01$).

The concentration of monoamines. Analysis of the results of the study of the MA metabolism in the brain at different periods after the blood loss showed a number of features that may be associated with increased seizure susceptibility in animals after the disruption of cerebral hemodynamics. It was found that the changes in the MA and their metabolites concentrations in the studied brain regions are regionally specific and depend on the time after the blood loss (Fig. 2). An increase in SS 1 h after the blood loss occurred together with a decrease in the NA level in the hippocampus and the middle brain by 37 and 27%, respectively. At the same time, the DA content in all studied brain regions was also significantly reduced and the DOPAC/DA ratio in the hypothalamus and the midbrain increased by 25 and 27%. This was possibly caused by an increase in DA deamination resulting in a decrease in its level in these parts of the brain. DOPAC is thought to be formed mainly from newly synthesized DA newly captured by terminals. Therefore, an increase in the DOPAC/DA ratio found in the hypothalamus and the midbrain 1 h after the acute blood loss may reflect an increase in the activity of the DA system occurring during a decrease in the cerebral hemodynamics and the capacity of metabolic and myogenic cascades of autoregulation. In addition, this period is accompanied by a decrease in the ST concentration in the midbrain and 5-HIAA concentration in all of the studied parts of the brain. In the hippocampus and hypothalamus, the 5-HIAA/ST ratio decreased by 29 and 43%, respectively.

The results of the study performed 24 hours after the blood loss showed that despite the recovery of

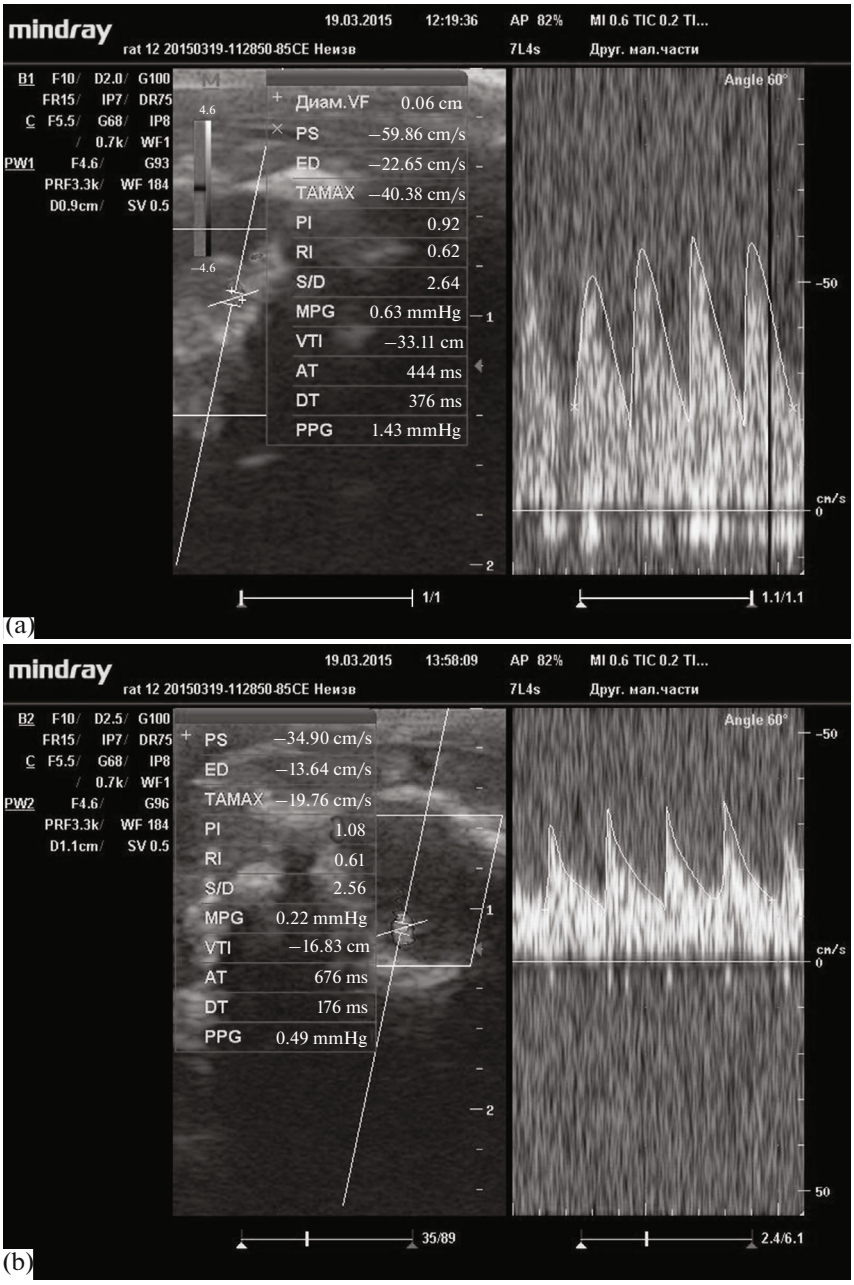

Fig. 1. An ultrasound of the basilar artery of the brain in B-, C-, and PW-modes in the control animals (a) and 1 h after non-compensated blood loss of 20 mL/kg of body weight (b).

