https://doi.org/10.15360/1813-9779-2026-3-2608

OPEN ACCESS (cc) BY

The Neuroprotective Effects of Lithium Chloride in a Model of Photochemically Induced Stroke

Georgy S. Klimenkov[1], Vladimir T. Dolgikh[1],
Mikhail V. Gabitov[1]*, Yuri V. Skripkin[2], Oleg A. Grebenchikov[1]

[1] V. A. Negovsky Research Institute of General Reanimatology, Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, Ministry of Education and Science of Russia,
25 Petrovka Str., Bldg. 2, 107031 Moscow, Russia
[2] M. F. Vladimirsky Moscow Regional Research Clinical Institute
61/2 Shchepkin Str., 129110 Moscow, Russia

For citation: *Georgy S. Klimenkov, Vladimir T. Dolgikh, Mikhail V. Gabitov, Yuri V. Skripkin, Oleg A. Grebenchikov.* The Neuroprotective Effects of Lithium Chloride in a Model of Photochemically Induced Stroke. *Obshchaya Reanimatologiya = General Reanimatology.* 2026; 22 (3): 21–27. https://doi.org/10.15360/1813-9779-2026-3-2608 [In Russ. and Engl.]

***Correspondence to:** Mikhail V. Gabitov, mgabitov@fnkcrr.ru

Summary

The aim of the study was to investigate the neuroprotective properties of lithium chloride in a model of photochemically induced stroke in rats.

Materials and Methods. The experimental work was conducted in the organoprotection laboratory for critical conditions at the V. A. Negovsky Research Institute of General Reanimatology, Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology. The study included 32 outbred Wistar rats, randomized into 2 equal groups: the NaCl (control) group, treated with physiological saline solution, and the LiCl group, which received a 4.2% lithium chloride solution (63 mg/kg). The solutions were administered intravenously 120 minutes after inducing a stroke. The ischemic stroke model was generated using photochemically induced thrombosis in cerebral sensorimotor cortex vessels. Neurological deficit was assessed using the «limb placement test». Ischemic lesion volume was measured using MRI (7 Tesla). Immunohistochemical analysis included markers for NeuN (survived mature neurons), Cas-3 (neuronal apoptosis), and Iba-1 (microglial activation). Statistical analysis was performed using the Shapiro–Wilk test, Student's *t*-test, and the Mann–Whitney *U* test with significance at $p < 0.05$.

Results. Lithium chloride infusion resulted in a 30% reduction in the ischemic lesion volume compared to the control group ($p = 0.0236$). The LiCl group showed an increase in signal intensity (relative units, RU) in the NeuN-positive neurons in the penumbra (80 RU vs 41 RU in the control group, $p = 0.0001$), a 25% decrease in signal intensity in Cas-3-positive cells ($p = 0.0008$), and a 58% decrease in signal intensity in Iba-1-positive cells ($p < 0.0001$). Neurological deficit in the LiCl group was less detectable (NaCL vs LiCl: 9,8 ± 1,2 vs 12,5 ± 1,5 scores, respectively, $p < 0.0001$).

Conclusion. Lithium chloride demonstrated significant neuroprotective properties in a model of ischemic stroke, reducing the volume of damage and favoring the suppression of apoptosis and inflammation. The findings validate the potential of lithium chloride as a therapeutic agent for treatment of ischemic stroke, owing in particular to ability to modulate key pathogenic mechanisms of the disease. The results underscore the need for further clinical research to assess the efficacy and safety of lithium in medical practice.

Keywords: lithium; neuroprotection; ischemic stroke; acute cerebrovascular accident; NeuN; Cas-3; Iba-1

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

Information about the authors:
Georgy S. Klimenkov: https://orcid.org/0009-0006-5853-7961
Vladimir T. Dolgikh: https://orcid.org/0000-0001-9034-4912
Mikhail V. Gabitov: https://orcid.org/0009-0005-9615-6118
Yuri V. Skripkin: https://orcid.org/0000-0002-6747-2833
Oleg A. Grebenchikov: https://orcid.org/0000-0001-9045-6017

Introduction

Stroke is one of the leading causes of death worldwide [1, 2]. Global stroke epidemiology shows a steady trend toward an increase in incidence, reaching 9.6 million new cases annually. This figure strongly correlates with the demographic aging of the population. According to studies, one in four people will suffer a stroke during their lifetime, with ischemic stroke being the predominant form of cerebrovascular disease [2].

