ALLEVIATION OF NEUROLOGICAL AND COGNITIVE IMPAIRMENTS IN RAT MODEL OF ISCHEMIC STROKE BY 0.5 MAC XENON EXPOSURE

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The majority of stroke patients have cognitive symptoms and about 50% of them live with neurological deficits that critically limit social adaptation capacities even in the absence of significant motor impairments. The aim of this study was to select the optimal length of 0.5 MAC xenon exposure in order to alleviate the neurological and cognitive impairments in experimental stroke. The focal ischemia-reperfusion injury was modeled in rats (n = 70) ising Longa method. The intervention was immediately followed by inhalation of 0.5 MAC xenon for 30, 60 or 120 min. The neurological deficit was assessed using a 'Limb placement' seven-test battery and the cognitive functionalities were assessed by the Morris water maze test. A 30 min 0.5 MAC xenon exposure provided a 40% increase in the limb placement scores and a 17.6% decrease in the Morris water maze test latency compared with the control group (p = 0.055 and p = 0.08, respectively). With a longer 60 min exposure, the trends became significant, the scores improving 2-fold and by 44.4% compared with the control group (p = 0.01 and p = 0.04, respectively), whereas 120 min exposures afforded 2-fold improvements in both tests (p = 0.01). We conclude that, although 30 min post-stroke inhalations provide negligible benefits in terms of neurological status and learning capacity, prolonged exposure times of 60–120 min afford significant improvement in neurological and cognitive indicators and largely alleviate the deteriorating ischemic damage.

Keywords: xenon, stroke, neurological deficiency, cognitive impairment

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ВЫРАЖЕННОСТЬ КОГНИТИВНЫХ И НЕВРОЛОГИЧЕСКИХ НАРУШЕНИЙ У КРЫС ПОСЛЕ ИШЕМИЧЕСКОГО ИНСУЛЬТА НА ФОНЕ ПРИМЕНЕНИЯ КСЕНОНА 0,5 МАК

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У подавляющего числа пациентов, перенесших острое нарушение мозгового кровообращения, выявляются остаточные явления, из них у 50% — когнитивные нарушения, ограничивающие самообслуживание в быту, трудовую деятельность и социальную адаптацию в целом и приводящие к инвалидности даже при отсутствии значительных двигательных нарушений. Целью исследования было подобрать наиболее эффективную продолжительность ингаляции ксенона с 0,5 МАК (максимальной альвеолярной концентрацией) для снижения выраженности неврологических и когнитивных нарушений при экспериментальном инсульте. На 70 крысах смоделирована фокальная ишемия-реперфузия по методу Лонга с последующей ингаляцией ксенона 0,5 МАК в течение 30, 60 или 120 мин. Неврологический дефицит оценивали с помощью серии из семи тестов «Постановка конечности на опору», когнитивные функции — тестом «Водный лабиринт Морриса». Экспозиция ксенона 0,5 МАК в течение 30 мин приводила к росту числа баллов в тесте «Постановка конечности на опору» на 40% (p = 0,055) и уменьшению латентного времени в тесте «Водный лабиринт Морриса» на 17,6% (p = 0,08) по сравнению с контрольной группой, экспозиция в течение 60 мин — в 2 раза (p = 0,01) и на 44,4% (p = 0,04), в течение 120 мин — тоже в 2 раза (p = 0,01) в обоих тестах соответственно. Сделан вывод, что ингаляция ксенона 0,5 МАК при экспозиции 30 мин не приводит к значительному улучшению состояния животных и их способности к обучению, о чем свидетельствует отсутствие статистически значимых различий. Экспозиция же ксенона в течение 60 мин значительно уменьшает неврологический и когнитивный дефицит в группе исследования, а увеличение времени экспозиции ксенона до 120 мин оказывает сопоставимый эффект.

Ключевые слова: ксенон, инсульт, неврологический дефицит, когнитивные нарушения

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According to the World Health Organization, about 1/3 of all diseases in developed countries are brain disorders, which are also the major cause of disability [1]. The contribution of brain disorders to the general structure of morbidity and invalidization is further boosted by the growing prevalence of neurodegenerative and cerebrovascular pathologies, as well as the increasing burden of risk factors: the incidence of diabetes mellitus, arterial hypertension, kidney pathology, environmental degradation, population ageing, car accidents and man-made disasters.

The leading place among the causes of disability is occupied by strokes. According to various sources, 40–60% of stroke patients become disabled and need medical and social support throughout their lives, which has a substantial social and economic impact [2, 3]. Moreover, stroke patients frequently present with cognitive impairments in the form of dementia, which dramatically undermines the quality of life for themselves and their families. Only 15% of the patients manage a return to their labor activities and daily routines, whereas 25% have pronounced dementia symptoms [4, 5].