cerebral circulation, increased SS and decreased concentration of NA and DA in all the studied parts of the brain persisted. In this case, the ratio of DOPAC/DA in the hypothalamus and the midbrain exceeded the control level by 62 and 45%. At the same time, a number of different changes were detected compared to the period 1 h after blood loss. At 24 h after the blood loss, unlike in the previous period, an increase in the content of the serotonin deamination product (5-HIAA) occurred in the hypothalamus and the middle brain and was accompanied by an increase in the 5-HIAA/ST ratio by 83 and 41%, respectively. These changes indirectly indicate an increase in the activity of the ST-ergic system.

At 5 days after the blood loss, unlike previous posthemorrhagic periods, the content of MA and their metabolites in the studied parts of the brain recovered to the control level or exceeded it.

Therefore, these results indicate that the SS increased both during a decrease in cerebral hemody-

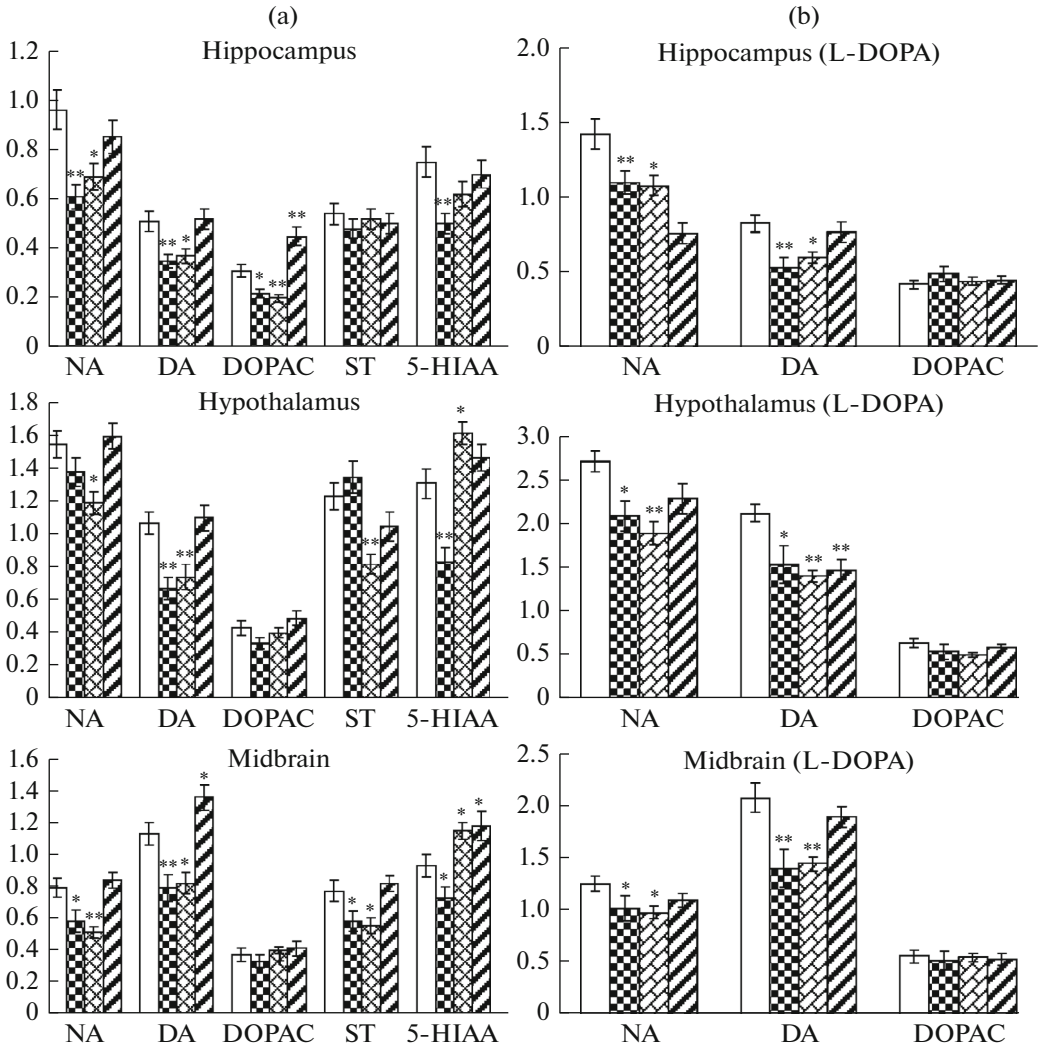

Fig. 2. (a) the contents of monoamines (ng/mg of tissue) in the central nervous system at different periods after acute blood loss: □, control ($n = 8$); ▩, in 1 h ($n = 8$); ▨, in 24 h ($n = 8$); ▨, in 5 days ($n = 8$); (b) administration of L-DOPA to the control and experimental animals at different periods after an acute blood loss: □, control ($n = 8$), ▩, in 1 h ($n = 8$), ▨, in 24 h ($n = 8$), ▨, in 5 days ($n = 8$). *, $p < 0.05$; **, $p < 0.01$.

namics 1 h after the blood loss and 24 h after it, when the cerebral circulation was restored. In both cases, the content of NA and DA in the studied parts of the brain was mostly reduced. According to the literature, a decrease in the functional capacity of the DA and ST-ergic systems increases the sensitivity of the brain to convulsants [6–8]. Considering the high DOPAC/DA and 5-HIAA/ST ratios in the hypothalamus and the midbrain accompanied by a decrease in NA, DA, and ST at 1 and 24 hours after the hemorrhage, we believe that the increase in SS in these animals may be associated with overexertion of MA-ergic systems and a decrease in the MA-synthesizing capabilities in the studied parts of the brain.

To clarify this issue, the monoamine-synthesizing capacity of the central nervous system was studied at different periods after the blood loss. The control and experimental animals were treated with precursors of DA or ST synthesis. It was found that the administration of L-DOPA at 1 and 24 hours after the blood loss led to a much smaller increase in NA and DA in the studied parts of the brain than in the control animals that received the same dose of L-DOPA (Fig. 2). Even 5 days after the blood loss, DA-synthesis in the hypothalamus was lower by 31%.