The pathophysiological mechanisms of ischemic stroke involve a complex cascade of interrelated processes, among which disruption of the blood-brain barrier plays a key role. Secondary damage in stroke involves oxidative stress and neuroinflammation, which lead to dysfunction of the cerebral vascular endothelium. These changes destabilize the brain microenvironment, initiating vasogenic edema and hemorrhagic transformation of ischemic tissue, while the activation of microglia

and astrocytes closes a vicious cycle that exacerbates ischemic damage and contributes to the progression of neurological deficits [3].

Acute cerebral ischemia triggers structural intracellular changes. The fate of neurons is determined by the degree and duration of pore opening, which alters the permeability of the mitochondrial membrane (Mitochondrial Permeability Transition Pore, mPTP), along with the development of energy deficiency, excitotoxicity, and oxidative stress. A moderate and transient increase in membrane permeability may be accompanied by reversible changes followed by cellular regeneration, whereas prolonged pore opening inevitably leads to death of cerebral structures. The pathophysiological process associated with mPTP opening is characterized by the release of key proapoptotic factors into the cytoplasm, including apoptosis-inducing factor (AIF) and secondary mitochondrial activator of caspases (SMAC/Diablo) [4]. In addition, the enzyme glycogen synthase kinase 3β (GSK-3β), which is involved in regulation of cell death, inflammation, and oxidative stress, is considered one of the important pathogenetic targets [5].

The use of lithium-containing drugs as a therapeutic agent has undergone significant evolution over the past decades, particularly in the field of neuroprotection [6–8]. Initially known for their mood-stabilizing properties in the treatment of mental disorders, lithium-containing drugs have recently become the focus of intense research interest due to their neuroprotective effects in traumatic brain injury, Alzheimer's disease, and amyotrophic lateral sclerosis [9–14].

Lithium is capable of modulating multiple signaling pathways, influencing apoptosis, autophagy, cytoskeletal remodeling, gene expression, energy metabolism, oxidative stress, and the inflammatory response. Key targets of its action include the Wnt/β-catenin pathway, adenylate cyclase, inositol monophosphatase, and cyclooxygenase. The molecular effects of lithium are mediated by its interaction with GSK-3β, as well as GPCRs, IMPA, and IPP [15]. The pleiotropic effect of this cation on cellular functions occurs through the phosphorylation of GSK-3β and its effects on cAMP-dependent, inositol-3-phosphate, and calcium-mediated signaling cascades. In addition, lithium influences the activity of GABA and NMDA receptors, participating in the regulation of calcium homeostasis [16]. Lithium treatment reduces the production of proinflammatory factors, including IL-1β and TNF-α, as well as other neuroinflammatory biomarkers in experimental animal models [17, 18]. Lithium exerts a cytoprotective effect on neuronal cell cultures in the presence of β-amyloid and colchicine [19]. The use of lithium ascorbate improves stress adaptation in in vitro and in vivo models [20].

The aim of this study is to investigate the neuroprotective properties of lithium chloride in a model of photochemically induced stroke in rats.

Materials and Methods

Experimental studies involving laboratory animals were conducted in accordance with the Principles of Good Laboratory Practice (Russian Federation National Standard GOST R 53434-2009, March 2010) and protocols reviewed and approved by the Animal Ethics Committee of the A. N. Belozersky Research Institute of Physico-Chemical Biology (Minutes No. 2/20 dated February 12, 2020). The study was approved by the Ethics Committee of the V. A. Negovsky Research Institute of General Reanimatology, Federal Research Center for Intensive Care Medicine (meeting minutes No. 1/25/5 dated February 7, 2025).

The study was conducted on 32 outbred male Wistar white rats weighing 310±12.5 g and aged 14–18 weeks.

