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Research Article

Neuroprotective effects of taurine and 3-hydroxypyridine derivatives in the intracerebral hemorrhage model in rats

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Abstract

Introduction: At present, the problem of pharmacological correction of free radical processess emerges full-blown. The aim of the study is an experimental study of the neuroprotective effect of taurine and 3-hydroxypyridine derivatives.

Materials and methods: The study was performed in Wistar rats. The neuroprotective effect of the substances was studied in the intracerebral hemorrhage model.

Results and discussion: The administration of the studied substances had a positive effect on the survival of the animals within the first day (50% of rats died in the control group, 30% – in the Mexidol- and Ethoxidol-treated groups, and 20% – in LKhT 3-17-treated group). Within the first day after the surgery, all rats with stroke had severe neurological disorders. However, by the 3rd day, the Ethoxidol- and LKhT 3-17-treated rats had a lower neurological deficit. By Day 14, all groups of animals treated with the test substances had a lower severity of post-stroke disorders than those in the control group, which was evident as a 1.5-time lower McGraw Stroke Index score. LKhT 3-17 substance showed the most pronounced neuroprotective effect.

Conclusions: The studied derivatives of taurine and 3-hydroxypyridine have a neuroprotective effect, which is manifested in the lower severity of neurological disorders,a more rapid reduction in the signs of neurodegeneration and accelerated hemorrhage processes.

Keywords

hemorrhagic stroke, taurine, 3-hydroxypyridines, neuroprotection

Introduction

Hemorrhagic stroke is a spontaneous intracranial hemorrhage caused by the most common vascular diseases of the brain, such as essential hypertension, secondary hypertension, vasculitis, etc., and causing 8–15% of all strokes (De Oliveira Manoel et al. 2016). According to the Russian Stroke Association (NABI), 40000 intracerebral

haemorrhages are registered annually in Russia. According to the disease progression rate, course and outcome of the disease, hemorrhagic stroke is the most dramatic of all the cerebrovascular processes.

The effused blood leads to compression of the surrounding brain matter, which is accompanied by a decrease in local cerebral blood flow in this area and a development of secondary ischemic damage (Vella et al. 2017). Reduction of the local cerebral blood flow in the area around hemorrhage triggers ischemic pathobiochemical cascades in the brain matter: changes in the glutamate and calcium metabolism, free radical reactions, lipid peroxidation, excessive synthesis of nitric oxide, activation of astro- and microglial cell pools, and immune changes and local inflammation associated with these changes. Fe^{3+} ions, which are also a powerful cellular oxidant, intensify lipid peroxidation and stimulate the formation of a large number of free radicals, are responsible for the permanent brain damage (Walsh et al. 2000).

Due to the constant increase in the number of patients with this pathology, high mortality (50–70% of patients) (Skvortsova et al. 2002) and disability rate (about 2/3 of patients) (Karpov et al. 2015), the issues of drug support for patients with this type of acute cerebrovascular disorder remain the most important problem of the modern neurology.

Intensive care of patients with hemorrhagic stroke is based on the concept of prevention and treatment of recurrent ischemic attacks. The basis of the concept is the separation of vascular factors that led to the brain damage and are directly related to the moment of the disease (primary factors) and pathological effects which the brain is exposed to in the subsequent period (secondary factors). It is fundamental that preventing and limiting the influence of the secondary pathological factors can significantly improve the outcome of the brain diseases.

A pathogenic therapy of the secondary ischemic brain damage is aimed at interrupting the reactions of glutamate-calcium cascade as rapid mechanisms of necrotic cell death. In this regard, the problem of pharmacological correction of the free-radical processes using exogenous drugs with antioxidant and antihypoxant effects is becoming relevant (Pohl and Kong Thoo Lin 2018).

The aim of this study was the experimental study of the therapeutic effects of taurine and 3-hydroxypyridine derivatives with potential neuroprotective effects in the intracerebral hemorrhage model (intracerebral posttraumatic hematoma) in rats.

Materials and methods

The study was performed in white male Wistar rats weighing 200 to 240g (Basov et al. 2019). Animal care was in compliance withthe laboratory practice of preclinical studies in the Russian Federation (GOST Z 51000.3-96 and 51000.4-96) and the Order of the Ministry of Healthcare of the Russian Federation №267 of 19 June 2003 *On Approval of the Rules of Good Laboratory Practice* (GLP), following the international recommendations of the *European Convention for the Protection of Vertebral Animals Used for Experimental and Other Scientific Purposes* (1997).