The post-stroke cognitive impairments encompass the higher mental performance deficiencies that manifest and progress over the course of one year after the accident. The early post-stroke cognitive impairments evident within three months (the acute phase) are encountered in 70% of the patients. The manifestations can be focal (aphasia, apraxia) or generalized; the latter may include disorientation in time and space, absent-mindedness and inability to hold attention for a long time, difficulty in choosing words, increased forgetfulness, decreased ability to switch between different types of activity, deterioration of reasoning, difficulties in performing ordinary actions and impaired abstract thinking [2, 3, 6].

Brain damage from ischemic or hemorrhagic stroke, as well as from cardiac arrest or traumatic brain injury, initiates a cascade of pathophysiological reactions based on NMDA receptor-mediated excitotoxicity implicated in pathogenesis of diverse acute and chronic neurodegenerative conditions including Alzheimer's, Huntington's and Parkinson's diseases [7].

The inert gas xenon, which acts as antagonist of NMDA receptors located on the postsynaptic membrane of neurons and also expressed by glial cells, monocytes, macrophages and neutrophils [8, 9], has been used in psychiatry for over 15 years. NMDA-receptors, which participate in memorization, learning and pain perception, have been implicated in acute and chronic neurological conditions, mental disorders and neuropathic pain syndrome. These receptors also contribute to hyperactivation of neurons under the influence of excitatory amino acids and development of the addiction to psychoactive substances [10, 11]. Xenon is known to exert an anti-stress effect and reduce anxiety levels at sub-narcotic concentrations. The use of xenon in the treatment of borderline mental disorders leads to a reduction in psychopathological and somato-vegetative symptoms [12].

The post-stroke cognitive impairments are difficult to manage and even more so to treat, since they are multifactorial in nature and apart from the direct devastating ischemic damage may involve aggravation of cognitive deficits already in place before the acute episode. Neuropro tective therapies are highly relevant in both pathogenetic and symptomatic treatment of the post-stroke cognitive impairments [13, 14]; however, no unified theoretical basis for the use of neuroprotective drugs and other modalities is available so far, with the efficiencies being studied. In recent years, noble gases and xenon in particular receive increased attention due to accumulating evidence of their neuroprotective effects [15–20]. At the same time, no established protocols for modes and doses of xenon administration in different clinical situations are available, and the impact of xenon on the cognitive sphere and restoration of neurological status after stroke is largely obscure.

This study aimed at selecting the optimal length of 0.5 minimum alveolar concentration (0.5 MAC) xenon exposure to alleviate the neurological and cognitive impairments that arise in experimental ischemic stroke.

METHODS

The experiments involved 70 male rats, 300–350 g body weight, purchased from breeding facilities (Krolinfo Ltd.; Russia). Before and after the intervention, the animals were housed under standard conditions with ad libitum access to food and water. Focal ischemia within the tree of the right middle cerebral artery was modeled as described by Longa et al. [21] in animals pre-anesthetized by intraperitoneal injection of 12% chloral hydrate solution at a dose of 300 mg/kg. The lethality constituted 14.3% (10 animals). Sham-operated animals (n = 10) were subject to the same procedures (chloral hydrate anesthesia, surgical access) except the artery occlusion; the sham interventions were performed to account for the bias of narcosis and surgical manipulations. The interventions lasted 7–10 min on average; upon completion the animals were transferred to an air-tight chamber where they received either oxygen-air mix (30% oxygen, control groups) or 0.5 MAC xenon (70% xenon + 30% oxygen, main groups) for 30, 60 or 120 min. The neurological deficiency status was assessed on day 3 of the experiment: the motor functionalities of fore- and hind limbs contralateral to the affected hemisphere were checked by the 'Limb placement on a support' battery of seven tests performed using a 'Staircase test' setup (OpenScience; Russia) [22]. Completion of the task earned 2 points, completion with delay (more than 2 s) and/or partially earned 1 point and a failure to complete the task brought 0 points.

The preservation of cognitive functionalities including learning capacity and spatial memory was assessed by the Morris water maze test. The setup involved a circular pool 150 cm in diameter and 60 cm in height, half-filled with water, and containing a 28 cm high submerged platform in one of the sectors [23, 24]. The training was conducted on days 7–10 of the experiment; each animal was given four attempts, 120 s long and starting from different points, to find and memorize the location of the platform. The times of mounting the platform in each attempt were recorded. The tests were conducted on day 14 of the experiment: the animal was given 60 s to determine the location of the platform when starting from a new position and the latent period of entering the sector where the platform was located at the training stage was recorded. After completion of the tests the animals were withdrawn from the experiment by chloral hydrate overdose.