Modeling of photoinduced ischemic stroke. The model was induced following intraperitoneal administration of chloral hydrate (Sigma-Aldrich, USA) at a dose sufficient to induce anesthesia (400 mg/kg body weight), diluted in a 0.9% sodium chloride solution (Solopharm, Russia) at a rate of 10 mL/kg body weight. Focal ischemic stroke was modeled in the sensorimotor cortex of rats using photochemically induced thrombosis of cortical vessels. The photosensitive dye Bengal rose (3%, 40 mg/kg intravenously; Sigma-Aldrich, USA) was injected into the jugular vein. Afterward, the rat's head was secured in a stereotaxic frame (Bregma coordinates: 0.5 mm distal and 2.5 mm lateral), and the skull was exposed via a midline incision, with the periosteum removed. The cerebral hemisphere in the area of the sensorimotor cortex was irradiated with a green laser at $\lambda = 550$ nm for 15 min. After the skin was sutured, the rats were placed in a cage under an infrared heating lamp until they emerged from anesthesia. Body temperature was maintained at 37 ± 0.5°C throughout the experiment. Body temperature was measured using a rectal sensor, and thermoregulation was performed automatically by connecting the heating module to a thermostat and setting the threshold values.

Grouping of animals. After regaining consciousness and the ability to regulate body temperature independently, 120 minutes following induced ischemic stroke, the animals were administered intravenously a 0.9% sodium chloride solution, 1.5 mL/kg (control group, NaCl, $n = 16$) or a 4.2% lithium chloride solution, 63 mg/kg (comparison group, LiCl, $n = 16$).

After administration of the solutions, the animal's general condition (level of consciousness, mobility) was assessed, and analgesia was administered

(paracetamol 50 mg/kg subcutaneously). The animal was then transferred to a cage with free access to water and food. Throughout the experiment, the partial pressures of O_2 and CO_2 in the animal chamber were continuously monitored using an indoor atmosphere control unit («INSOVT» JSC, Russia).

Instrumental methods. The studies were performed using a magnetic resonance imaging (MRI) scanner with a magnetic field strength of 7 Tesla and a gradient system of 105 mT/m (BioSpec 70/30 USR, Bruker, Germany). The extent of brain damage was assessed using graphical analysis of MRI images, with calculation of the volume of the damaged brain area.

Immunohistochemical studies. The immunohistochemical analysis included NeuN, Cas-3, and Iba-1 markers. These markers were selected based on their biological functions.

The NeuN protein (Neuronal Nuclei, also known as Fox-3 or RBFOX3) is expressed in most mature neurons but is absent in glial cells, stem cells, and immature neuroblasts. Decreased NeuN expression is associated with loss of neuronal integrity [21].

Caspase-3 is an enzyme involved in the process of apoptosis.

The Iba-1 protein (Ionized calcium-binding adapter molecule 1) is a specific marker of microglia and macrophages involved in the immune response and inflammatory processes in nervous and other tissues [22].

The cells in which expression of these proteins was detected were designated as NeuN-positive, Cas-3-positive, and Iba-1-positive.

For immunohistochemical analysis on the 14th day after stroke, immediately following euthanasia (decapitation under anesthesia with 6% chloral hydrate), the rat brains were fixed in 4% formalin, embedded in paraffin, and sectioned to a thickness of 4 µm. The sections were deparaffinized in xylene and rehydrated in ethyl alcohol. High-temperature antigen retrieval was performed in citrate buffer, pH 6 (Target Retrieval Solution, DAKO, Glostrup, Denmark). The sections were cooled, washed three times in distilled water, and three times in phosphate-buffered saline (PBS IHC Wash Buffer + Tween, Cell Mark, Rocklin, USA) with a 5-minute exposure time. To suppress endogenous peroxidase, the sections were incubated in 3% hydrogen peroxide for 10 minutes. To prevent non-specific binding of primary or secondary antibodies to tissue proteins, Protein Block Serum-free (Abcam, UK) was used with a 30-minute exposure. The sections were incubated at 37°C for 1 hour with primary antibodies against Iba1 (ab5076, 1:500) and NeuN (ab177487, 1:200), Anti-Caspase-3 (ab13847, 1:100), and anti-Von Willebrand factor (ab9378, 1:200) diluted in Antibody Diluent (ab64211, Abcam, UK). The sections were then washed in PBS twice for 5 minutes each. After washing the sections in PBS, they were stained with hematoxylin, rinsed in running water, dehydrated, and mounted. Images were acquired using a Nikon Eclipse Ni-e microscope (Japan), and digital analysis was performed using NIS-Elements software (Nikon Europe B.V., Netherlands) and ImageJ, Fiji. Results were presented as signal intensity (Mean Intensity) in arbitrary units (AU).