The animals were divided into several groups: Group 1 – sham operated rats (10 animals), which were anesthetized, then scalping and cranial trepanation were performed, without destruction of the brain tissue; Group 2 – untreated animals with hemorrhagic stroke (control group, 20 rats); Groups 3 and 4–animals with hemorrhagic stroke, which were treated with Mexidol and Ethoxidol, respectively (20 rats in each group); Group 5 – animals with simulated pathology, which received LKhT 3-17 (20 rats).

Acute autohemorrhagic stroke was simulated in the region of the internal capsule of the right hemisphere, according to the method by A. N. Makarenko et al. (Makarenko et al. 1990) modified for the current study. The operation was performed under general anesthesia by means of intraperitoneal administration of Xyla at a dose of 0.1 ml for premedication; after anxiolysis, the rats were administered intraperitoneally with chloral hydrate at a dose of 300 mg/kg as a basic narcosis. Upon deep general anesthesia, blood was sampled with a syringe from the tail vein of the rat. Then preoperative showering and a linear incision of the scalp in the parietal region were performed. The incision was performed in the frontal plane, followed by hemostasis. The length of the incision was 1.5 cm. Subsequently, skeletization and periosteal separation were performed. A burr hole was applied in the right parietal region, using a dental bur. The diameter of the burr hole was 3 mm. Later, using a puncture needle and a specially designed device for stereotactic administration, a puncture needle was inserted in the area of the internal capsule (coordinates H=4 mm, L=3.0 mm, A=1.5 mm from bregma, according to Paxinos' reference atlas) to a depth of 3 mm. Then the device was fixed, and a mandrin knife was inserted into the needle, destroying the brain tissue (the mandrin knife was turned three times clockwise and three times counterclockwise). The mandrin knife was removed, and then aseptically, autologous blood was infused into rats, the blood being taken from the tail vein of the animal in the amount of 0.11 ml/100g of weight. The effectiveness of the administration was determined by the presence of stem seizures. After that, the puncture needle was removed, the wound was drained, hemostasis was controlled, and layer-by-layer suturing of the wound was performed. In the sham operated animals, scalping and cranial trepanation were performed.

The test drugs were administered to the animals once intraperitoneally, 1 hour before surgery. LKhT 3-17 (a derivative of magnesium and bisaminoethansulfonic acid) (All-Russian Scientific Center for the Safety of Biologically Active Substances, Kupavna) was administered at a dose of 10 mg/kg (1/100 LD_{50}). Mexidol (Pharmasoft,

Russia) and Ethoxidol (Synthesis, Russia) at a dose of 50 mg/kg each (according to the interspecies conversion of the average human dose), used in clinical practice to treat cerebrovascular diseases, were selected as the reference drugs. The control animals were administered with saline solution in equivalent volume.

The animals were observed for14 days after the operation. The behavior and condition of the animals on the 1st, 3rd, 7th and 14th days were recorded.

To assess disruptions of the behavior and condition of the animals after hemorrhagic stroke, a set of traditional methods applied for such purposes in the experiment was used. To evaluate the neurological status, the neurological deficit assessment method according to McGraw Stroke Index modified by I.V. Gannushkina (Gannushkina 1996) was applied, along with the muscle tone evaluation by measuring the grip strength of the animals' limbs using a dynamometer.

When assessing the neurological status according to McGraw Stroke Index modified by I.V. Gannushkina, the rats were divided into a group with mild symptoms (up to 3 points) – sluggish movements, weakness of limbs, one-sided hemiptosis, tremor, circus movement – and a group with severe manifestations of the neurological impairment (from 3.5 to 10 points) – paresis and paralysis of the limbs, lateral position, and depression of consciousness.

Measurement of the animals' strength in the grasping test was carried out using a hardware-software complex, designed in the Student Robotics Development Laboratory by A.Yu. Aleynikov. The relative value (specific force) calculated as the ratio of the maximum grip force to the rat body weight was determined as a comparison criterion.

The platform for studying the motor activity of laboratory animals ACTI-TRACK (Panlab Harvard Apparatus, Barcelona, Spain) was used to assess the investigative behavior. The rat was tested for 5 minutes by the infrared activity monitor before the pathology simulation and then on the 1st, 3rd, 7th and 14th days after the simulation of hemorrhagic stroke.

