https://doi.org/10.15360/1813-9779-2023-2-2274

The Effect of Xenon on the Activity of Glycogen Synthase Kinase-3β in the Perifocal Zone of Ischemic Cerebral Infarction (Experimental Study)

Anton V. Ershov[1,2], Ivan A. Krukov[1,3], Victoria V. Antonova[1], Anastasia A. Baeva[1]

[1] V. A. Negovsky Research Institute of General Reanimatology,
Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology,
25 Petrovka Str., Bldg. 2, 107031 Moscow, Russia
[2] I. M. Sechenov First Moscow State Medical University, Ministry of Health of Russia,
3 Rakhmanovsky Lane, GSP-4, 127994 Moscow, Russia
[3] D. Rogachev National Medical Research Center for Pediatric Hematology,
Oncology and Immunology, Ministry of Health of Russia,
1 Samora Mashela Str., GSP-7, 117997 Moscow, Russia

For citation: *Anton V. Ershov, Ivan A. Krukov, Victoria V. Antonova, Anastasia A. Baeva.* The Effect of Xenon on the Activity of Glycogen Synthase Kinase-3ß in the Perifocal Zone of Ischemic Cerebral Infarction. *Obshchaya Reanimatologiya = General Reanimatology. Общая реаниматология.* 2023; 19 (2): 60–67. https://doi.org/10.15360/1813-9779-2023-2-2274 [In Russ. and Engl.]

***Correspondence to:** Anton V. Ershov, salavatprof@mail.ru

Summary

Aim of the study. To determine the effects of xenon exposure at a dose of 0.5 MAC of different duration on the content and enzyme-inactivating phosphorylation of the glycogen synthase kinase-3β (GSK3β) in the perifocal zone of ischemic cerebral infarction in an experimental setting.

Materials and methods. The Long method was used for modelling brain ischemia/reperfusion in 39 rats weighing 300–350 g. Study group animals was exposed to xenon at a dose of 0.5 MAC during 30, 60 and 120 minutes whereas control group animals received an oxygen-air mixture. Sham-operated animals served as a comparison group. The levels of GSK3β and phospho-GSK3β in brain homogenates were determined by blotting using specific antibodies.

Results. In ischemic stroke model, the content of GSK3β did not significantly change in control animals compared to comparison group. However, control group animals exhibited significant (2.7-fold, $P<0.001$) decrease in the content of its phospho-GSK3β in the perifocal zone of ischemic cerebral infarction. Inhalation of 0.5 MAC xenon during 30 minutes did not lead to an increase in phosphorylation of the GSK3β enzyme ($P=0.9$), however, 60 and 120 minutes of 0.5 MAC xenon exposures resulted in the increase in phosphorylated form of the enzyme by a factor of 2.1 ($P=0.005$) and 2.3 ($P=0.001$), respectively, compared to the control group.

Conclusion. The results reveal a possible molecular mechanism (i. e., execution of neuroprotective and anti-inflammatory effects of xenon due to GSK-3β inactivation) and show the prospects for using 60 and 120 minutes of 0.5 MAC xenon exposures in ischemic brain damage after a stroke, traumatic brain injury and other brain lesions.

Key words: glycogen synthase; GSK3ß; brain ischemia model; ischemic stroke; xenon; neuroprotection

Conflict of interest. The authors declare no conflict of interest.

Introduction

According to the World Health Organization, brain diseases account for one-third of all diseases in developed countries, and cerebrovascular disorders are the second leading cause of death in a group of cardiovascular diseases [1]. The brain mostly depends on energy metabolism, which is driven by an adequate supply of glucose and oxygen in the bloodstream and follows mainly aerobic glycolysis pathways. Disturbances in gas exchange or blood supply to the brain trigger neurometabolic and neurotransmitter processes that lead to ischemic damage of neuronal tissue. Similar pathophysiological responses can occur as a result of traumatic brain injury, tumor-associated brain compression, cardiac arrest, or surgical intervention [2, 3]. Ischemic brain injury is multi-component, with excitotoxicity mediated by upregulation of NMDA receptors being a key factor [4, 5]. The cascade of subsequent responses is complex and not fully understood, with glycogen synthase kinase-3 (GSK-3) playing a key role [6]. Its uniqueness in regulating cellular functions is due to its effect on the activity of about fifty proteins, whereas activity of the enzyme is mediated by numerous extracellular stimuli [7].

GSK-3 enzyme is a serine/threonine protease with multiple functions, including participation in cell division, proliferation, differentiation and adhesion [8]. Impaired function of GSK-3 has been found in cancer, diabetes mellitus, Alzheimer's disease and several other diseases. For example, GSK-3, together with phosphodiesterase type 4 (PDE-4), was found to regulate the activity of type 2 dopamine receptors, which play a role in the pathogenesis of schizophrenia. This kinase has also been implicated in mood regulation and in the mechanisms of affective disorders [9]. In mammals, GSK-3 exists in two isoforms, alpha (α) and beta (β), which are encoded

by different genes. In the brain, GSK-3β is found in both neurons and glial cells in almost all regions. In the cell, GSK-3 is mainly found in the cytoplasm, predominantly in the active form, but is also present in nuclei and mitochondria, where its activity is higher. Prolonged kinase activation leads to neurodegeneration [7]. GSK-3 inactivation occurs through its phosphorylation under the influence of various stimuli (e. g., neurotransmitters, growth factors, cytokines, etc.) [7, 8]. The basal activity of GSK-3β depends on the phosphorylation at tyrosine 216 [10]. Phosphorylation at serine 9 inactivates GSK-3β representing the main mechanism of regulation [11]. In addition, its phosphorylation at serine 389 by the protein kinase p38 is an important pathway of GSK-3β inhibition in the brain [12].