Administration of the precursor for the ST (5-HTP) synthesis to the experimental animals 1 and 24 hours after the blood loss led to a smaller increase in its level in the studied parts of the brain compared to the control animals that received the same dose of 5-HTP (Fig. 3). However, after 5 days, ST-synthesis was restored in all the studied parts of the brain.

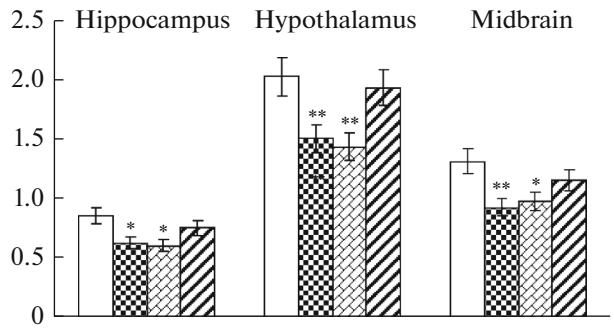

Fig. 3. The change in the serotonin content (ng/mg of tissue) in different parts of the brain after 5-HTP administration to the control and experimental animals at different periods after an acute blood loss: □, control ($n = 8$), ▩, in 1 h ($n = 8$), ▨, in 24 h ($n = 8$), ▨, in 5 days ($n = 8$). * $p < 0.05$; **, $p < 0.01$.

DISCUSSION

According to current views, blood loss provokes complex dynamics of pathological disorders in most organs and tissues, especially in the central nervous system, which is the most sensitive to the lack of oxygen, as well as substances that provide energy and the plastic needs of the brain [2, 8]. Reduction of cerebral hemodynamics often leads to a generalized metabolic disorder that underlies cerebral disorders. In each case, the nature of the disorders is determined by a variety of parameters: the volume of blood loss, its replacement or lack of replacement, the functionality of specific brain structures, etc. For this reason, it is often impossible to reliably predict the severity of cerebral disorders, and even to objectively evaluate the nature of neurochemical disorders at different periods after a blood loss. To address such a complex issue it is important to understand the neurochemical mechanisms in regard to the pathogenesis of neurophysiological processes induced by a cerebral hemodynamics deficiency.

Taking the fact into account that the changes in the brain are very different at different periods after the cerebral microcirculation disruption [9], it was necessary to compare the cerebral hemodynamic disruption at different stages of posthemorrhagic recovery with corresponding changes in the state of MA-ergic brain systems and to clarify their relationship to the severity of functional disorders in the central nervous system. This helps one to understand whether it is possible to prevent the formation of pathological plasticity of the brain [10], which is manifested as convulsive activity, by modulating the activity of MA-ergic systems at different periods after the blood loss.