For morphological evaluation, the animals were removed from the experiment 24, 72 hours, 7 and 14 days after the study start. The rats were decapitated; the brain was withdrawn, fixed in 10% neutral buffered formalin for 24–48 hours and embedded into paraffin. The frontal histological sections of the brain of 7 μm thick were stained with hematoxilin and eosin. A MIKMED-6 microscope with binocular adjustment, backlight illumination, a digital camera MS-5 and a computer with MCview software were used in the study.

Statistical processing of the obtained data was performed using STATISTICA 10.0 and MICROSOFT EXCEL 2016. Descriptive statistics was 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 Student's test and Bonferroni-corrected Mann-Whitney tests. Differences at $p<0.05$ were recognized as statistically significant.

Results and discussion

The influence of the drugs on the survival of the animals within 1 day

During the operation and within 1 day after it, 50% of rats with hemorrhagic stroke died in the control group. In the group of animals treated with the studied substances, mortality within 1 day was lower than in the control group. In particular, in the groups of animals treated with Mexidol or Ethoxidol, the daily survival rate was 70%. In the LKhT 3-17 group, 80% of rats survived. In the group of sham operated animals, no deaths were recorded during the entire observation period.

In the surviving animals with hemorrhagic stroke, various neurological and behavioral disorders were subsequently recorded.

The influence of the drugs on the McGraw Stroke Index score of neurologic deficit after the stroke

Within the first day after the operation, neurological disorders in almost all rats with simulated intracerebral hematoma were observed in the form of fatigue and slow movements, whereas in the sham operated rats, these disorders were observed in 30% of individuals. No pronounced neurologic deficit, manifested in the form of circus movements and limb paralysis was observed in the group of the sham operated animals, but it was noted in 100% of animals with hemorrhagic stroke.

Throughout days 1–7, the rats treated with Mexidol did not have any significant differences in the McGraw Stroke Index score with the control group, whereas the animals treated with Ethoxidol and LKhT 3-17 had statistically significantly less pronounced neurologic deficit throughout the entire observation period. However, by the 14th day, all the animals receiving the studied substances had more than 1.5-time lower McGraw Stroke Index score than in the control group. There were no significant differences in the severity of neurologic deficit on the 14th day in the groups of rats with simulated pathology, receiving different substances.

The influence of the studied drugs on the grip strength of the rats after stroke in the dynamometer test

The registration of the grip strength in the rats with hemorrhagic stroke showed that on the first day after stroke, loss of the muscle tone in the control group and in the Mexidol group did not differ significantly and averaged 58.2% (Table 1). In the groups treated with Ethoxidol and LKhT 3-17, the average decrease in the muscle tone on the 1st day was 37.2%, which was significantly lower than in the control group.

There was an increase in muscle strength in all groups on the 3rd day, and in the groups receiving the studied sub-

Table 1. Influence of Mexidol, Ethoxidol and LKhT 3-17 on the Indicators of Neurological Status on the 1st, 3rd, 7th and 14th Days after Hemorrhagic Stroke Simulation.

	Before pathology simulation			
	Control	**Mexidol**	**Ethoxidol**	**LKhT 3-17**
Specific force	6.7±0.2	7.4±0.3*	6.0±0.4*	6.1±0.3*
McGraw	0	0	0	0
1st day				
	Control	**Mexidol**	**Ethoxidol**	**LKhT 3-17**
Specific force	2.8±0.2	3.1±0.1	3.7±0.3*	3.9±0.3*
McGraw	8.1±2.0	7.0±2.2	6.7±2.4*	5.8±2.3*
3rd day				
	Control	**Mexidol**	**Ethoxidol**	**LKhT 3-17**
Specific force	3.6±0,4	5.0±0.2*	4.6±0.5*	4.6±0.5*
McGraw	5.8±1.7	5.2±2.1	4.3±1.8*	4.2±1.7*
7th day				
	Control	**Mexidol**	**Ethoxidol**	**LKhT 3-17**
Specific force	4.2±0.4	4.5±0.5	4.52±0,3	5.0±0.6*
McGraw	5.4±2.0	4.7±1.8	3.6±1.9*	3.7±1.8*
14th day				
	Control	**Mexidol**	**Ethoxidol**	**LKhT 3-17**
Specific force	4.90±0.3	4.8±0.4	5.15±0.5	5.7±0.6*
McGraw	5.1±2.2	3.3±0.3*	3.2±0.4*	3.1±0.3*

Note: * – $p<0.05$ – the differences are statistically significant in comparison with the control group of animals.

stances, an increase was significantly higher than in the control group. On the 7th and 14th days, a statistically significant increase in the muscle strength was recorded only in the group treated with LKhT 3-17.