The GSK-3β enzyme plays a fundamental role in neuroplasticity and neurodegeneration. Active GSK-3β has been shown to inhibit axonal growth. Exposure to growth factors inhibits this kinase, which enables the synthesis of cytoskeletal proteins and promotes axon growth and branching [13]. Activation and blockade of GSK-3β in glutamatergic synapses plays an important role in synaptic plasticity underlying sleep, learning and memory processes [14]. Inhibition of this kinase has also been shown to stimulate the production of neuroprotective chaperones and block pro-apoptotic caspase-3. These effects are generally considered to be neuroprotective [15].

In addition, GSK-3β is a key enzyme that regulates the permeability of the mitochondrial pore, the opening of which during ischemia leads to the entry of water and solutes, contributing to matrix swelling and rupture of the outer mitochondrial membrane. Meanwhile, cytochrome C is released from the intermembrane space, triggering the process of apoptosis and ferroptosis. GSK-3β phosphorylation decreases its activity, which prevents pore opening and protects the cell from ischemic damage [16, 17].

In addition to neurons, high levels of GSK-3 have been found in neutrophils, and high levels of phosphorylated GSK-3 indicate their activation and participation in the inflammatory response through increased production of proinflammatory interleukins (IL-1β, IL-6, IL-12) and decreased anti-inflammatory IL-10 [19-20].

Given the important role of GSK-3β in cell and tissue function, it can be considered a promising biological target for pharmacotherapy [7]. Synthetic inhibitors of GSK-3β have been developed that exhibit antidepressant, mood stabilizing, and neuroprotective effects in experimental studies [21, 22].

According to literature data, halogenated anesthetics also inactivate GSK-3 through its phosphorylation, which results in reduction of systemic inflammatory response due to inhibition of proinflammatory cytokine production, leukocyte activity and tissue infiltration, maintenance of intercellular endothelial contacts and endothelial barrier integrity, and also due to normalization of cellular antioxidant enzyme levels, which reduces cellular damage [23].

The use of inert xenon gas to protect the brain during ischemia from stroke, traumatic brain injury, and other causes is a promising avenue of research. Recent studies have shown that 30 min exposure to 0.5 MAC xenon increases the levels of phosphorylated GSK-3β and antioxidant protective enzymes such as catalase, superoxide dismutase, heme oxygenase in rat brain homogenates, suggesting a novel molecular mechanism of its neuroprotective activity [24]. Thoresen M. et al. experimentally demonstrated a reduction in the extent of damage and an improvement in neurological outcome after xenon inhalation following traumatic brain injury [25]. Campos-Pires R. et al. found that 50% xenon can reduce the severity of secondary brain damage during ischemia [26]. In addition, this concentration of xenon has a marked analgesic effect and has been successfully used in inhalation for pain after injury and burns [27], as well as for post-traumatic stress disorder [28]. Xenon has been shown to increase the neutrophil apoptosis potential. This confirms the anti-inflammatory properties of this gas [29].

The pathological cascade of glutamate excitotoxicity is implemented in the first minutes and hours after ischemic brain injury. During the first three days, neuronal and glial apoptosis occurs in the penumbra zone, often leading to the subsequent development of postischemic encephalopathy [30], so the study of the molecular mechanisms of neuroprotection during this period and the search for its pharmaceutical correction are essential for intensive care medicine.

Aim of the study: To determine the effect of different times of exposure to 0.5 MAC xenon on the level and phosphorylation (inactivation) of the enzyme glycogen synthase kinase-3β in the perifocal area of experimental ischemic stroke.

Materials and Methods

Experiments were performed on male Wistar rats weighing 300–350 g (*N*=49). The animals were deprived of food on the eve of the experiment, but had free access to water. The study protocol was approved by the local ethics committee. The experiments were performed in accordance with the requirements of Directive 2010/63/EU of the European Parliament and of the Council of the European Union on the protection of animals used for scientific purposes.

Under intraperitoneal anesthesia with 12% chloral hydrate 300 mg/kg, focal ischemia was simulated using the Long method. After a midline cervical incision and separation of the common carotid

artery from the right side, it was clamped with a vascular clip and a Vicryl 3–0 ligature was applied to the internal carotid artery. A 0.25-mm diameter silicone-coated nylon thread was inserted through a section of the external carotid artery into the internal carotid artery to a depth of 19–21 mm until it was occluded and fixed to the internal carotid artery with a vascular clip. Blood flow was occluded for 60 minutes, after which the suture was removed from the vessel, restoring blood supply to the area of the middle cerebral artery. Immediately after suture removal, the animals were randomly divided into 4 groups based on postoperative inhalation therapy:

— control group (*N*=10) with ischemic stroke received the oxygen-air mixture;

— study groups — 0.5 MAC xenon with exposures of 30 (*N*=10), 60 (*N*=9), and 120 (*N*=10) minutes.

The control group also consisted of sham-operated animals (*N*=10) that were anesthetized and underwent all phases of surgery except for blood flow occlusion and inhalation therapy.

