https://doi.org/10.23934/2223-9022-2020-9-1-85-95

Neuroprotective Properties of Xenon According to Experimental Studies

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ABSTRACT An increase in the number of patients with severe brain damage of various etiologies determines the need to improve neuroprotection technologies. The review is devoted to modern views on the mechanisms of brain protection, as well as the basic processes underlying damage to neurons. The article discusses the results of the most important experimental studies in this area using inert xenon gas. The authors analyzed a number of works highlighting neurotective properties of the xenon inhalation anesthetic in studies performed in vitro and in vivo. The main mechanisms of neuronal death depending on the type of damage are shown, the points of application of the protective effect of xenon on the brain and the prospects for further research in this area are demonstrated in the article.

Keywords: xenon, neuroprotection, stroke, traumatic brain injury, subarachnoid hemorrhage

For citation Grebenchikov OA, Shpichko AI, Yevseyev AK, Molchanov IV, Shabanov AK, Khusainov SZ, et al. Neuroprotective Properties of Xenon According to Experimental Studies (a Literature Review). *Russian Sklifosovsky Journal of Emergency Medical Care.* 2020;9(1):00–00. https://doi.org/10.23934/2223-9022-2020-9-1- (in Russ.)

Conflict of interest Authors declare lack of the conflicts of interests

Acknowledgments, sponsorship The study had no sponsorship

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ATP — adenosine triphosphate
SAH — subarachnoid hemorrhage
TBI — traumatic brain injury
tPA — tissue plasminogen activator

INTRODUCTION

Pathologies associated with acute circulatory disorders of organs and their subsequent dysfunction occupy a leading place in the structure of mortality throughout the world. Diseases associated with cardiovascular disorders are in the first place. Ischemic stroke ranks second among the causes of death, and more than 450,000 people suffer from it in the Russian Federation annually. The early 30-day mortality rate after stroke is more than 25%, and about half of the cases die within a year, which is more than 200,000 people [1].

The consequences of stroke rank first among the causes of primary disability [2, 3]. No more than 15% of stroke survivors return to work or full-fledged fulfillment of their previous household duties, and the rest, due to disability, need lifelong medical and social support. The number of people with disabilities who have suffered a stroke is approaching 1,000,000 and 25% of them have severe dementia. As a result, the quality of life of not only the patient, but also the relatives and friends living with him sharply deteriorates [4]. It is important to note that in the last decade there has been an increase in the number of strokes by more than 25% [5].

At the same time, there is an increase in the number of patients with traumatic brain injury (TBI), mortality and disability from TBI, as in stroke, is extremely high [6]. About 600,000 people get TBI in Russia every year. More than 50,000 of them die, and about 240,000 become disabled [7, 8].

However, to date, all available neuroprotective drugs tested in multifocal clinical trials are not effective enough [9, 10]. Therefore, the development of new approaches to the treatment of severe brain injuries of various etiologies is one of the most important tasks of critical care medicine. Understanding the molecular mechanisms underlying neuronal damage will enable the search for effective therapeutic strategies and technologies that provide their protection.

The latter requirements can be met by the inhalation anesthetic xenon, which, judging by a large amount of recent experimental data, has pronounced neuroprotective properties. Neuroprotection is the ability of therapy to prevent the death of neuronal cells by suppressing the pathogenetic cascade that leads to their dysfunction and possible death [11].

Xenon is an inert gas that contains only 89 ppb in the atmosphere. Half a century after the discovery of xenon by Sir William Ramsay and Dr. Morris Travers in 1838, Lawrence reported on its anesthetic properties obtained in preclinical studies in mice [12]. Shortly thereafter, Cullen and Gross first used xenon as a general anesthetic. They reported successful anesthesia in two patients using a breathing mixture containing 80% xenon and 20% oxygen. One patient was an 81-year-old man who underwent orchiectomy, and the other was a 38-year-old woman who underwent tubal ligation surgery [13]. This was followed by a report on the use of xenon in 5 patients who underwent hernioplasty [14]. It is important to note that when examining 28 patients, the same group of authors found that the minimum alveolar concentration of xenon is 71% [15]. More recent estimates of the minimum alveolar xenon concentration range from 63 to 68% [16, 17]. Over the next two decades, little attention was paid to the use of xenon as a general anesthetic.

It is important to note that only 50 years after the first clinical use of xenon, thanks to the works of Russian researchers under the guidance of Professor N.E. Burov in 2000, Russia received permission for the clinical use of xenon as a general anesthetic, while in Western Europe its use was allowed for general anesthesia in patients of groups 1–2 on the ASA scale only in 2005 [18].

The approval for the clinical use of xenon has largely stimulated the experimental work that revealed its neuroprotective properties [19–21].

When it was discovered that xenon is an inhibitor of NMDA receptors [22], it was shown that xenon can protect neuronal cell cultures from damage caused by NMDA, glutamate, or oxygen-glucose deprivation [19].

Brain damage from ischemic or hemorrhagic stroke, cardiac arrest, or TBI triggers a number of similar (but not identical) types of pathophysiological responses.

All such damage is based on a common mechanism of excitotoxicity, through which NMDA receptors contribute to the pathogenesis of neurodegenerative disorders.

The mechanisms mediating neuronal damage are multifactorial, with NMDA receptor-mediated excitotoxicity being the major factor.

The NMDA receptor is a type of cation-permeable ionotropic receptor that provides rapid excitatory synaptic transmission via glutamate, the main excitatory neurotransmitter in the mammalian central nervous system [23, 24]. Physiological activity of the NMDA receptor is required for many important neurological functions, including synaptic plasticity, memory formation, mood control, reward motivation, brain development and neuronal survival [23, 25–27]. However, overactivation of the NMDA receptor under pathological conditions can lead to neuronal death in a process known as excitotoxicity [25, 28, 29].

Excitotoxicity occurs when neurons are exposed to high doses of glutamate, which causes persistent activation of N-methyl-d-aspartate receptors (NMDA receptors) and α-amino-3-hydroxy-5-methylisoxazole propionic acid receptors (AMPA receptors), resulting in to excess calcium intake through calcium channels and creates conditions for the “lethal” influx of extracellular calcium [30–32].

The mechanisms when excessive calcium influx leads to apoptosis are complex and not well understood. Accumulating evidence suggests several intracellular molecular and signaling pathways, including mitochondrial dysfunction, production of reactive oxygen species, and activation of catabolic enzymes that degrade proteins, nucleic acids, and other cellular components. While similar mechanisms by which NMDA receptor overactivation occurs leading to excitotoxicity, a large body of evidence suggests that NMDA receptor-mediated excitotoxicity is a common mechanism mediating the pathogenesis of many neurodegenerative disorders, from acute events such as stroke and brain trauma, to chronic neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and Huntington's disease [33].