Statistical analysis

Statistical processing of the data used Statistica 10.0 software (StatSoft Inc.; USA). The data are presented in the 'median (lower quartile; upper quartile)' Me (LQ; HQ) format. Between-the-group differences were assessed by Mann–Whitney U-test, the critical level of significance was $p < 0.05$.

RESULTS

Sham-operated animals presented with zero neurological deficit and invariably got the highest scores (14 points) in the

Table. Alleviation of neurological and cognitive impairments by 0.5 MAC xenon exposure of varying time length, Me (LQ; HQ)

Parameter	Group of animals						
	SO (n = 10)	Exposure time 30 min		Exposure time 60 min		Exposure time 120 min	
		Control (n = 10)	Xenon (n = 10)	Control (n = 10)	Xenon (n = 10)	Control (n = 10)	Xenon (n = 10)
Neurological deficit, points	14	5 (3; 7)^	7 (5; 10)^	6 (3; 8)^	12 (8;13)*	6 (3; 7)^	12 (8;13)*
Latent period of finding the platform, s	8 (7; 9)	17 (14; 19)^	14 (8; 20)^	18 (15; 20)^	10 (5; 15)*	18 (16; 20)^	9 (5; 13)*

Note: SO — sham-operated animals; ^ — significant differences compared to sham-operated animals ($p < 0.05$; Mann–Whitney test); * — significant differences compared to the control group ($p < 0.05$; Mann–Whitney test).

'Limb placement' tests. The control group with 30 min exposure to air-oxygen mixture presented with apparent neurological deficit and 64.3% lower scores in the 'Limb placement' tests compared to sham-operated animals (p = 0.005). For 30 min 0.5 MAC xenon exposure, the scores were 40% higher compared to the control group (p = 0.055; Table), but 2-fold lower compared to sham-operated animals (p = 0.0001), indicating sustained neurological deficit.

The control group with 60 min exposure to air-oxygen mixture also presented with apparent neurological deficits. The total score in the 'Limb placement' tests for this group was 57.1% lower compared to sham-operated animals (p = 0.004). The animals exposed to 0.5 MAC xenon for 60 min scored 2-fold higher than the control group (p = 0.01) and only 14.3% lower than sham-operated animals (p = 0.08), thus showing minimal neurological changes. It should be noted that the total score obtained with 60 min exposure was 71.4% higher than corresponding value obtained with 30 min exposure (p = 0.0002), confirming the higher benefits of 60 min 0.5 MAC xenon inhalations compared to 30 min inhalations of the same composition.

The control group with 120 min exposure to air-oxygen mixture presented with neurological deficits very similar to those obtained with 60 min exposure to air-oxygen mixture, with the total scores 57.1% lower compared to sham-operated animals (p = 0.004). The animals exposed to 0.5 MAC xenon for 120 min scored 2-fold higher than the control group (p = 0.01) and only 14.3% lower than sham-operated animals (p = 0.08), which was identical to the corresponding results obtained with 60 min exposure.

In the Morris water maze test, the latent period of finding the platform by sham-operated animals was 8 (7; 9) s. For the control group with 30 min exposure to air-oxygen mixture the latent period was 2.1 times longer (p = 0.007), which indicates significant deterioration of learning and spatial recognition capacities in the aftermath of ischemic injury to the brain. For 30 min exposure to 0.5 MAC xenon, the latent period was 17.6% shorter compared to the control group (p = 0.08; Table), but 75% longer compared to sham-operated animals (p = 0.001).

For the control group with 60 min exposure to air-oxygen mixture the latent period was 2.25 times longer compared to sham-operated animals (p = 0.006). When using 60 min exposure to 0.5 MAC xenon, the latent period was reduced by 44.4% compared to the corresponding control group (p = 0.04) while being 25% longer compared to sham-operated animals (p = 0.57).

For the control group with 120 min exposure to air-oxygen mixture the latent period was also 2.25 times longer compared to sham-operated animals (p = 0.005). When using 120 min exposure to 0.5 MAC xenon, the latent period was reduced 2-fold compared to the corresponding control group (p = 0.01) while being only 12.5% longer compared to sham-operated animals (p = 0.74).

Taken together, the data demonstrate that modeling of cerebrovascular ischemic stroke in rats by the chosen method causes pronounced neurological and cognitive deficits. The 30 min 0.5 MAC xenon inhalations, applied as a rescue measure immediately post-intervention, provide negligible benefits in terms of neurological status and learning capacity, as demonstrated by the lack of statistical differences between the corresponding groups. Most notably, the prolongation of xenon exposure to 60–120 min largely alleviates the deteriorating ischemic damage as indicated by significant improvement in neurological and cognitive outcomes.