On day 7 after ischemia, euthanasia was performed (decapitation under chloral hydrate anesthesia), brains were extracted and lysed in hot buffer (62.5 mM Tris-HCl, pH 6.8; 2% SDS; 10% glycerol; 50 mM DTT, 0.01% bromophenol blue) at 94°C for 4 minutes. Proteins were separated on a 12% polyacrylamide gel and transferred to PVDF membranes (Amersham, USA). Subsequently, 5% BSA in Tris buffer (25 mM Tris pH 7.4, 0.15M NaCl, 0.1% Tween20) blocked the nonspecific binding sites. The membranes were then incubated for 12 hours at +4°C with antibodies in 5% BSA/tris-buffer solution (antibodies against GSK-3β and phospho-GSK-3β (Cell Signaling, USA)). The membranes were incubated for 1 hour with the second antibodies (anti-mouse or rabbit immunoglobulins conjugated to horseradish peroxidase and diluted in 5% BSA/tris-buffer solution). Visualization was performed using a SuperSignal West Pico blotting panel (ThermoFisher, USA) on a Hitachi-557 spectrophotometer (Hitachi Ltd., Japan). ImageJ software was used for densitometric analysis. Levels of GSK-3β and the phosphorylated form of GSK-3β were expressed in arbitrary units (AU).

Statistical analysis was performed using Statistica 10.0 (StatSoft, Inc.) and MedCalc 12.5.0.0 (MedCalc Software bvba). The Shapiro-Wilk criterion was used to determine the type of distribution of the variables. Considering the non-normal distribution, the median with interquartile range was used for descriptive statistics. Intergroup differences in independent groups were assessed by the Kruskal-Wallis H-criterion with Dunn's a posteriori test (to address multiple hypothesis testing), and to compare GSK-3β and phospho-GSK-3β in related groups, the Wilcoxon test was used. Differences were considered significant at $P<0.05$.

Results and Discussion

Thrombolysis is the most effective treatment for ischemic stroke according to controlled trials; however, reperfusion therapy is performed in only 10% of cases due to potential contraindications [31]. Therefore, the search for neuroprotective therapies aimed at preventing, slowing down or interrupting molecular and biochemical processes during ischemic damage, such as mitochondrial dysfunction, overproduction of reactive oxygen species, production of pro-apoptotic proteins, apoptosis or neuronal necrosis, becomes important [32–36].

Inhalational anesthetics are widely used in medical practice, but the mechanisms of their anesthetic action, as well as their neuroprotective and neurotoxic effects when acting on the central nervous system remain incompletely studied and are the subject of active research [37, 38]. The neuroprotective effect of xenon has been demonstrated in a number of experimental works, but the molecular mechanisms of this phenomenon are still under investigation [3]. The protective properties of xenon have been shown to occur in ischemia even at preconditioning doses [39, 40], as demonstrated in an experiment in neonatal rats that had a reduced area of ischemic damage after gas inhalation [41], as well as in clinical studies of subanesthetic doses of 50% xenon in perinatal hypoxia-ischemia [42]. One of the key enzymes involved in neuroprotection may be GSK-3β [7, 8]. The Kruskal–Wallis test showed no significant differences in GSK-3β levels between all groups of animals studied (*P*=0.765). Thus, we found that ischemic stroke had no significant effect on GSK-3β levels, which increased by only 2.3% in the perifocal area compared to sham-operated animals (*P*=0.765). The inhalation of 0.5 MAK xenon with an exposure time of 30 minutes after restoration of brain blood flow also had no effect on GSK-3β levels, which were 0.7% higher than the control and 3% higher than the same parameter in the sham-operated animals (*P*=0.765).

Inhalation of 0.5 MAK xenon at 60 min exposure after restoration of brain blood flow did not result in a decrease in GSK-3β compared to the 30 min exposure: GSK-3β levels remained only 0.4% higher compared to control and 1.9% higher compared to sham-operated animals (*P*=0.765). Inhalation of 0.5 MAK xenon at 120 min exposure did not result in a decrease of GSK-3β compared to 60 min exposure, control and sham-operated animals (*P*=0.765). Thus, no significant differences were found between all groups studied, indicating the lack of effect of 0.5 MAK xenon on GSK-3β levels.

Phosphorylation of GSK-3β through a cascade of sophisticated reactions is known to limit inflammation and reduce neuronal apoptosis in the ischemic zone [19, 20].

Table. Densitometric analysis of Western blots for GSK-3β and phospho-GSK-3β enzyme levels in the perifocal zone of ischemic stroke on exposure to 0.5 MAC xenon, *Me* (*LQ*; *HQ*).

Animal groups (*n*) and exposure time	Levels, arbitrary units	
	GSK-3β	Phospho-GSK-3β
Sham-operated (*n*=10)	2058917 (1887323; 2587112)	1458767 (1287333; 1785132)#
Control (*n*=10)	2105765 (1907123; 2754439)	540277* (487337; 685111)
30 min exposure (*n*=10)	2121112 (1888543; 2659531)	752112 (598344; 878444)
60 min exposure (*n*=9)	2098155 (1785548; 2444768)	1109375* (998376; 1289335)
120 min exposure (*n*=10)	2020334 (1831546; 2567731)	1239325* (989444; 1315128)
Kruskal–Wallis H test	#*P*=0.765	**P*<0.001

Note. *P* — when comparing GSK-3β and Phospho-GSK-3β within groups.

We found significant differences in the levels of phosphorylated GSK-3β in the groups of animals studied ($P<0.001$, Kruskal-Wallis test).