It should be noted that to date, a role has been discovered in the implementation of molecular mechanisms of neuroprotection by xenon of double-pore potassium channels (TREK-1), which provide a basic ionic current that weakens neuronal excitability, in turn, thereby ensuring the protection of neurons from damage (a similar mechanism has been described for implementation the phenomenon of preconditioning caused by sevoflurane) [34]. The scientific literature also discusses the role of adenosine triphosphate (ATP)-sensitive potassium channels of the plasma membrane in the implementation of the protective properties of xenon. It was shown that in vitro xenon protected them from damage caused by deprivation of glucose and oxygen by activating ATP-sensitive potassium channels in the plasmalemma in cultured neurons [35].

In our review, we propose to consider the points of application for the implementation of the neuroprotective properties of xenon in different mechanisms of neuronal damage.

TRAUMATIC BRAIN INJURY

Macroscopically, several types of brain damage can be noted. These include diffuse axonal injury, brain contusion, intracerebral hematoma, and cerebral edema. After a few hours or days, a second wave of damage develops, which is characterized by excitotoxicity, free radical formation, mitochondrial dysfunction, mass effect, ischemia, and an inflammatory response. Thus, we can assume that TBI is a progressive disease in which internal pathophysiological and systemic secondary processes (for example, hypoxia and hypotension) aggravate the primary injury [36]. In addition, it has been demonstrated that axonal damage may be secondary to metabolic changes [37]. This finding is extremely important because it opens a window for potential therapeutic interventions.

In vivo animal studies show that the use of xenon directly or even 1–3 hours after injury reduces the amount of damage and improves neurological parameters in mice [38]. An increase in the duration of inhalation up to 3 hours, in addition to reducing the area of secondary damage, improves vestibulomotor function and prevents the development of memory deficit in the late period of TBI. In addition, there was a decrease in white matter loss in the contralateral corpus callosum and in neuronal death in the CA1 contralateral hippocampus and dentate gyrus after 20 months. The long-term neuroprotective effects of xenon have been shown to be associated with a significant reduction in neuroinflammation in multiple brain regions involved in associative memory, including a decrease in reactive astrogliosis and microglial cell proliferation [39]. Thus, we can talk about persistent neuroprotection, the effects of which persisted even 20 months after TBI.

Modeling TBI in vitro using damage to organotypic cultures of mouse hippocampus slices by explosive exposure to air showed that treatment of drugs with 50% xenon 1 hour after injury shows a decrease in the severity of damage to 31–47%, and the most significant neuroprotective effects are manifested up to 72 hours after injury. In addition, caspase-dependent cell death was established in a model of explosive injury [40].

In the model of mechanical damage in vitro, we see that in the preparations of organotypic cultures of sections of the mice hippocampus treated with 50% xenon, much more significant cell survival is observed, and a decrease in the development of secondary damage is also noted. In addition, glycine was shown to weaken the action of xenon on the NMDA receptor, which suggests that the neuroprotective effect of xenon is mediated by inhibition of the NMDA receptor at the glycine site [41].

Table 1 shows experimental studies proving the neuroprotective properties of xenon in in vitro and in vivo models of TBI.

Table 1.

Experimental works demonstrating neuroprotective properties of xenon in models with TBI in vitro and in vivo.

Study	Model	Procedure	Results
In vitro			
Campos-Pires R., Koziakova M., Yonis A., et al. (2018) [40].	Organotypic cultures of hippocampal slices of 5-7-day-old mice were blown by air from a tube (simulating an explosive injury) — shock wave 55 kPa (duration 0.4 msec; pulse 10.3 kPa • msec)	In 1 hour, culture sections were placed in a chamber with 50% Xe and 50% air	31-47% reduction in damage Xenon prevents explosive damage that develops up to 72 hours after injury Explosion exposure triggers caspase- dependent cell death
Lavaur J., Le Nogue D., Lemaire M., et al. (2017) [72].	Midbrain cells containing dopamine neurons, and astroglial cells of 15.5-day-old mouse embryos, were exposed to a synthetic analogue of glutamate – L-trans-pyrrolidine-2.4-dicarboxylic acid (l-trans-pyrrolidine-2.4-dicarboxylic acid (PDC)) and from day 12 to 16 days they were cultivated in a growth medium to create a slow and steady process of excitotoxicity	The tablets are gas-treated: Xe 75%/O_2 20%/CO_2 5%	Xenon protects dopamine receptors from degeneration through antagonism of NMDA receptors, preventing oxidative stress Neuroprotection of dopamine neurons by xenon is the result of repression of the glial-dependent mechanism Xenon reduces damage to dopamine neurons caused by oxidative stress due to excess glutamate
	Mid-brain cell culture containing dopamine neurons of 15.5-day-old embryos in the culture medium that spontaneously degenerated over time, from the 7th to the 14th day of cultivation in a growth medium	The tablets are gas-treated: Xe 75%/O_2 20%/CO_2 5%	Xenon provides protection for the spontaneous death of dopamine neurons

Harris K., Armstrong S.P., Campos-Pires R[EE1]., et al. (2013) [41].	Organotypic cultures of hippocampal slices of 6-day-old mice were mechanically damaged by stylus drop, impact energy 3.5 μJ, impact caused focal injury with a diameter of 340 ± 12 μm, damage was quantified by the fluorescence of propidium iodide	In 1 hour, the culture sections were placed in a chamber with 50% xenon and 50% air	Damage in sections treated with xenon is less than in untreated ones: In 24 hours – by 57 ± 3% (*P* <0.001), In 48 hours – by 56 ± 3%; *P* <0.001), In 72 hours – 43 ± 3% (*P* <0.001) Xenon reduces the development of secondary damage to neurons Glycine weakens the effect of xenon on the NMDA receptor The neuroprotective effect of xenon is mediated by inhibition of the NMDA receptor in the glycine site
Coburn M., Maze M., Franks N.P. (2008) [42].	Organotypic cultures of hippocampal sections of 7-day-old C57 / BL6 mice were mechanically damaged by stylus drop, impact energy 3.5 μJ, impact caused focal injury with a diameter of 750 ± 17 μm, damage to neurons was quantified using propidium iodide	Slice cultures treated with gas composition: Xe 75%/O_2 20%/CO_2 5%	Processing of 75% xenon immediately after trauma: primary damage is twice smaller, secondary damage is more than four times smaller in comparison with the control group Xenon shown neuroprotective properties in the processing sections 2 and 3 hours after the injury in respect of primary and secondary damage, but with less efficiency
In vivo			
Campos-Piries R., Himet T., Valeo F., et al. (2019) [39].	Male mice, controlled cortical exposure	Inhalation of 75% Xe, 25% O_2 for 3 hours	Significantly reduced secondary damage (*P* <0.05), Improving short-term vestibulomotor function (*P*<0.01) and Prevention of memory deficiency in the late TBI Reducing the loss of white matter in the contralateral corpus callosum and the loss of neurons in the contralateral hippocampus CA1 and dentate gyrus 20 months later. Decreased neuroinflammation in areas of the brain involved in associative memory Decreased reactive astrogliosis and microglia cell proliferation Significant survival improvement (*P* <0.05) 12 months after injury
Campos-Pires R., Armstrong S.P., Sebastiani A., et al. (2015) [38].	Male mice, controlled cortical exposure	75% Xe, 50% Xe or 30% Xe	The use of xenon after head injury improves neurological outcome and reduces the amount of damage in mice