The influence of the studied drugs on the motor activity of the animals with hemorrhagic stroke

During the entire observation period (1–14 days) after the hemorrhagic stroke simulation, the indices of total activity, stereotype of movements, locomotor activity, maximum speed, average speed, total distance under the influence of Ethoxidol and LKhT 3-17 were significantly higher than those in the control group (Table 2).

The motor scores of the rats treated with Mexidol on the 1st, 3rd and 7th days were significantly inferior to the results of the animals treated with Ethoxidol and LKhT 3-17, and on the 1st and 3rd days after surgery, they had no significant differences from those of the control group. However, the motor activity of the animals treated with Mexidol increased by the 14th day and had no statistically significant differences from those of the groups treated with the other studied substances.

LKhT 3-17 substance increased the motor score most on the 1st and 3rd days in comparison with other groups.

The high motor scores of the control group on the 14th day can be explained by high mortality in this group, in which only the strongest animals with high regenerative potential survived.

Table 2. Influence of Mexidol, Ethoxidol and LKhT 3-17 on the Ethological Indicators Calculated by Using ActiTrack Software on the 1st, 3rd, 7th and 14th Days after Hemorrhagic Stroke Simulation.

	Before pathology simulation			
	Control	**Mexidol**	**Ethoxidol**	**LKhT 3-17**
Total activity	1010±76	1188±49	1177±44	1139±46
Stereotype of movements	27±3	29±1	28±1	30±1
Locomotor activity	983±74	1036±51	986±34	1016±34
Maximum speed	22±1	22±1	22±1	23±1
Average speed	1.8±0.1	2.2±0.3	2.2±0.3	1.9±0.2
Total distance	545±43	594±24	557±24	557±29
1st day				
	Control	**Mexidol**	**Ethoxidol**	**LKhT 3-17**
Total activity	495±74	407±47	680±86*	941±192*
Stereotype of movements	40±4	39±7	58±9*	73±14*
Locomotor activity	422±35	369±40*	622±78*	868±178*
Maximum speed	21±2	16±2*	29±2*	30±4*
Average speed	2.0±1.0	1.7±0.0*	3.9±0.6*	6.5±1.0*
Total distance	610±77	520±78*	1160±193*	1930±545*
3rd day				
	Control	**Mexidol**	**Ethoxidol**	**LKhT 3-17**
Total activity	580±136	658±99	1092±102*	1704±788*
Stereotype of movements	18±6	61±10*	83±8*	70±8*
Locomotor activity	661±137	597±89	1009±95*	801±123
Maximum speed	14±1	28±2*	34±2*	34±4*
Average speed	1±0	3.8±0.6*	7.1±0.9*	5.9±1.4*
Total distance	276±51	1128±181*	2132±271*	1721±402*
7th day				
	Control	**Mexidol**	**Ethoxidol**	**LKhT 3-17**
Total activity	431±91	689±115*	1016±146*	858±142*
Stereotype of movements	20±8	64±12*	82±16*	67±15*
Locomotor activity	411±88	625±104*	934±131*	792±130*
Maximum speed	19±3	27±3*	35±3*	31±1*
Average speed	1±0.3	4±0.8*	6.6±1*	5.1±1.2*
Total distance	304±82	1198±226*	1940±297*	1524±353*
14th day				
	Control	**Mexidol**	**Ethoxidol**	**LKhT 3-17**
Total activity	1133±90	829±43*	807±144*	874±155*
Stereotype of movements	69±9	86±7*	68±14	76±6
Locomotor activity	1097±92	749±36*	739±132*	770±166*
Maximum speed	19±2	34±4*	33±2*	32±5*
Average speed	2.0±0.2	5.1±0.5*	5±1*	5.5±1.7*
Total distance	586±65	1524±159*	1503±290*	1393±65*

Note: * – $p<0.05$ – the differences are significant in comparison with the control group of animals.

The results of the morphological study of the brain

In the control group during the 1-3 days after hemorrhage, there was perivascular and pericellular edema in the narrow

Table 3. Dynamics of the Morphological Changes in the Rat Brain Under the Influence of Mexidol, Ethoxidol and LKhT 3-17 on the 1st, 3rd, 7th and 14th Days after Hemorrhagic Stroke Simulation.