The level of phosphorylated GSK-3β was 29.1% lower in sham-operated animals compared to its active form (Wilcoxon test, $P=0.005$). Ischemic stroke in control animals resulted in a marked decrease in phosphorylated GSK-3β in the perifocal area compared to sham-operated animals (2.7-fold, Dunn's test, $P<0.001$), with the level of phosphorylated GSK-3β being 74.3% lower compared to GSK-3β (Wilcoxon test, $P=0.005$), all indicating activation of the enzyme in the penumbral area.

Inhalation of 0.5 MAC xenon for 30 minutes after restoration of cerebral blood flow did not increase phosphorylated GSK-3β in the penumbra compared to controls (Dunn's test, $P=0.9$), but it remained 48.4% lower than in sham-operated animals (Dunn's test, $P<0.001$). The level of phosphorylated GSK-3β was 64.5% lower compared to its active form (Wilcoxon test, $P=0.003$). Sixty minutes of inhalation of 0.5 MAC xenon after restoration of cerebral blood flow resulted in a 2.1-fold increase in the level of phosphorylated GSK-3β in the penumbral area compared with controls (Dunn's test, $P=0.005$), but its level did not differ from that observed after 30 minutes of exposure to 0.5 MAC xenon (Dunn's test, $P=0.177$) or from that in sham-operated animals (Dunn's test, $P=0.461$). The level of phosphorylated GSK-3β was 47.1% lower than that of the active form (Wilcoxon test, $P=0.008$).

Inhalation of 0.5 MAC xenon after 120 minutes of exposure resulted in a 2.3-fold increase in phosphorylated GSK-3β in the perifocal area of ischemic stroke compared to controls (Dunn's test, $P=0.001$), but no increase in phosphorylated GSK-3β compared to 60 minutes of exposure (Dunn's test, $P=0.9$) and compared to sham-operated animals (Dunn's test, $P=0.9$). The level of phosphorylated GSK-3β in this group was 38.7% lower than its active form (Wilcoxon test, $P=0.005$).

The results showed that ischemic stroke in control animals led to a remarkable (2.7-fold, Dunn's test, $P<0.001$) decrease in the level of phosphorylated GSK-3β in the perifocal area of ischemic stroke, indicating activation of the enzyme in the penumbra and activation of neuronal apoptosis. The level of phosphorylated GSK-3β increased with prolonged exposure, whereas the level of the major form of GSK-3β did not change significantly. Inhalation of 0.5 MAC xenon for 30 minutes had no effect on phosphorylation (inactivation) of GSK-3β enzyme, whereas inhalation of xenon for 60 and 120 minutes resulted in increased phosphorylation of GSK-3β enzyme, decreased ratio of phosphorylated and active forms, and probably inhibition of neuronal apoptosis in the perifocal area of ischemic stroke.

Cytokines, NO derivatives, hormones, and oxidation products of nucleic acids and proteins are known to be involved in the initiation of apoptosis [34, 43]. Resolution of excitotoxicity plays a key role in primary neuroprotection in the acute phase of stroke [44]. Secondary neuroprotection includes reduction of delayed neuronal death and the severity of remote sequelae of ischemia, such as inactivation of NO synthase, blockade of oxidative stress, inhibition of proinflammatory cytokine production, mitochondrial protection, normalization of protein synthesis, and interruption of neuroapoptosis pathways [45]. In general, neuroprotective therapy should aim to both preserve and restore affected neurons as well as other cell populations that may have suffered ischemia, such as macro- and microglia, endothelial cells, and neutrophils [44, 46]. According to Smith W.S., therapeutic exposure to xenon reduces the severity of perivascular inflammation and decreases infarct volume, leading to improved neurological outcome [43]. Xenon inhalation has been found to disrupt abnormal functional connections between neurons and alter their metabolism by improving microcirculation and oxygen delivery [48, 49].

The observed increase in the level of phosphorylated GSK-3β confirms the possibility of its inactivation upon exposure to xenon. Kuzovlev A. N. et al. found that inhalation of 50% xenon for 30 minutes did not affect the level of GSK-3β enzyme, but caused an almost twofold increase in its phosphorylated form [24]. Likhvantsev V. V. et al. showed that the increase of phosphorylated GSK-3β can be observed after administration of sevoflurane and desflurane after experimental ischemia/reperfusion

simulation [23, 37]. Grebenchikov O. A. et al. demonstrated that phosphorylation of GSK-3β in neutrophils downregulates the expression of CD66b and CD11b degranulation markers on their surface [29, 50, 51].

Conclusion

Our results reveal a possible molecular mechanism of the neuroprotective and anti-inflammatory effect of xenon during brain ischemia/reperfusion through the inactivation of GSK-3β, which leads to the inhibition of neuroapoptosis in the perifocal area of ischemic stroke by reducing the ratio of phosphorylated to active forms of the enzyme. The results of the study show the prospects for clinical use of 0.5 MAC xenon inhaled for 60 and 120 minutes in ischemic and reperfusion brain damage due to stroke, traumatic brain injury and other causes.