Methods for assessing neurological disorders. The limb placement test (LPT) was conducted according to a protocol based on the method described by De Ryck et al. [23] and modified by Jolkkonen et al. [24]. The rats were habituated to human hands 3 days prior to testing. The test consisted of seven trials assessing the sensorimotor integration of the forelimbs and hindlimbs in response to tactile, proprioceptive, and visual stimulation.

Statistical analysis of the data was performed using Microsoft Excel (Microsoft Corporation, 2021), Statistica 12.0 (StatSoft, Inc., 2014), and MedCalc 23.1.2 (MedCalc Software Ltd, 2025). The data were tested for normality of distribution of variables in the samples using the Shapiro–Wilk test. Samples with a normal distribution were tested for equality of variances (F-test). Data were presented as mean and standard deviation (*M*±*SD*), as well as median with interquartile range (*Me* [*Q1*–*Q3*]). Samples with a normal distribution and equal variances were compared using Student's *t*-test. Parameters in groups with a non-normal distribution and samples with unequal variances were compared using the Mann–Whitney *U*-test. Results of LPT test across groups were compared using the area under the curve (AUC) for serial measurements. A two-sided significance level of $p<0.05$ was used to assess intergroup differences.

Results

The animals in the NaCl and LiCl groups were comparable in terms of body weight ($p=0.585$) and age (0.931) (Table).

The test results showed a statistically significant reduction in the severity of neurological deficits in the LiCl group compared with the NaCl group ($p<0.0001$). (Fig. 1).

The average extent of brain damage resulting from induced ischemic stroke was statistically significantly lower by nearly 30% in the LiCl group ($p=0.0236$) (Fig. 2).

NeuN-positive cells were present in the area of ischemic damage in both groups. At the same time, in the penumbra zone, the signal intensity of NeuN-positive cells was statistically significantly higher in the LiCl group than in the control group, amounting to 80 AU vs. 41 AU ($p=0.0001$) (Table, Fig. 3).

In the area outside the ischemic lesion, there was no significant difference in the signal intensity of NeuN-positive cells between the groups. When determining the signal intensity of Cas-3-positive

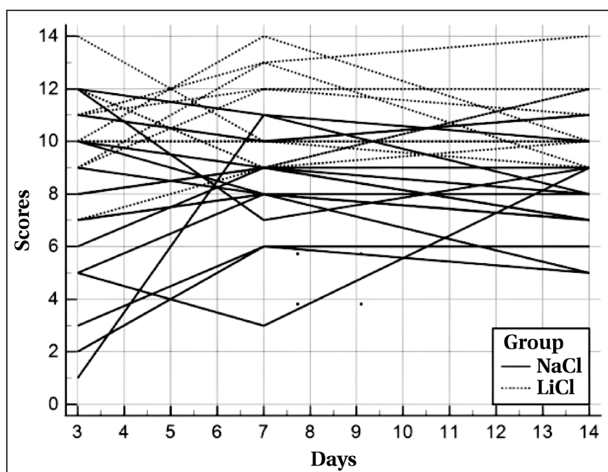

Fig. 1. Results of the «Limb placement test» test over time.
Note. Each line represents the individual trend in test results for a single animal in the study group.

and Iba-1-positive cells, a statistically significant decrease was observed in the LiCl group compared to the control group: by 25% and 58%, respectively (Table).

Discussion

The present study demonstrated significant neuroprotective effects of lithium chloride in a model of photochemically induced ischemic stroke in rats. The results showed that LiCl treatment reduced the volume of the ischemic lesion by 30% compared to the control group, as confirmed by MRI data. This is consistent with previously published studies in which lithium exhibited neuroprotective properties by modulating key pathogenic mechanisms of ischemia, such as oxidative stress, neuroinflammation, and apoptosis [25–27].