Groups	1st–3rd days	7th day	14th day
Microcirculatory disorders			
Control	+	+++	++
Mexidol	+/++	++	+
Ethoxidol	++/+++	+/++	+
LKhT 3-17	+++	+/++	+
Changes of neurons			
Control	+++	++	+
Mexidol	++/+++	+/++	-
Ethoxidol	++	+	-
LKhT 3-17	+/++	+	-
Glial reaction			
Control	+++	++/+++	++
Mexidol	++/+++	++	+/++
Ethoxidol	++/+++	+/++	+
LKhT 3-17	++	+/++	+
Neutrophil infiltration			
Control	+++	++/+++	++
Mexidol	++	++	+
Ethoxidol	++	+/++	+
LKhT 3-17	++/+++	+	-
Macrophage infiltration			
Control	+	+/++	++
Mexidol	++/+++	++	+/++
Ethoxidol	++/+++	++/+++	+/++
LKhT 3-17	++/+++	+++	+/++
Hemosiderophage infiltration			
Control	-	+	++
Mexidol	-	+/++	++
Ethoxidol	-	++	+/++
LKhT 3-17	-	+++	+/++
Blood pigment			
Control	-	-	+
Mexidol	-	+	++
Ethoxidol	-	+	++
LKhT 3-17	-	+/++	+++

Note: the severity of morphological changes range from + to +++, where + – means minimal morphological changes; +++ – maximum morphological changes.

zone (0.5–1.0 mm), surrounding the hematoma; disrupted cytoarchitectonics of six layers of cortical neurons, pronounced ischemic changes, karyolysis of neurons; there was also a pronounced perifocal leukocytic reaction and a less pronounced glial reaction. Cerebral edema was accompanied by a number of successive morphological changes in the vascular wall and microcirculatory bloodstream (Table 3). At first, there was spasm of the arterioles, followed by their emptying of blood. By day 3 after hemorrhage, this condition was replaced by paretic dilatation of capillaries, arterioles and venules. In the lumen of the vessels during this period, there was the accumulation and margination of blood corpuscles, in particular leukocytes (Fig. 1). Dilated perivascular spaces filled with plasma indicated a significantly increased permeability of the vascular wall, leading to secondary diapedetic perivascular hemorrhages.

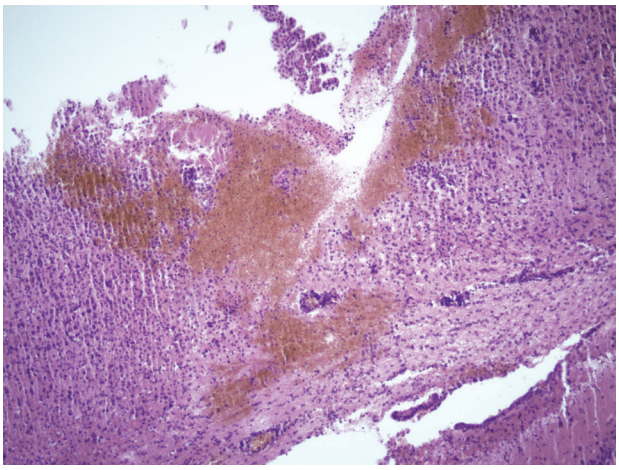

Figure 1. Neuronal degeneration of the brain in the hematoma area in rats of the control group on the 3rd day. Hematoxylin and eosin stain. ×100.

Starting from the 7th day, the pronounced perifocal leukocytic reaction gave way to a pronounced glial macrophage reaction; there started to aappear macrophage clumping with intracellular accumulation of a blood pigment (hemosiderophages) (Fig. 2).

Subsequently, by the 14th day, the regenerative processes of the glial cells led to the formation of a thin capsule around the hemorrhage site with aggregates of single hemosiderophages and blood pigment (Fig. 3).