DISCUSSION

Two-thirds of the patients after acute cerebrovascular episodes present with residual effects often associated with primary disability. About 50% of them have cognitive impairments that limit self-help abilities, as well as participation in labor activities and social adaptation in general, even in the absence of significant motor impairments. With a reported 25% increase in the incidence of stroke among people of young and middle working age over the past 20 years, these figures are particularly appalling [1, 2]. The frequency of post-stroke dementia varies from 7.4 to 41.3%, according to different studies, and the condition tends to aggravate [2]. For instance, one study identifies cognitive impairments in 68% of patients in the acute phase of ischemic stroke (days 1–3), growing to 83% within 1 month follow-up, including 52% of moderate cognitive impairment and 30% of dementia cases [3]. Another study reveals cognitive impairments in 84% of the patients in a four years follow-up [25].

The problem of cognitive impairment in ischemic brain damage requires active multidisciplinary attitude fueling the quest for drugs and other modalities that will possibly reduce the rates of post-stroke disability. The use of xenon endowed with neurotrophic and neuroprotective properties as a component of such therapy is of particular interest. According to the published evidence, xenon has a positive psychotropic effect, which manifests itself in improving attention and intellectual performance, while also reducing anxiety and improving sleep [8, 26–29].

The use of subnarcotic doses of xenon in a course of 5–10 procedures contributed to the reduction of anxiety in patients with various forms of anxiety-phobic disorder without organic brain pathology [10]. A positive effect of oxygen-xenon mixture inhalations (5–10% Xe, 95–90% O_2) was demonstrated against the background of stabilization of systemic hemodynamic parameters in patients with Parkinson's disease and age-related cerebral atrophy [30].

Administration of the oxygen-xenon mixture (50% Xe, 50% O_2) inhalation courses to patients with acute encephalopathy against the background of alcohol, drug and mixed forms

of addiction promoted substantial reduction in severity of mental and somato-neurological manifestations. The patients reported reduced anxiety, better mood, vivacity, a need for communication and an expansion of active vocabulary. They also presented with enhanced memorization, improvement of short-term memory and attention switching indicators, faster rates of thinking and better self-help skills. Thus, xenon therapy outdid standard regimens in terms of both psychosomatic correction and cognitive and intellectual improvement [31].

Still, no unified method for the use of xenon under various pathological conditions is available. In experimental settings, the agent can be delivered in the form of xenon liposomes [32]. The authors demonstrate a positive effect of intravenous infusions of such liposomes in the aftermath of focal cerebral ischemia in rat model: alleviation of neurological deficit as measured by forelimb placement tests on days 3 and 5, as well as increased swimming time compared to animals with modeled stroke unaccompanied by xenon therapy (interpreted as reduced depressiveness). The majority of studies use xenon in the form of inhalations of varying length. A neuroprotective effect of xenon inhaled as a mixture of 50% xenon, 25% argon and 25% oxygen for 6 h or 3 h was demonstrated in rodent models of traumatic brain injury [33, 34]. Similarly, inhalations of 70% xenon for 1 h or 5 h improved cognitive and neurological indicators by days 1–3 in pig model of cardiac arrest followed by cardiopulmonary resuscitation [35]. Inhalations of 70% xenon reduced the total infarction volume and improve the 24 h neurological outcomes after transient focal cerebral ischemia in mice as compared with 70% nitrogen, whereas the effect of 35% xenon was intermediate [36]. We considered it important to study the effects of subanesthetic doses of xenon (0.5 MAC) at short exposures on the severity of neurological disorders and cognitive functions in experimental ischemic brain damage modeled by occlusion of the middle cerebral artery; to the best of our knowledge, no such experiments have been published so far. Incidentally, the use of 0.5 MAC xenon allows combining the treatment with oxygen supplementation often required in patients with acute ischemic brain injury. The inhalations were started immediately after modeling the middle cerebral artery stroke and lasted a relatively short time (30, 60 and 120 min) in spontaneously breathing animals, simulating a scenario in which the emergency treatment is started by a visiting medical team to be continued in a hospital setting.

CONCLUSIONS

The experimental use of 30 min 0.5 MAC xenon inhalations provided no significant improvement of neurological status and learning capacity of animals i.e. showed negligible therapeutic efficiency. The prolongation of exposure to 60 min provided significant alleviation of the neurological and cognitive deficits during the recovery as indicated by significant increase in the relevant behavioral test scores (2-fold on average), whereas 120 min inhalations had a comparable effect. Thus, 1–2-hour xenon inhalations represent a promising therapeutic option when administered on the 'as soon as possible' basis after cerebrovascular accident. Alleviation and correction of the neurological and cognitive sequelae of ischemic brain injury by this method requires further clinical evaluation.

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