STROKE

There are 2 main types of stroke - ischemic and hemorrhagic stroke. Ischemic strokes account for about 87% of all strokes [42].

Ischemic stroke occurs as a result of thrombotic or embolic block of cerebral arteries, which leads to restriction of blood flow in the affected brain tissue, followed by depletion of energy. This causes a number of complex pathophysiological events, including impairment of ion homeostasis, accumulation of synaptic and extrasynaptic glutamate, impaired function of ion channels, damage to membranes and DNA, inflammation, and so on, ultimately leading to ischemic brain damage and neuronal death [28, 43– 45].

Intracerebral hemorrhage is any bleeding within the skull, including the brain parenchyma and surrounding meningeal spaces. During intracerebral hemorrhage, blood accumulates in the brain parenchyma, which leads to damage to anatomical structures and an increase in local pressure. Primary damage to the brain tissue occurs within minutes or hours and is mainly the result of mechanical stress on the tissue associated with the mass effect [46]. Secondary damage can be realized through many pathological mechanisms. These include blood cytotoxicity [47, 48], hypermetabolism [49], excitotoxicity [50], oxidative stress and inflammation [48, 51-57]. At the site of hemorrhage, inflammatory mediators are produced, causing secondary damage, involving microglial cells and macrophages in the process, which are necessary to remove cellular debris from the hematoma area, as well as a source of ongoing inflammation [58].

Xenon neuroprotection in these conditions may have good prospects, since according to modern concepts, in all types of ischemic or hemorrhagic stroke or subarachnoid hemorrhage (SAH), common pathogenetic mechanisms of neuronal death are ultimately observed.

In a model of ischemic stroke in vivo by intraluminal injection of an autologous blood clot followed by inhalation of xenon during ischemia and in the postischemic period, distinct neuroprotective properties of xenon are shown.

In addition, it has been shown in vitro that xenon can alter the catalytic efficiency of tissue plasminogen activator (tPA). This study found xenon to be a tPA inhibitor; xenon, which was used during ischemia, dose-dependently inhibits tPA-induced thrombolysis and subsequent reduction of ischemic brain damage; inhalation of xenon after ischemia actually suppresses ischemic brain damage and tPA-induced cerebral hemorrhages, as well as disruption of the blood-brain barrier. Taken together, these data indicate that xenon should not be administered prior to or during tPA therapy; Xenon can possibly be used to treat acute ischemic stroke if it is used after tPA-induced reperfusion [59].

Exposure to xenon after transient ischemia in rats leads to a decrease in the infarction volume depending on the concentration, exposure time and improvement of neurological function 7 days after the ischemic event. Although xenon did not improve the neurological assessment 28 days after ischemia, its combination with mild hypothermia improves neurological outcome, and the combination of its inhalation with hypothermia improves the outcome in cerebral hemorrhage [60].

Subarachnoid hemorrhage after ruptured aneurysm accounts for about 5% of all strokes, affects a relatively young age and has a poor prognosis [63].

Although occlusion of the aneurysm using endovascular surgery effectively prevents repeated bleeding, cerebral vasospasm and subsequent cerebral ischemia are the cause of high mortality in this pathology. A significant number of experimental and clinical studies have been carried out to find ways to prevent these complications, but so far no significant results have been achieved [64].

Therefore, the solution to the problem of neuroprotection in this pathology is also beyond doubt.

Recently, interesting experimental work has appeared on the study of the protective properties of xenon in subarachnoid hemorrhage.

The study of subarachnoid hemorrhage in rats by M. Veldeman et al. (2017) is of particular interest. In animals that received 50 vol.% Xenon for 1 hour after SAH, less significant damage to neurons in the ipsilateral regions of the hippocampus (CA3 region) and dentate gyrus was noted compared to the control group. In animals treated with xenon, fewer microglial cells were observed, which indicates the immunomodulatory effect produced by xenon [65].

In the work of Y.F. Miao et al. (2018) carried out an interesting study on the delivery of xenon to the lesion focus by xenon-containing echogenic liposomes (Xe-ELIP) using a SAH model in rodents by means of ultrasound-controlled release. The drug was administered intravenously in combination with ultrasound stimulation of the common carotid artery to induce the release of xenon from circulating Xe-ELIPs. The study showed a decrease in apoptotic neuronal death and bleeding volume. The authors note an improvement in neurological assessment, a decrease in the severity of motor dysfunction, and a decrease in mortality in the Xe-ELIP treated group compared with the control group [66].

Table 2 shows experimental studies proving the neuroprotective properties of xenon in in vitro and in vivo models for stroke and SAH

Table 2.

Experimental works demonstrating neuroprotective properties of xenon in models with stroke and SAH in vitro and in vivo.

Study	Model	Procedure	Results
In vitro			
Shu Y., Patel S.M., Pac-Soo C., et al. (2010) [66].	Preparations of cortex and hyppocampus of 7-day-old rats after anesthetic treatment in vivo (neuronal apoptosis induced with anesthetics in vivo)	Preconditioning of 70% Xe or 70% N_2O or 8% O_2 within 2 hours, after 24 hours inhalation of 70% N_2O +0,75% isoflurane for 6 hours	Xe – significantly reduces the number of caspase-3 cells N_2O – no significant effect Hypoxic preconditioning – a significant increase in caspase-3 positive cells
	Organotypic cultures of hippocampal slices (neuronal apoptosis induced by anesthetics in vitro) were stained with cleaved caspase-3	Preconditioning of 70% Xe or 70% N_2O or 8% O_2 for 2 hours, after 24 hours treatment with 70% N_2O+0, 75% isoflurane for 6 hours	Xenon – significantly reduces the number of caspase-3 cells N_2O – no significant effect Hypoxic preconditioning – a significant increase in the number of caspase-3 positive cells Xenon is effective in suppressing induced apoptosis.