The analysis of the LKhT 3-17 group revealed that perifocal edema was decreasing more quickly in comparison with the control group and other experimental groups (Mexidol, Ethoxidol) and almost completely disappeared by the 7th day. In the animals treated with LKhT 3-17, the signs of the inflammatory reaction with the development of neutrophil infiltration were more pronounced (Table 3). At the same time, the severity of the inflammatory reaction did not reach the intensity of that in the control group. Within the same period of time, similar changes were observed in the microcirculatory bloodstream (Table 3). Then, starting from the 3rd day and up to the end of the observation, against the background of more active regenerative processes, the stabilization processes of microcirculatory disorders proceeded more rapidly, and the severity of the microcirculatory bloodstream disorders was decreasing much more quickly than in the control group and a bit more quickly than the other experimental groups (Mexidol, Ethoxidol) (Table 3). This was accompanied by less pronounced damage to neurons and glial cells, accelerated processes of resorption and organization of the lesion, especially after the 3rd day of the disease (Table 3).

The results of the study confirm a neuroprotective action of all the studied substances. However, the neuroprotective activity of Mexidol developed more slowly – by the 14th day, unlike Ethoxidol and LKhT 3-17, which showed their cerebroprotective activity as early as on the 1st day

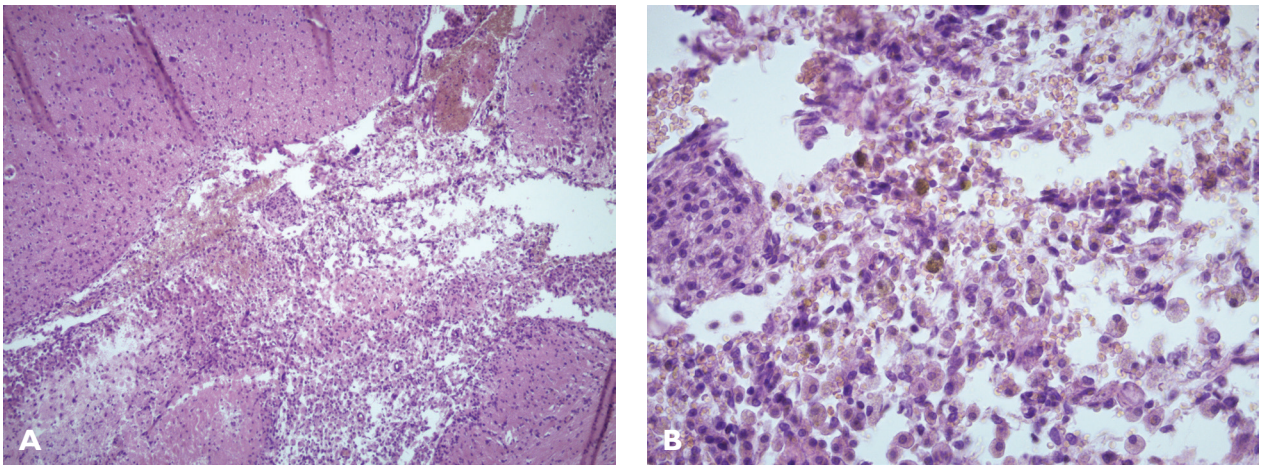

Figure 2. Neuronal degeneration of the brain in the hematoma area in rats of the control group on the 7th day. Hematoxylin and eosin stain. **A:**×100; **B:**×400.