A key finding of the study was the significant increase in the signal intensity of NeuN-positive neurons in the penumbra zone observed in animals treated with lithium chloride. This indicates that neuronal viability is preserved and the extent of neuronal damage is reduced. At the same time, no intergroup differences in the signal intensity of NeuN-positive neurons were observed in the area outside the ischemic lesion, which underscores the selective action of lithium chloride on the ischemic zone. The data obtained support the hypothesis that lithium is capable of inhibiting apoptosis by

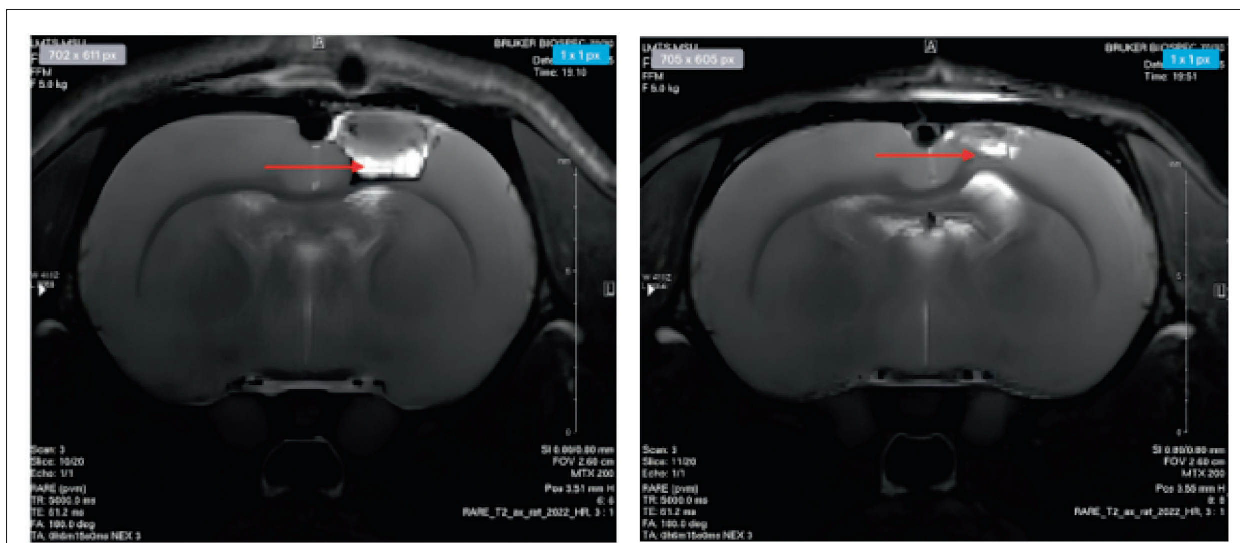

Fig. 2. T2-weighted MRI images in the axial plane, acquired on a 7-Tesla scanner (BioSpec 70/30 USR, Bruker).
Note. The hyperintense signal (white) corresponds to an area of vasogenic edema and ischemic injury. The red arrows indicate the boundaries of the ischemic lesion in the sensorimotor cortex of the brain. Left: NaCl group (control); right: LiCl group. A reduction in the area of ischemic damage was visually noted in the LiCl group.

Table. Comparison of groups by study parameters.

Parameters	Parameter values in the groups		*p*
	NaCl	LiCl	
Bode weight, g	350±36	350±31	0,585
Age, weeks	17 [14–17]	16,5 [14–17]	0,931
LPT, AUC	86±18	115±13	<0,0001
Lesion volume, mm^3	12,9 [10–13,8]	10 [5–11,8]	0,0236
NeuN penumbra, AU	41 [25–50,2]	80 [40–83]	0,0001
NeuN outside lesion	350 [180–451,2]	362,5 [200–435]	0,920
Cas-3, AU	13856 [10448–18142,2]	10385 [9000–12681,2]	0,0008
Iba, AU	2836±486	1179±319	<0,0001