Banks P., Franks N.P., Dickinson R. (2010) [21].	Organotypic cultures of hippocampal sections were subjected to oxygen-glucose deprivation	50% xenon immediately after damage 50% xenon 3 hours after damage 50% xenon 6 hours after damage	70% reduction in neuronal damage 40% reduction in neuronal damage Abscence of neuroprotection
David H.N., Haelewyn B., Risso J.J., et al. (2010) [60].	A recombinant form of tissue plasminogen activator (tPA) in human and mice in vitro	The substrate was diluted in distilled water and saturated with xenon from 25 to 75 vol.%	Xenon is a tissue plasminogen inhibitor
Bantel C., Maze M., Trapp S. (2009) [35].	Cultures of neuroclonal- glial cells of 1-2-day-old mice were subjected to oxygen-glucose deprivation for 75 min	Preconditioning with gas composition for 2 hours: Xe75%/O_2 20%/CO_2 5% or Sevoflurane 3.3%/N_2 71.7%/O_2 20%/CO_2 5%	Preconditioning with xenon or sevoflurane opening potassium channels 24 hours before oxygen-glucose deprivation effectively prevents neuron death (survival rate: 80–100%) Adding the inhibitor of K_{ATP}-channel tolbutamide to the group xenon during preconditioning completely eliminated protective effect of xenon For preconditioning neurons with xenon, it is important to open the KATP-channels of the plasmalemma, and not the mitochondrial K_{ATP}-channels Recombinant K_{ATP} channels are activated by xenon but are inhibited by halogenated volatile anesthetics Xenon can very closely mimic the internal mechanism of ischemic preconditioning
Wilhelm S., Ma D., Maze M., Franks N.P. (2002) [19].	The culture of neurons and glial cells of the cortex of newborn mice was exposed to NMDA, glutamate, or oxygen deprivation	The culture was put in a gas chamber with xenon (Xe 75%/O_2 20%/ $CO_2$5%) for 24 hours	Xenon is not neurotoxic. Xenon has a concentration- dependent neuroprotective effect in vitro Protective effect: 100% in the oxygen deprivation group 80% in the NMDA group 80% in the glutamate group
In vivo			
Miao Y.F., Peng T., Moody M.R., et al. (2018) [65].	Rats, SAH model caused by endovascular perforation of the middle cerebral artery	Xenon-containing echogenic liposomes (Xe-ELIP), intravenous administration combined with ultrasound of the common carotid artery to induce the release of Xe from circulating Xe-ELIP.	Bleeding reduction Improving overall neurological assessment Reduced motor function damage Decrease in apoptotic death of neurons Mortality reduction.
Yang Y.W., Wang Y.L., Lu J.K., et al. (2018) [73].	Rabbits, ischemic/reperfusion injury to the spinal cord (balloon occlusion of the infrarenal aorta) for 22 minutes	Immediately after reperfusion – inhalation of Xe 50% / O_2 50% 1 hour, then N_2 50% / O_2 50% 2 hours Delayed inhalation after reperfusion – inhalation N_2 50% / O_2 50% 2 hours, then Xe 50% / O_2 50% 1 hour	Xenon increases IL-6 and IL-10 levels with immediate post-conditioning and decreases these levels in delayed post-conditioning Xenon postconditioning with delay improves neurological function and attenuates mediated microglial inflammatory response Immediate xenon post-conditioning enhances microglia- mediated inflammatory response
Sheng S.P., Lei B., James M.L., et. al. (2012) [61].	Rats, subarachnoid hemorrhage (SAH)	Inhalation of Xe 50% / O_2 50% after SAH for 1 hour with an assessment of histological damage after 24 hours	Less pronounced neuronal damage was noted in the CA_3 hippocampus and dentate gyrus compared with the control group. A smaller number of microglia cells was observed, which indicates the immunomodulating effect created by xenon.
Sheng S.P., Lei B., James M.L., et. al. (2012) [61].	Rats, temporary focal ischemia for 70 minutes	In 90 min, 0, 15, 30, or 45% Xe for 20 hours or 0 or 30% Xe for 8, 20, or 44 hours was administered to rats .	The size of the heart attack decreased depending on the duration of treatment, neurological functions improved on longer exposure to xenon (8, 20 and 44 hours).

	Temporary focal ischemia and subtherapeutic hypothermia (36° C)	Inhalation 20 hours 30% Xe and/or subtherapeutic hypothermia (36° C)	Postischemic treatment using 30% Xe or subtherapeutic hypothermia (36° C) did not affect the 28-day outcome; a combination of these methods improves outcome
	Intracerebral hemorrhage and subtherapeutic hypothermia (36° C)	20 h inhalation 30% Xe	The combination of inhalation of 30% Xe and Subtitle therapeutically hypothermia (36° C) improved the indicators of the outcome of intracerebral hemorrhage.
David H.N., Haelewyn B., Risso J.J., et al. (2010) [60].	Male rats, occlusion of the middle cerebral artery by introducing an autologous blood clot by in vivo intraluminal method	Xenon inhalation from 37.5 to 75 vol.% During ischemia and in the postischemic period	And the x-ray dose of xenon dependently inhibits tPA-induced thrombolysis with a subsequent decrease in ischemic brain damage; Inhalation of xenon after ischemia actually suppresses ischemic damage to the brain and tPA-induced hemorrhages in the brain, as well as damage to the blood-brain barrier
Homi H.M., Yokoo N., Ma D., et al. (2003) [20].	Male mice, occlusion of the middle cerebral artery, 60 min	70% Xe +30 % O_2 or 70% N_2O + 30% O_2 or 35% Xe + 35% N_2O + 30% O_2 followed by assessment of neurological and histological damage after 24 hours	The neurological result is better in animals of the 70% Xe group compared to the 70% N_2O group. The 35% Xe + 35% N_2O group had an intermediate result Histological analysis: 70% Xe and 35% Xe + 35% N_2O - lower infarct volume compared to the 70% N_2O group Neuroprotective efficacy of Xe has a dose-dependent result Neuroprotective effect is most pronounced in the cortex, with little effect in the subcortex
Wilhelm S., Ma D., Maze M., Franks N.P. (2002) [19].	Female rats in vivo received an injection of NMDA + xenon, followed by histological examination	Inhalation of 20, 40, 60 and 75% xenon	Xenon has a concentration- dependent in vivo neuroprotective effect

CARDIAC ARREST

Severe cognitive deficit remains an important and far from being resolved problem in patients undergoing cardiac arrest. As a consequence, the development of strategies aimed at reducing neurological functional deficits is a major challenge.