References

1. *Kleindorfer D.O., Towfighi A., Chaturvedi S., Cockroft K.M., Gutierrez J., Lombardi-Hill D., Kamel H. et al.* Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2021; 52 (7): e364-e467. DOI: 10.1161/STR.0000000000000375. PMID: 34024117.
2. *Бабаева С.М., Полухова Ш.М., Казимова А.У., Алиев С.Г., Таиров И.А.* Нейропротекция и лимфоваскулярный компонент при нарушениях мозгового кровообращения. *Международный научно-исследовательский журнал*. 2022; 1 (115) 2: 71–74. [*Babayeva S.M., Polukhova Sh.M., Kazimova A.U., Aliyev S.H., Tahirov I.A.* Neuroprotection and lymphovascular component in cerebral circulatory disorders. *International Research Journal/ Mezhdunarodniy Nauchno-Issledovatelskiy Zhurnal*. 2022; 1 (115) 2: 71–74. (in Russ.)]. DOI: 10.23670/IRJ.2022.115.1.054.
3. *Гребенчиков О.А., Молчанов И.В., Шпичко А.И., Евсеев А.К., Шабанов А.К., Хусаинов Ш.Ж., Петриков С.С.* Нейропротективные свойства ксенона по данным экспериментальных исследований. *Журнал им. Н.В. Склифосовского Неотложная медицинская помощь*. 2020; 9 (1): 85–95. [*Grebenchikov O.A., Molchanov I.V., Shpichko A.I., Yevseyev A.K., Shabanov A.K., Khusainov S.Z., Petrikov S.S.* Neuroprotective properties of xenon according to experimental studies. *Russian Sklifosovsky Journal «Emergency Medical Care». Neotlozhnaya Meditsinskaya Pomoshch*. 2020; 9 (1): 85–95. (in Russ.)]. DOI: 10.23934/2223-9022-2020-9-1-85-95.
4. *Yang Q., Huang Q., Hu Z., Tang X.* Potential neuroprotective treatment of stroke: targeting excitotoxicity, oxidative stress and inflammation. *Front Neurosci*. 2019; 13: 1036. DOI: 10.3389/ fnins.2019.01036. PMID: 31611768.
5. *Ladak A.A., Enam S.A., Ibrahim M.T.* A Review of the molecular mechanisms of traumatic brain injury. *World Neurosurg*. 2019; 131: 126–132. DOI: 10.1016/j.wneu.2019.07.039. PMID: 31301445.
6. *Kim U.J., Lee B.H., Lee K.H.* Neuroprotective effects of a protein tyrosine phosphatase inhibitor against hippocampal excitotoxic injury. *Brain Res*. 2019; 1719: 133–139. DOI: 10.1016/j.brainres.2019.05.027. PMID: 31128098.
7. *Иванова С.А., Лосенков И.С. Бохан Н.А.* Роль киназы гликогенсинтазы-3 в патогенезе психических расстройств. *Журнал неврологии и психиатрии им. С.С. Корсакова*. 2014; 114 (6): 93–100. [*Ivanova S.A., Losenkov I.S., Bokhan N.A.* Role of glycogen synthase kinase-3 in the pathogenesis of mental disorders. *S.S. Korsakov Journal of Neurology and Psychiatry/ Zhurnal Nevrologii i Psikhiatrii imeni S.S. Korsakova*. 2014; 114 (6): 93–100. (In Russ.)]. https: //www.mediasphera.ru/issues/zhurnal-nevrologii-i-psikhiatrii-im-s-s-korsakova/2014/6/031997-72982014617.
8. *Григорьян Г.А.* Роль гликоген синтазы киназы-3 в механизмах обучения и памяти. *Журнал высшей нервной деятельности им. И. П. Павлова*. 2013; 63 (5): 507–519. [*Grigoryan G.A.* Role of glycogen synthase kinase-3 in mechanisms of learning and memory. *I.P. Pavlov Journal of Higher Nervous Activity / Zh Vyssh Nerv Deiat Im I P Pavlova*. (in Russ.)]. DOI: 10.7868/s0044467713050043. PMID: 25438579.
9. *Jope R.S.* Glycogen synthase kinase-3 in the etiology and treatment of mood disorders. *Front Mol Neurosci*. 2011; 4: 16. DOI: 10.3389/fnmol.2011.00016. PMID: 21886606.
10. *Li X., Jope R.S.* Is glycogen synthase kinase-3 a central modulator in mood regulation? *Neuropsychopharmacology*. 2010; 35 (11): 2143–2154. DOI: 10.1038/npp.2010.105. PMID: 20668436.
11. *Beaulieu J.M., Del'guidice T., Sotnikova T.D., Lemasson M., Gainetdinov R.R.* Beyond cAMP: the regulation of Akt and GSK3 by dopamine receptors. *Front Mol Neurosci*. 2011; 4: 38. DOI: 10.3389/fnmol.2011.00038. PMID: 22065948.
12. *Thornton T.M., Pedraza-Alva G., Deng B., Wood C.D., Aronshtam A., Clements J.L., Sabio G., Davis R.J. et al.* Phosphorylation by p38 MAPK as an alternative pathway for GSK3beta inactivation. *Science*. 2008; 320 (5876): 667–670. DOI: 10.1126/science.1156037. PMID: 18451303.
13. *Kim T.Y., Hur E.-M., Snider W.D., Zhou F-.Q.* Role of GSK3 signaling in neuronal morphogenesis. *Front Mol Neurosci*. 2011; 4: 48. DOI: 10.3389/fnmol.2011.00048. PMID: 22131966.
14. *Brabley C.A., Peineau S., Taghibiglou C., Nicolas C.S., Whitcomb D.J., Bortolotto Z.A., Kaang B.K., Cho K. et al.* A pivotal role of GSK-3 in synaptic plasticity. *Front Mol Neurosci*. 2012; 5: 13. DOI: 10.3389/fnmol.2012.00013. PMID: 22363262.
15. *Li X., Bijur N.G., Jope R.S.* Glycogen synthase kinase-3β, mood stabilizers, and neuroprotection. *Bipolar Disord*. 2002; 4: 2: 137–144. DOI: 10.1034/j.1399-5618.2002.40201.x. PMID: 12071511.
16. *Juhaszova M., Wang S., Zorov D.B., Nuss H.B., Gleichmann M., Mattson M.P., Sollott S.J.* The identity and regulation of the mitochondrial permeability transition pore where the known meets the unknown. *Ann N Y Acad Sci*. 2008; 1123: 197–212. DOI: 10.1196/annals.1420.023. PMID: 18375592.
17. *Zorov D.B., Juhaszova M., Yaniv Y., Nuss H.B., Wang S., Sollott S.J.* Regulation and pharmacology of the mitochondrial permeability transition pore. *Cardiovascular. Research*. 2009; 83 (2): 213–225. DOI: 10.1093/cvr/cvp151. PMID: 19447775.
18. *Borgquist J.D., Quinn M.T., Swain S.D.* Adhesion to extracellular matrix proteins modulates bovine neutrophil responses to inflammatory mediators. *J Leukoc Biol*. 2002; 71 (5): 764–774. PMID: 11994500.
19. *Wang H., Kumar A., Lamont R.J., Scott D.A.* GSK3β and the control of infectious bacterial diseases. *Trends Microbiol*. 2014; 22 (4): 208–217. DOI: 10.1016/j.tim.2014.01.009. PMID: 24618402.
20. *Ko R., Lee S.Y.* Glycogen synthase kinase 3p in Toll-like receptor signaling. *BMB Rep*. 2016; 49 (6): 305–310. DOI: 10.5483/BMBRep.2016.49.6.059. PMID: 26996345.
21. *Enman N.M., Unterwald E.M.* Inhibition of GSK3 attenuates amphetamine-induced hyperactivity and sensitization in the mouse. *Behav Brain Res*. 2012; 231 (1): 217–225. DOI: 10.1016/j.bbr.2012.03.027. PMID: 22649795.
22. *Gould T.D., Einat H., Bhat R., Manji H.K.* AR-A014418, a selective GSK-3 inhibitor, produces antidepressant-like effects in the forced swim test. *Int J Neu-*