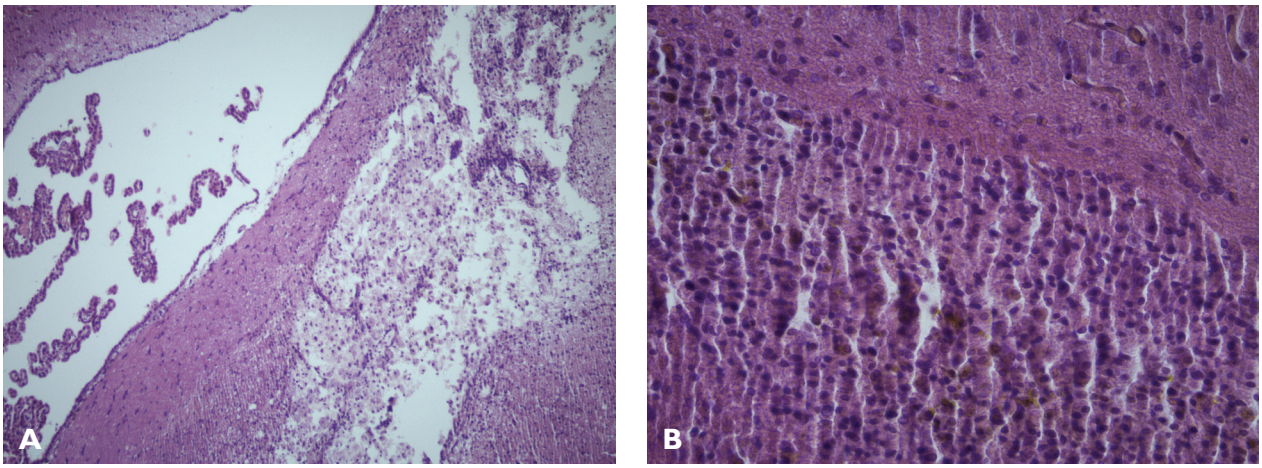

Figure 3. Neuroregenerative processes of the brain in the hematoma area in rats of the control group on the 14th day. Hematoxylin and eosin stain. **A:**×100; **B:**×400.

(less severe neurological disorders and higher activity of the animals of these groups in the infrared monitor).

LKhT 3-17 has a more pronounced neuroprotective activity, which is manifested by a significant decrease in the severity of post-stroke disorders. These differences are especially noticeable by the 3rd day of the disease, which is confirmed by a 1.5-time higher activity of the animals of this group compared to those in the Ethoxidol group,by almost a 3-time higher activity compared to that of the control; as well as by histological examination of the brain sections. According to the histological study, LKhT 3-17 administration is accompanied by a decrease in perifocal edema and microcirculation disorders within a shorter period of time, less damage to neurons and glial cells and faster processes of hemorrhage resorption and organization.

A high neuroprotective activity of LKhT 3-17 substance is probably due to its chemical structure, as it is a derivative of magnesium and bisaminoethansulfonic acid.

The presence of magnesium ion in the structure of the substance provides its antioxidant (Shahmardanova et al. 2016) and membrane trophic activities. Magnesium ions block NMDA channels in a voltage-dependent manner, preventing the development of a complex of glutamate excitotoxicity reactions (Muir et al. 2004).

Bisaminoethansulfonic acid residue, a derivative of taurine, provides neuroregenerative properties. The protective action of taurine in relation to stroke and atherosclerotic lesions of the arteries were convincingly shown in the experiments (Yamori et al. 1996, Yamori et al. 2001, Yamori et al. 2009).

Taurine is one of the five quantitatively predominant amino acids in the brain and is called “brain growth factor” (Chen et al. 1998). Taurine influences cell migration, modulates synaptic neurotransmission and can accelerate brain development, (at an extracellular concentration of 10 mM), attenuates the release of dopamine and its metabolites caused by over-activation of NMDA receptors, thus preventing neuronal death (Sato et al. 1991).

The ability to regulate the concentration of intracellular calcium is one of the most important properties of taurine (Schaffer and Kim 2018). It is known that glutamate causes a rapid increase in the concentration of free Ca^{2+} ions in the cytoplasm, which leads to the collapse of the mitochondrial electrochemical gradient and subsequent cell death. Not only does taurine reduce the intensity of Ca^{2+} output, but also contributes to the rapid return of these ions to their original state, which is one of the mechanisms for preventing or reducing the glutamate neurotoxicity (Ripps and Shen 2012).

One of the factors of cell damage is the membrane integrity breach, followed by an inflow of water and osmotic ions. This leads to cell swelling and subsequent negative effects. There is sufficient evidence about the role of taurine as an active osmoregulator, which is especially important for brain neurons (Terrill et al. 2017, McCarty 2017).

The obtained results showed the possibility of a further study of taurine derivatives, in particular, the substance under code LKhT 3-17 as neuroprotective drugs, and their future practical application in clinical practice for the treatment and prevention of cerebrovascular diseases.

Conclusion

1. The studied derivatives of taurine and 3-hydroxypyridine have a neuroprotective effect, which is manifested in less severe neurological disorders, a more rapid decrease in the signs of neurodegeneration, and accelerated processes of the hemorrhage organization.
2. A neuroprotective activity of Mexidol developed more slowly – by the 14th day, unlike Etxydol and LKhT 3-17 which showed their cerebroprotective activity on the 1st day.
3. LKhT 3-17 has a more pronounced neuroprotective activity, which is manifested by a significant decrease in the severity of post-stroke disorders. These differences are especially noticeable by the 3rd day of the disease, which is confirmed by the higher activity of the animals of this group, as well as by the histological examination of the brain sections – a more rapid decrease in the perifocal edema and microcirculation disorders, less damage to neurons and glial cells, and faster processes of the hemorrhage resorption and organization.

Conflict of interests

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

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