Cardiac arrest and subsequent pulmonary cardiac resuscitation are a classic example of ischemia-reperfusion brain injury followed by a cascade of excitotoxicity, apoptosis, and neuroinflammation reactions.

Previous research has shown that N-methyl-D-aspartate receptors are expressed in myelin of white matter oligodendrocytes and are activated during ischemia [67], and xenon is an antagonist of the N-methyl-D-aspartate receptor and a competitive inhibitor at the glycine coactivation site of this receptor [21, 22]. The volume of white matter is 50% of the total brain volume in humans and is very vulnerable even to short-term ischemia [68].

The use of xenon in combination with hypothermia has been shown to be effective in a pig model of cardiac arrest. In the study, after 10 minutes of cardiac arrest and 6 minutes of cardiopulmonary resuscitation, the animals underwent hypothermia up to 33 ° C and inhalation of 70% xenon for one hour. Animals in the main and control groups showed significantly fewer necrotic lesions in the cerebral cortex, caudate nucleus, putamen, and hippocampal sectors CA1 and CA3 / 4. However, only a combination of mild therapeutic hypothermia and xenon inhalation led to a decrease in astrogliosis in the CA1 sector, microgliosis, and perivascular inflammation in putamen. In addition, only animals with mild therapeutic hypothermia treated with xenon showed significantly improved indicators of neurological deficit over time [69].

In a study by R. Laitio et al. (2016), the use of xenon in combination with hypothermia in a clinical setting was first studied.

In patients who experienced cardiac arrest outside the hospital, inhalation of xenon at a concentration of 40 vol% for 24 hours, which was combined with hypothermia compared with the group in which only hypothermia was used, resulted in less damage to the white matter, as measured by fractional anisotropy diffusely weighted magnetic resonance imaging [70].

This study was not powerful enough (110 patients) to detect differences in functional endpoints; 6-month mortality was 27% in the xenon-hypothermia group and 35% in the hypothermia group (aHR, 0.49 [95% CI, 0.23-1.01]) - but this difference in mortality did not reach statistical significance ($p = 0.053$). The authors note that the degree of damage to the white matter of the brain was the strongest predictor of 6-month mortality. The obtained results allowed initiating a large multicenter international study, which will include 1,436 patients after out-of-hospital cardiac arrest (XePOHCAS - NCT03176186 - clinicaltrials.gov/ct2/show/NCT03176186]) to evaluate the efficacy and safety of 24-hour xenon inhalation in order to reduce mortality and improve functional outcome in patients after successful resuscitation, but in a coma [71].

OTHER CONDITIONS FOR NEUROPROTECTION

In addition to situations of acute damage to neurons, the protective effect of xenon has been shown in vitro under conditions of low-level excitotoxic stress.

J. Lavaur et al. (2017) showed the importance of neuroprotective properties for the protection of dopamine receptors. under in vitro conditions simulating low-level excitotoxic stress. A culture of midbrain cells containing dopamine neurons and astroglial cells of 15.5-day-old mouse embryos was treated with a synthetic analogue of glutamate, L-trans-pyrrolidine-2,4-dicarboxylic acid (L-trans-pyrrolidine-2,4-dicarboxylic acid (PDC)). It was found that xenon protects dopamine receptors from degeneration through antagonism to NMDA receptors, preventing oxidative stress, and neuroprotection of dopamine neurons with xenon is the result of repression of the glial-dependent mechanism, and also provides protection for spontaneous death of dopamine neurons [61].

It should be noted that the neuroprotective ability of xenon was also shown in the case of spinal cord injury in the work of Y.W. Yang et al. (2018) on a model of ischemia-reperfusion injury of the spinal cord in rabbits. Delayed xenon postconditioning has been shown to improve neurological function and attenuate microglia-mediated inflammatory response, while immediate xenon postconditioning enhances microglia-mediated inflammatory response [73].

CONCLUSION

As we can see, interest in the properties of xenon as a neuroprotector remains in the focus of attention of researchers. The search for new mechanisms of action can significantly expand the range of clinical applications of xenon as an effective means of protecting the brain - both in a situation of acute injury and in the long-term period. It seems important to note that the convincing data accumulated to date, obtained in experimental studies, which revealed the neuroprotective properties of xenon, make it possible to initiate its clinical trials in severe traumatic brain injury, ischemic stroke, and subarachnoid hemorrhage.