ropsychopharmacol. 2004; 7 (4): 387–390. DOI: 10.1017/S1461145704004535. PMID: 15315719.

23. *Pizarro J.G., Yeste-Velasco M., Rimbau V., Casadesus G., Smith M.A., Pallàs M., Folch J. et al.* Neuroprotective effects of SB-415286 on hydrogen peroxide-induced cell death in B65 rat neuroblastoma cells and neurons. *Int J Devl Neurosci*. 2008; 26 (3): 269–276. DOI: 10.1016/j.ijdevneu.2008.02.002. PMID: 18342477.
24. *Лихванцев В.В., Гребенчиков О.А., Черпаков Р.А., Скрипкин Ю.В., Борисов К.Ю.* Влияние прекондиционирования десфлураном на содержание фосфорилированной формы гликоген синтетазы-киназы 30 в эксперименте. *Общая реаниматология*. 2016; 12 (6): 8–15. [*Likhvantsev V.V., Grebenchikov O.A. Cherpakov R.A., Skripkin Y.V. Borisov K.Yu.* Effect of preconditioning with desflurane on phosphorylated glycogen synthase kinase 3β contents in an experiment. *General Reanimatology/Obshchaya Reanimatologya*. 2016; 12 (6): 8–15. (in Russ.)]. DOI: 10.15360/1813-9779-2016-6-8-15.
25. *Кузовлев А.Н., Шпичко А.И., Рыжков И.А., Гребенчиков О.А., Шабанов А.К., Хусаинов Ш.Ж., Цоколаева З.И., Лобанов А.В.* Влияние ксенона на фосфорилирование киназы гликогенсинтазы-3р и антиоксидантные ферменты в мозге крыс. *Журнал им. Н.В. Склифосовского Неотложная медицинская помощь*. 2020; 9 (4): 564–572. [*Kuzovlev A.N., Shpichko A.I., Ryzhkov I.A., Grebenchikov O.A., Shabanov A.K., Khusainov S.Z., Tsokolaeva Z.I. et al.* Effect of xenon on the phosphorylation of glycogen synthase kinase 3β and antioxidant enzymes in rat brain. *Russian Sklifosovsky Journal «Emergency Medical Care». Neotlozhnaya Meditsinskaya Pomoshch*. 2020; 9 (4): 564–572. (in Russ).] DOI: 10.23934/ 2223-9022-2020-9-4-564-572.
26. *Thoresen M., Hobbs C.E., Wood T., Chakkarapani E., Dingley J.* Cooling combined with immediate or delayed xenon inhalation provides equivalent long-term neuroprotection after neonatal hypoxia-ischemia. *J Cereb Blood Flow Metab*. 2009; 29 (4): 707–714. DOI: 10.1038/jcbfm.2008.163. PMID: 19142190.
27. *Campos-Pires R., Armstrong S.P., Sebastiani A., Luh C., Gruss M., Radyushkin K., Hirnet T. et al.* Xenon improves neurological outcome and reduces secondary injury following trauma *in* an *in vivo* model of traumatic brain injury. *Crit Care Med*. 2015; 43 (1): 149–158. DOI: 10.1097/CCM. 0000000000000624. PMID: 25188549.
28. *Генов П.Г., Смирнова О.В., Тимербаев В.Х.* Ксенон для послеоперационного обезболивания. А почему бы и нет? *Анестезиология и реаниматология*. 2011; 3: 74–77. [*Genov P.G., Smirnova O.V., Timerbaev V.H.* Xenon for postoperative analgesia. Why not? *Anesthesiol.Reanimatol/ Anesteziologiya i Reanimatologiya*. 2011; 3: 74–77. (in Russ).] eLIBRARY ID: 16501272.
29. *Герасимова Ю.Ю., Ермаков М.А.* Нейропротективные эффекты субнаркотических и наркотических концентраций медицинского ксенона. *Вестник совета молодых ученых и специалистов Челябинской области*. 2017; 3 (3): 21–24. [*Gerasimova Y.Y., Ermakov M.A.* Neuroprotective effects of sub-narcotic and narcotic concentrations of medical xenon. *Bulletin of the Council of Young Scientists and Specialists of the Chelyabinsk region/ Vestnik Soveta Molodyh Uchenyh i Spetcialistov Chelyabinskoy Oblasti*. 2017; 3 (3): 21–24. (in Russ.)]. eLIBRARY ID: 30672509. UDC: 616.89-008.441.33-085.21. EDN: ZVFJIV.