Our studies showed that changes in the content of MA and their metabolites in the examined parts of the brain and seizure susceptibility did not always correspond to the pattern of the cerebral hemodynamics impairment. Thus, increased SS and decreased MA contents in the studied brain regions were detected both during a decrease in cerebral hemodynamics at 1 h after a blood loss and after its recovery 24 h later. Moreover, after the restoration of hemodynamics, the MA-synthesizing capacity remained reduced. We suggest that the long-term disruptions of the state of MA-ergic systems after the blood loss seem to prolong the increased SS, despite the restoration of cerebral hemodynamics.

Our results are in agreement with studies on different experimental models, which have shown that endogenous NA reduces convulsive activity, whereas its depletion, as well as a decrease in the activity of enzymes involved in the synthesis of DA, increase SS and accelerate epileptogenesis [11–13]. The effectiveness of anticonvulsant therapy is attenuated by the deficiency of NA in animals [13, 14]. Analysis of the literature data suggests that DA and its precursor (L-DOPA) can increase the reduced cerebral blood flow in the areas of disrupted microcirculation [15–17]. These results provide evidence that a decrease in the level of DA and DA-synthesis found in the studied parts of the brain at 1 hour after a blood loss could aggravate and prolong the pathological processes associated with cerebral hypocirculation. This is confirmed by the high SS detected after the recovery of cerebral hemodynamics 24 hours after a blood loss.

Moreover, a low level of MA and their synthesis during this period may affect the excitability of hippocampal structures that modulate the level of SS. This corresponds to the results of studies that showed that the decrease in the activity of the NA-ergic nucleus of the brain (*locus ceruleus*) by the chronic inhibition of the NA transporter blocks the NA-ergic innervation of the hippocampus and leads to the hyperexcitability of its neurons, thus contributing to an increase in SS [11].

The analysis of the results showed that changes in the state of MA-ergic systems and an increase in SS detected at 1 hour and at 1 day after the blood loss were not always caused by the impairment of cerebral hemodynamics. In the former case, changes were associated mainly with the inhibition of microcirculation and hypoxia caused by cerebral hemodynamics insufficiency, and in the latter case, with prolongation of disorders, which had been already formed, after the recovery of cerebral hemodynamics.

Despite the complete restoration of cerebral circulation and autoregulation 5 days after the blood loss, DA-synthesis in the hypothalamus remained lower than in control animals. This indicates that in some parts of the brain, abnormalities in the MA-ergic mechanisms occurring during the initial stages of cerebral hemodynamic decrease may persist for a long time in the post-hemorrhagic period, and the prospect of their recovery is not always determined only by the recovery of cerebral circulation. Our results are in agreement with the results of morphological studies of neuronal populations, which showed that the disrup-

tion of cerebral microcirculation caused the structural and functional changes of neurons that develop for a long period of time after the restoration of blood circulation [2, 3, 18, 19]. These facts suggest that prolonged changes in the state of MA-ergic systems that occur after the recovery of cerebral hemodynamics may be a pathological basis for the development of delayed cerebral disorders.

Therefore, our results made it possible to study the relationship between the recovery of cerebral hemodynamics and the corresponding neurochemical and functional impairments of the brain at different stages after an acute blood loss. We found that the resulting deficit of MA synthesis in the brain prolongs functional disorders even after the restoration of cerebral circulation. This is in agreement with one of the concepts of cerebral microcirculatory-disorder therapy, which indicates the possibility of using L-DOPA to enhance the compensatory and recovery capabilities of the brain in the rehabilitation of patients after ischemic stroke [20–22]. The results of our studies are the fundamental basis for the development of therapy for posthemorrhagic conditions and methods for the rehabilitation of patients after cerebral hemodynamics impairments caused by blood loss.

CONCLUSIONS

The analysis of the results of complex neurochemical and neurophysiological studies brings us to the conclusion that the causes of the changes in the MA-ergic systems and the increase in SS found 1 h and 24 h after blood loss are different and not always due to impaired cerebral hemodynamics. In the first case, changes are associated mainly with a disruption of microcirculation and hypoxia due to cerebral hemodynamics insufficiency, and in the second case, they are associated with the prolongation of existing disorders, which persist after the recovery of cerebral hemodynamics. Deficiency of MA and MA-synthesis in the brain after acute blood loss prolongs the functional disorders, even after the restoration of cerebral circulation. Understanding the role of MA-ergic mechanisms of the brain in the formation of SS in the post-hemorrhagic period provides more possibilities for pharmacological targeting of these processes via modulation of MA-ergic activity taking the state of cerebral hemodynamics into account.

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