REFERENCES

1. Vilenskiy BS, Yakhno NN. *Sovremennoye sostoyaniye problemy insul'ta*. Vestnik Rossiyskoy AMN Publ. 2006; 9–10:18–23. (in Russ.)
2. Piradov MA, Krylov VV, Belkin AA, Petrikov SS. Insul'ty. In: Gel'fand BR, Zabolotskiy IB (eds.). *Intensivnaya terapiya*. 2nd ed., ed. and exp. Moscow: GEOTAR-Media Publ.; 2017. pp. 288–309. (in Russ.)
3. Shevchenko EV, Ramazanov GR, Petrikov SS. Causes of Dizziness in Patients with Suspected Stroke. *Russian Sklifosovsky Journal Emergency Medical Care*. 2018;7(3):217–221. (In Russ.) https://doi.org/10.23934/2223-9022-2018-7-3-217-221
4. Gusev EL, Skvortsova VL, Stakhovskaya LV. Stroke in the Russian Federation: time for united concentrated activites. *SS Korsakov Journal of Neurology and Psychiatry*. 2007;107(8):4–10. (in Russ.)
5. *Ministerstvo Zdravookhraneniya RF. Statisticheskiy sbornik 2017 g*. Available at: https://www.rosminzdrav.ru/ministry/61/22/stranitsa-979/statisticheskie-i-informatsionnye-materialy/statisticheskiy-sbornik-2017-god [Accessed 05 Feb 2020] (In Russ.)
6. Krylov VV, Petrikov SS, Talypov AE, Puras YV, Solodov AA, Levchenko OV, et al. Modern Principles of Surgery Severe Craniocerebral Trauma. *Russian Sklifosovsky Journal Emergency Medical Care*. 2013;(4):39–47. (In Russ.)
7. Vella MA, Crandall ML, Patel MB. Acute Management of Traumatic Brain Injury. *Surg Clin North Am.* 2017;97(5):1015–1030. PMID: 28958355 https://doi.org/10.1016/j.suc.2017.06.003
8. Shabanov AK, Kartavenko VI, Petrikov SS, Marutyan ZG, Rozumny PA, Chernenkaya TV, et al. Evere Multisystem Craniocerebral Injury: Features of the Clinical Course and Outcomes. *Russian Sklifosovsky Journal Emergency Medical Care.* 2017;6(4):324–330. (In Russ.) https://doi.org/10.23934/2223-9022-2017-6-4-324-330
9. Janowitz T, Menon DK. Exploring new routes for neuroprotective drug development in traumatic brain injury. *Sci Transl Med*. 2010;2(27):27rv1. PMID: 20393189 PMID: 20393189 https://doi.org/10.1126/scitranslmed.3000330
10. Ostrova IV, Grebenchikov OA, Golubeva NV. Neuroprotective Effect of Lithium Chloride in Rat Model of Cardiac Arrest. *General Reanimatology*. 2019;15(3):73–82. (In Russ.) https://doi.org/10.15360/1813-9779-2019-3-73-82
11. Schapira Anthony H.V. Neuroprotection in Parkinson's Disease. Chapter 18. In: Anthony H.V. Schapira, Anthony E.T. Lang, Stanley Fahn (eds.). *Movement Disorders 4. Blue Books of Neurology.* Vol. 34. Elsevier Inc; 2010. p.301–320. https://www.sciencedirect.com/bookseries/blue-books-of-neurology/vol/34/suppl/C
12. Lawrence JH, Loomis WF. Preliminary observations on the narcotic effect of xenon with a review of values for solubilities of gases in water and oils. *J Physiol*. 1946; 105(6): 197–204. PMID: 20283155 https://doi.org/10.1113/jphysiol.1946.sp004164
13. Cullen SC, Gross EG. The anesthetic properties of xenon in animals and human beings, with additional observations on krypton. *Science*. 1951;113(2942):580–582. PMID: 14834873 https://doi.org/10.1126/science.113.2942.580
14. Pittinger CB, Moyers J, Cullen SC, Featherstone RM, Gross EG, et al. Clinicopathologic studies associated with xenon anesthesia. *Anesthesiology*. 1953; 14(1):10–17. PMID: 13017008 https://doi.org/10.1097/00000542-195301000-00002
15. Cullen SC, Eger 2nd EI, Cullen BF, Gregory P. Observations on the anesthetic effect of the combination of xenon and halothane. *Anesthesiology*. 1969;31(4):305–309. PMID: 5811596 https://doi.org/10.1097/00000542-196910000-00003
16. Nakata Y, Goto T, Ishiguro Y, Terui K, Kawakami H, Santo M, et al. Minimum alveolar concentration (MAC) of xenon with sevoflurane in humans. *Anesthesiology*. 2001; 94(4):611–614. PMID: 11379681 https://doi.org/10.1097/00000542-200104000-00014 .
17. Eger EI 2nd, Laster MJ, Gregory GA, Katoh T, Sonner JM, et al. Women appear to have the same minimum alveolar concentration as men: a retrospective study. *Anesthesiology*. 2003; 99(5):1059–1061. PMID: 14576539 https://doi.org/10.1097/00000542-200311000-00009
18. Burov NE, Potapov VN, Makeev GN. *Ksenon v anesteziologii*. Moscow: Pul's Publ.; 2000. (In Russ.)
19. Wilhelm S, Ma D, Maze M, Franks NP. Effects of xenon on in vitro and in vivo models of neuronal injury. *Anesthesiology*. 2002;96(6):1485–1491. PMID: 12170064 https://doi.org/10.1097/00000542-200206000-00031
20. Homi HM, Yokoo N, Ma D, Warner DS, Franks NP, Maze M, et al. The neuroprotective effect of xenon administration during transient middle cerebral artery occlusion in mice. *Anesthesiology*. 2003;99(4):876–881. PMID: 14508320 https://doi.org/10.1097/00000542-200310000-00020
21. Banks P, Franks NP, Dickinson R. Competitive inhibition at the glycine site of the N-methyl-D-aspartate receptor mediates xenon neuroprotection against hypoxia-ischemia. *Anesthesiology*. 2010;112(3):614–622. PMID: 20124979 https://doi.org/10.1097/aln.0b013e3181cea398
22. Franks NP, Dickinson R, de Sousa SL, et al. How does xenon produce anaesthesia? *Nature*. 1998;396(6709):324. PMID: 9845069 https://doi.org/10.1038/24525
23. Raja SN, Sivanesan E, Guan Y. Central Sensitization, N-methyl-D-aspartate Receptors, and Human Experimental Pain Models: Bridging the Gap between Target Discovery and Drug Development. *Anesthesiology*. 2019;131(2):233–235. PMID:31233408 https://doi.org/10.1097/aln.0000000000002808
24. Greger IH, Mayer ML. Structural biology of glutamate receptor ion channels: towards an understanding of mechanism. *Curr Opin Struct Biol*. 2019;57:185–195. PMID: 31185364 https://doi.org/10.1016/j.sbi.2019.05.004
25. Huang H, Liu S, Kornberg TB. Glutamate signaling at cytoneme synapses. *Science*. 2019;363(6430):948–955. PMID: 30819957 https://doi.org/10.1126/science.aat5053
26. Kaneko Y, Tuazon JP, Ji X, Borlongan CV. Pituitary Adenylate Cyclase Activating Polypeptide Elicits Neuroprotection Against Acute Ischemic Neuronal Cell Death Associated with NMDA Receptors. *Cell Physiol Biochem*. 2018;51(4):1982–1995. PMID: 30513524 https://doi.org/10.1159/000495722
27. Liu Y, Li AQ, Ma W, Ma W, Gao YB, Deng LQ, et al. Limb Remote Ischemic Preconditioning Reduces Repeated Ketamine Exposure-Induced Adverse Effects in the Developing Brain of Rats. *J Mol Neurosci*. 2019;68(1):58–65. https://doi.org/ 10.1007/s12031-019-01282-3
28. Yang Q, Huang Q, Hu Z, Tang X. Potential Neuroprotective Treatment of Stroke: Targeting Excitotoxicity, Oxidative Stress, and Inflammation. *Front Neurosci*. 2019;13:1036. PMID: 31611768 https://doi.org/10.3389/fnins.2019.01036