30. *Гребенчиков О.А., Шабанов А.К., Николаев Л.Л., Шпичко А.И., Братищев И.В., Марченко Л.Ю. Хусаинов Ш.Ж. с соавт.* Влияние ксенона на провоспалительную активацию и апоптоз нейтрофилов человека в условиях *ex vivo*. *Журнал им. Н.В. Склифосовского Неотложная медицинская помощь*. 2021; 10 (3): 511–520. [*Grebenchikov O.A., Shabanov A.K., Nikolaev L.L., Shpichko A.I., Bratishchev I.V., Marchenko L.Yu. Khusainov Sh.Zh. et al.* Effect of xenon on proinflammatory activation and apoptosis of human neutrophils under *ex vivo* conditions. *Russian Sklifosovsky Journal «Emergency Medical Care» / Zhurnal im. N.V. Sklifosovskogo «Neotlozhnaya Meditsinskaya Pomoshch»*. 2021; 10 (3): 511–520. (in Russ.)]. DOI: 10.23934/2223-9022-2021-10-3-511-520.
31. *Laitio R., Maze M.* Xenon limits brain damage following cardiac arrest. *Management & Practice*. 2018; 18 (3): 192–195. https: //healthmanagement.org/c/icu/issuearticle/xenon-limits-brain-damage-following-cardiac-arrest.
32. *Домашенко М.А., Максимова М.Ю., Сергеев Д.В., Пирадов М.А.* Цитиколин в лечении ишемических нарушений мозгового кровообращения. *РМЖ*. 2013; 30: 1540. [*Domashenko M.A., Maksimova M.Yu., Sergeev D.V., Piradov M.A.* Citicoline in the treatment of ischemic cerebral circulatory disorders. *Russian Medical Journal /Rossiyskiy Meditsinskiy Zhurnal*. 2013; 30: 1540. (in Russ).] eLIBRARY ID: 21092041. EDN: RTOMLL.
33. *Ginsberg M.D.* Neuroprotection for ischemic stroke: past, present and future. *Neuropharmacology*. 2008; 55 (3): 363–389. DOI: 10.1016/j.neuropharm.2007.12.007. PMID: 18308347.
34. *Беленичев И.Ф., Черний В.И., Нагорная Е.А., Павлов С.В., Черний Т.В., Горчакова Н.А., Бухтиярова Н.В. с соавт.* Нейропротекция и нейропластичность. Киев: Полиграф Плюс; 2014: 512. [*Belenichev I.F., Cherniy V.I., Nagornaya E.A., Pavlov S.V., Cherniy T.V., Gorchakova N.A., Bukhtiyarova N.V. et al.* Neuroprotection and neuroplasticity. Kiev: Polygraph Plus; 2014: 512. (in Russ.)]. ISBN 978-966-171-899-8.
35. *Chen S.-D., Yang D.-I., Lin T.-K. Shaw F.-Z., Liou C.-W., Chuang Y.-C.* Roles of oxidative stress, apoptosis, PGC-la and mitochondrial biogenesis in cerebral ischemia. *Int J Mol Sci*. 2011; 12 (10): 7199–7215. DOI: 10.3390/ ijms12107199. PMID: 22072942.
36. *Ginsberg M.D.* Neuroprotection for ischemic stroke: past, present and future. *Neuropharmacology*. 2008; 55 (3): 363–389. DOI: 10.1016/j.neuropharm. 2007.12.007. PMID: 18308347.
37. *Muresanu D.F.* Neuroprotection and neuroplasticity — a holistic approach and future perspectives. *J Neurol Sci*. 2007; 257 (1–2): 38–43. DOI: 10.1016/j.jns. 2007.01.041. PMID: 17331543.
38. *Лихванцев В.В., Скрипкин Ю.В., Гребенчиков О.А.* Изучение клинической значимости анестетического прекондиционирования (открытая база данных). *Общая реаниматология*. 2014; 10 (4): 82–85. [*Likhvantsev V.V., Skripkin Yu.V., Grebenshchikov O.A.* Investigation of the clinical value of

anesthetic preconditioning (an openaccess database). *General Reanimatology/Obshchaya Reanimatologya*. 2014; 10 (4): 82–85. (in Russ.)]. DOI: 10.15360/1813-9779-2014-4-82-85.