29. Simon RP, Swan SH, Griffiths T, Meldrum BS. Blockade of N-methyl-D-aspartate receptors may protect against ischemic damage in the brain. *Science*. 1984; 226(4676):850–852. PMID: 6093256 https://doi.org/ 10.1126/science.6093256
30. Ladak AA, Enam SA, Ibrahim MT. A Review of the Molecular Mechanisms of Traumatic Brain Injury. *World Neurosurg*. 2019;131:126–132. PMID: 31301445 https://doi.org/10.1016/j.wneu.2019.07.039
31. Kim UJ, Lee BH, Lee KH. Neuroprotective effects of a protein tyrosine phosphatase inhibitor against hippocampal excitotoxic injury. *Brain Res*. 2019;1719:133–139. PMID: 31128098 https://doi.org/10.1016/j.brainres.2019.05.027
32. Andreasen SR, Lundbye CJ, Christensen TB, Thielsen KD, Schmitt-John T, Holm MM, et al. Excitatory-inhibitory imbalance in the brain of the wobbler mouse model of amyotrophic lateral sclerosis substantiated by riluzole and diazepam. *Neurosci Lett*. 2017;658:85–90. PMID: 28823891 https://doi.org/10.1016/j.neulet.2017.08.033
33. Wong TP, Howland JG, Wang YT. NMDA Receptors and Disease+C464. In: *Encyclopedia of Neuroscience*. 2009:1177–1182. https://doi.org/10.1016/b978-008045046-9.01223-7
34. Gruss M, Bushell TJ, Bright DP, Lieb WR, Mathie A, Franks NP, et al. Two-pore-domain K+ channels are a novel target for the anesthetic gases xenon, nitrous oxide, and cyclopropane. *Mol Pharmacol*. 2004;65(2):443-452. PMID: 14742687 https://doi.org/10.1124/mol.65.2.443
35. Bantel C, Maze M, Trapp S. Neuronal preconditioning by inhalational anesthetics: evidence for the role of plasmalemmal adenosine triphosphate-sensitive potassium channels. *Anesthesiology*. 2009;110(5):986–995. PMID: 19352153 https://doi.org/10.1097/ALN.0b013e31819dadc7
36. Maas A. Traumatic brain injury: Changing concepts and approaches. *Chin J Traumatol*. 2016;19(1):3–6. PMID: 27033264 https://doi.org/ 10.1016/j.cjtee.2016.01.001
37. Hill CS, Coleman MP, Menon DK. Traumatic Axonal Injury: Mechanisms and Translational Opportunities. *Trends Neurosci*. 2016; 39(5):311–324. PMID: 27040729. https://doi.org/10.1016/j.tins.2016.03.002
38. Campos-Pires R, Armstrong SP, Sebastiani A, Luh C, Gruss M, Radyushkin K, et al. Xenon improves neurologic outcome and reduces secondary injury following trauma in an in vivo model of traumatic brain injury. *Crit Care Med*. 2015;43(1):149–158. PMID: 25188549 https://doi.org/10.1097/CCM.0000000000000624
39. Campos-Piries R, Himet T, Valeo F, Luh C, Gruss M, Radyushkin K, et al. Xenon improves long-term cognitive function, reduces neuronal loss and chronic neuroinflammation, and improves survival after traumatic brain injury in mice. *Br J Anaesth*. 2019;123(1):60–73. PMID: 31122738. https://doi.org/ 10.1016/j.bja.2019.02.032
40. Campos-Pires R, Koziakova M, Yonis A, Pau A, Macdonald W, Harris K, et al. Xenon Protects against Blast-Induced Traumatic Brain Injury in an In Vitro Model. *J Neurotrauma*. 2018;35(8):1037–1044. PMID: 29285980 https://doi.org/10.1089/neu.2017.5360
41. Harris K, Armstrong SP, Campos-Pires R, Kiru L, Franks NP, Dickinson R, et al. Neuroprotection against traumatic brain injury by xenon, but not argon, is mediated by inhibition at the N-methyl-D-aspartate receptor glycine site. *Anesthesiology*. 2013;119(5):1137–1148. PMID: 23867231 https://doi.org/10.1097/ALN.0b013e3182a2a265
42. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. *Lancet*. 2008;371(9624):1612–1623. PMID: 18468545. https://doi.org/10.1016/S0140-6736(08)60694-7
43. Guruswamy R, ElAli A. Complex Roles of Microglial Cells in Ischemic Stroke Pathobiology: New Insights and Future Directions. *Int J Mol Sci*. 2017;18(3).pii:E496. PMID: 28245599 https://doi.org/10.3390/ijms18030496
44. Tymianski M. Emerging mechanisms of disrupted cellular signaling in brain ischemia. *Nat Neurosci*. 2011;14(11):1369–1373. PMID: 22030547 https://doi.org/10.1038/nn.2951
45. Lai TW, Zhang S, Wang YT. Excitotoxicity and stroke: identifying novel targets for neuroprotection. *Prog Neurobiol*. 2014;115:157–188. PMID: 24361499 https://doi.org/10.1016/j.pneurobio.2013.11.006
46. Cordonnier C, Demchuk A, Ziai W, Anderson CS. Intracerebral haemorrhage: current approaches to acute management. *Lancet*. 2018;392(10154):1257–1268. PMID: 30319113 https://doi.org/10.1016/S0140-6736(18)31878-6
47. Paroutoglou K, Parry-Jones AR. Hyperacute management of intracerebral haemorrhage. *Clin Med (Lond)*. 2018;18(Suppl 2):s9–s12. PMID: 29700086 https://doi.org/10.7861/clinmedicine.18-2-s9
48. Kaiser S, Frase S, Selzner L, Lieberum JL, Wollborn J, Niesen WD, et al. Neuroprotection after Hemorrhagic Stroke Depends on Cerebral Heme Oxygenase-1. *Antioxidants (Basel)*. 2019;8(10).pii: E496. PMID: 31635102 https://doi.org/10.3390/antiox8100496
49. Ardizzone TD, Lu A, Wagner KR, Tang Y, Ran R, Sharp FR. Glutamate receptor blockade attenuates glucose hypermetabolism in perihematomal brain after experimental intracerebral hemorrhage in rat. *Stroke*. 2004;35(11):2587–2591. PMID: 15375303 https://doi.org/10.1161/01.STR.0000143451.14228.ff
50. Qureshi AI, Ali Z, Suri MF, Shuaib A, Baker G, Todd K, et al. Extracellular glutamate and other amino acids in experimental intracerebral hemorrhage: An in vivo microdialysis study. *Crit Care Med*. 2003;31(5):1482–1489. PMID: 12771622 https://doi.org/10.1097/01.CCM.0000063047.63862.99
51. Aronowski J, Hall CE. New horizons for primary intracerebral hemorrhage treatment: Experience from preclinical studies. *Neurol Res*. 2005;27(3):268–279. PMID: 15845210 https://doi.org/10.1179/016164105X25225
52. Wang JA, Tong ML, Zhao B, Zhu G, Xi DH, Yang JP. Parthenolide ameliorates intracerebral hemorrhage-induced brain injury in rats. *Phytother Res*. 2020;34(1):153–160. PMID: 31497910 https://doi.org/ 10.1002/ptr.6510
53. Hickenbottom SL, Grotta JC, Strong R, Denner LA, Aronowski J. Nuclear factor-kappab and cell death after experimental intracerebral hemorrhage in rats. *Stroke*. 1999;30(11):2472–2477. PMID: 10548686 https://doi.org/ 10.1161/01.str.30.11.2472
54. Wu J, Sun L, Li H, Shen H, Zhai W, Yu Z, et al. Roles of programmed death protein 1/programmed death-ligand 1 in secondary brain injury after intracerebral hemorrhage in rats: selective modulation of microglia polarization to anti-inflammatory phenotype. *J Neuroinflammation*. 2017;14(1):36. PMID: 28196545 https://doi.org/ 10.1186/s12974-017-0790-0
55. Wang J, Dore S. Inflammation after intracerebral hemorrhage. *J Cereb Blood Flow Metab*. 2007;27(5):894–908. PMID: 17033693 https://doi.org/ 10.1038/sj.jcbfm.9600403
56. Wang J, Fields J, Zhao C, Langer J, Thimmulappa RK, Kensler TW, et al. Role of nrf2 in protection against intracerebral hemorrhage injury in mice. *Free Radic Biol Med*. 2007; 43(3):408–414. PMID: 17602956 https://doi.org/ 10.1016/j.freeradbiomed.2007.04.020
57. Veltkamp R, Purrucker J. Management of Spontaneous Intracerebral Hemorrhage. *Curr Neurol Neurosci Rep*. 2017;17(10):80. PMID: 28887767 https://doi.org/ 10.1007/s11910-017-0783-5
58. Sansing LH. Intracerebral Hemorrhage. *Semin Neurol*. 2016;36(3):223–224. PMID: 27214696 https://doi.org/ 10.1055/s-0036-1583296
59. David HN, Haelewyn B, Risso JJ, Colloc'h N, Abraini JH. Xenon is an inhibitor of tissue-plasminogen activator: adverse and beneficial effects in a rat model of thromboembolic stroke. *J Cereb Blood Flow Metab*. 2010;30(4):718–728. PMID: 20087367 https://doi.org/10.1038/jcbfm.2009.275
60. Sheng SP, Lei B, James ML, Lascola CD, Venkatraman TN, Jung JY, et al. Xenon neuroprotection in experimental stroke: interactions with hypothermia and intracerebral hemorrhage. *Anesthesiology*. 2012;117(6):1262–1275. PMID: 23143806 https://doi.org/10.1097/ALN.0b013e3182746b81
61. Lavaur J, Le Nogue D, Lemaire M, Pype J, Farjot G, Hirsch EC, et al. The noble gas xenon provides protection and trophic stimulation to midbrain dopamine neurons. *J Neurochem*. 2017;142(1):14–28. PMID: 28398653 https://doi.org/ 10.1111/jnc.14041
62. Coburn M, Maze M, Franks NP. The neuroprotective effects of xenon and helium in an in vitro model of traumatic brain injury. *Crit Care Med*. 2008;36(2):588–595. PMID: 18216607 https://doi.org/10.1097/01.CCM.0B013E3181611F8A6
63. Macdonald RL, Schweizer TA. Spontaneous subarachnoid haemorrhage. *Lancet*. 2017;389(10069):655–666. PMID: 27637674 https://doi.org/ 10.1016/S0140-6736(16)30668-7
64. Grasso G, Alafaci C, Macdonald RL. Management of aneurysmal subarachnoid hemorrhage: State of the art and future perspectives. *Surg Neurol Int*. 2017;8:11. PMID: 28217390 https://doi.org/10.4103/2152-7806.198738
65. Veldeman M, Coburn M, Rossaint R, Clusmann H, Nolte K, Kremer B, et al. Xenon Reduces Neuronal Hippocampal Damage and Alters the Pattern of Microglial Activation after Experimental Subarachnoid Hemorrhage: A Randomized Controlled Animal Trial. *Front Neurol*. 2017; 8:511. PMID: 29021779 https://doi.org/10.3389/fneur.2017.00511
66. Miao YF, Peng T, Moody MR, Klegerman ME, Aronowski J, Grotta J, et al. Delivery of xenon-containing echogenic liposomes inhibits early brain injury following subarachnoid hemorrhage. *Sci Rep*. 2018;8(1):450. PMID: 29323183 https://doi.org/10.1038/s41598-017-18914-6
67. Káradóttir R, Cavelier P, Bergersen LH, Attwell D. NMDA receptors are expressed in oligodendrocytes and activated in ischaemia. *Nature*. 2005;438(7071):1162–1166. PMID: 16372011 https://doi.org/ 10.1038/nature04302
68. Pantoni L, Garcia JH, Gutierrez JA. Cerebral white matter is highly vulnerable to ischemia. *Stroke*. 1996;27(9):1641–1646. PMID: 8784142 https://doi.org/10.1161/01.str.27.9.1641
69. Fries M, Brücken A, Çizen A, Westerkamp M, Löwer C, Deike-Glindemann J, et al. Combining xenon and mild therapeutic hypothermia preserves neurological function after prolonged cardiac arrest in pigs. *Crit Care Med*. 2012;40(4):1297–1303. PMID: 22425822 https://doi.org/10.1097/CCM.0b013e31823c8ce7