39. *Сабинина Т.С., Багаев В.Г., Алексеев И.Ф.* Перспективы применения лечебных свойств ксенона в педиатрии. *Педиатрическая фармакология*. 2018; 15 (5): 390–395. [*Sabinina T.S., Bagaev V.G., Alekseev I.F.* Prospects for applying xenon curative properties in pediatrics. *Pediatric pharmacology/Pediatricheskaya Farmakologiya*. 2018; 15 (5): 390–395. (in Russ.)]. DOI: 10.15690/pf.v15i5.1961.
40. *Esencan E., Yuksel S., Tosun Y.B., Robinot A., Solaroglu I. Zhang J.H.* Xenon in medical area: emphasis on neuroprotection in hypoxia and anesthesia. *Med Gas Res*. 2013; 3 (1): 4. DOI: 10.1186/2045-9912-3-4. PMID: 23369273.
41. *Rizvi M., Jawad N., Li Y., Vizcaychipi M.P., Maze M., Ma D.* Effect of noble gases on oxygen and glucose deprived injury in human tubular kidney cells. *Exp Biol Med (Mayywood)*. 2010; 235 (7): 886–891. DOI: 10.1258/ebm.2010.009366. PMID: 20472713.
42. *Dingley J., Tooley J., Porter H., Thoresen M.* Xenon provides short-term neuroprotection in neonatal rats when administered after hypoxia-ischemia. *Stroke*. 2006; 37 (2): 501–506. DOI: 10.1161/01.STR.0000198867.31134.ac. PMID: 16373643.
43. *Dworschak M.* Pharmacologic neuroprotection — is xenon the light at the end of the tunnel? *Crit Care Med*. 2008; 36 (8): 2477–2479. DOI: 10.1097/CCM.0b013e31818113d2. PMID: 18664813.
44. *Smith W.S.* Pathophysiology of focal cerebral ischemia: a therapeutic perspective. *J Vasc Interv Radiol*. 2004; 15 (1 Pt 2): S3–12. DOI: 10.1097/01.rvi.0000108687.75691.0c. PMID: 15101511.
45. *Belov Kirdajova D., Kriska J., Tureckova J., Anderova M.* Ischemia-Triggered Glutamate Excitotoxicity From the Perspective of Glial Cells. *Front Cell Neurosci*. 2020; 14: 51. DOI: 10.3389/fncel.2020.00051. PMID: 32265656.
46. *Yang C., Hawkins K.E., Doré S., Candelario-Jalil E.* Neuroinflammatory mechanisms of blood-brain barrier damage in ischemic. *Am J Physiol Cell Physiol*. 2019; 316 (2): C135–153. DOI: 10.1152/ajpcell.00136.2018. PMID: 30379577.
47. *Буров Н.Е., Потапов В.Н.* Ксенон в медицине: очерки по истории и применению медицинского ксенона. М.: Пульс. 2012: 406. [*Burov N.E., Potapov V.N.* Xenon in medicine: essays on the history and application of medical xenon. M.: Pulse. 2012: 406. (in Russ.)]. ISBN: 978-5-93486-066-1.
48. *Старостин Д.О., Кузовлев А.Н., Гребенчиков О.А., Долгих В.Т.* Влияние севофлурана на активацию нейтрофилов человека в моделях *ex vivo*. *Вестник анестезиологии и реаниматологии*. 2022; 19 (1): 32–39. [*Starostin D.O., Kuzovlev A.N., Grebenshchikov O.A., Dolgikh V.T.* Effect of sevoflurane on activation of human neutrophils in *ex vivo* models. *Messenger of Anesthesiology and Resuscitation/Vestnik Anesthesiologii i Reanimatologii*. 2022; 19 (1): 32–39. (in Russ.)] DOI: 10.21292/2078-5658-2022-19-1-32-39.
49. *Кузовлев А.Н., Гребенчиков О.А., Мешков М.А., Долгих В.Т., Прокофьев М.Д., Шпичко Н.П., Ершов А.В.* Влияние хлорида лития на эндотелиоциты при синдроме системной воспалительной реакции у пациентов с тяжелой сочетанной травмой. *Вестник интенсивной терапии им. А.И. Салтанова*. 2020; 3: 115–121. [*Kuzovlev A.N., Grebenchikov O.A., Meshkov M.A., Dolgikh V.T., Prokofiev M.D., Shpichko N.P., Ershov A.V.* Influence of lithium chloride on the apoptosis of endotheliocytes in systemic inflammatory response syndrome in patients with severe multiple injury. A retrospective study. *Ann Crit Care /Vestnik Intensivnoy Terapii im AI Saltanova*. 2020; 3: 115–121. (in Russ.)]. DOI: 10.21320/1818-474X-2020-3-115-121.
50. *Гребенчиков О.А., Кулабухов В.В., Шабанов А.К., Игнатенко О.В., Антонова В.В., Черпаков Р.А., Редкин И.В. с соавт.* Перспективы применения ингаляционной седации в интенсивной терапии. *Анестезиология и реаниматология*. 2022; (3): 84–94. [*Grebenchikov O.A., Kulabukhov V.V., Shabanov A.K., Ignatenko O.V., Antonova V.V., Cherpakov R.A., Redkin I.V.* et al. Prospects of inhalation sedation in intensive care. *Anesthesiol.Reanimatol/ Anesteziologiya i Reanimatologiya*. 2022; (3): 84–94. (in Russ.)]. DOI: 10.17116/anaesthesiology202203184.

Received 17.10.2022
Accepted 02.03.2023