70. Laitio R, Hynninen M, Arola O, Virtanen S, Parkkola R, Saunavaara J. et al. Effect of Inhaled Xenon on Cerebral White matter Damage in Comatose Survivors of Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. *JAMA*. 2016;315(11):1120–1128. PMID:26978207 https://doi.org/10.1001/jama.2016.1933
71. Laitio T, Maze M. Xenon limits brain damage following cardiac arrest. Shock. 2018;18(Is3):192–195.
72. Shu Y, Patel SM, Pac-Soo C, Fidalgo AR, Wan Y, Maze M, et al. Xenon pretreatment attenuates anesthetic-induced apoptosis in the developing brain in comparison with nitrous oxide and hypoxia. *Anesthesiology*. 2010;113(2):360–368. PMID: 20613483 https://doi.org/ 10.1097/ALN.0b013e3181d960d7
73. Yang YW, Wang YL, Lu JK, Tian L, Jin M, Cheng WP, et al. Delayed xenon post-conditioning mitigates spinal cord ischemia/reperfusion injury in rabbits by regulating microglial activation and inflammatory factors. *Neural Regen Res*. 2018;13(3):510–517. PMID: 29623938 https://doi.org/ 10.4103/1673-5374.228757

Received on 30.08.2019

Accepted on 05.12.2019