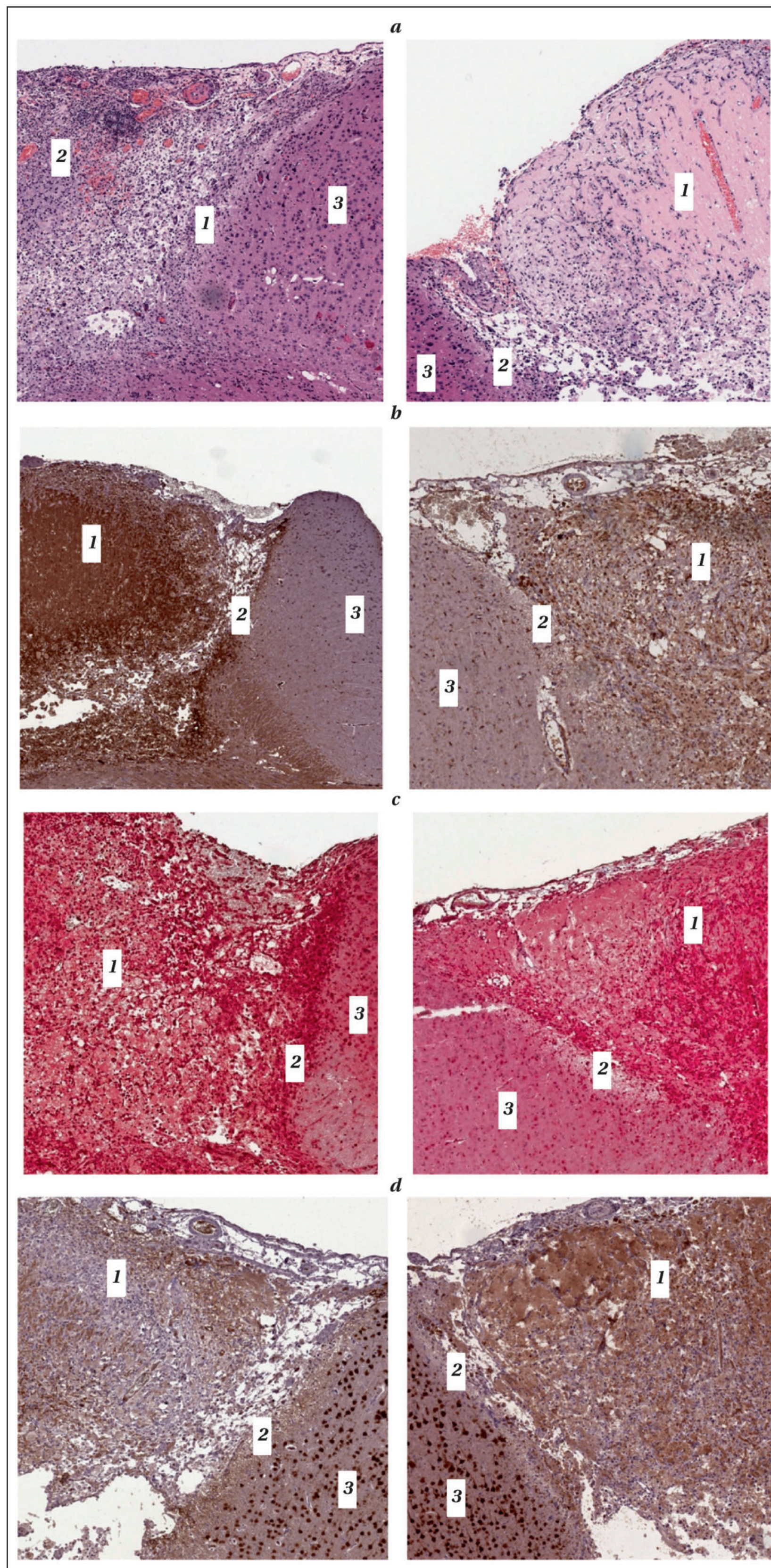

Fig. 3. Representative images of histological sections of rat brain.
Note. 20× objective. *a* — hematoxylin and eosin staining; *b* — sections with a lesion site stained for Iba-1; *c* — combined cell staining: von Willebrand factor (vWf) in red, caspase-3 (Cas-3) in brown; *d* — NeuN-positive cells. *1* — lesion; *2* — penumbra; *3* — intact tissue.

suppressing caspase-3 activity, which is consistent with the results of other studies [28, 29].

The decrease in the intensity of Iba-1-positive cells in the LiCl group indicates a reduction in microglial activation and, consequently, a weakening of the neuroinflammatory response. This confirms the role of lithium in modulating inflammatory processes, which has been previously described in a study focusing on its effects on pro-inflammatory cytokines [30].

Lithium mechanisms of action, such as inhibition of GSK-3β and regulation of calcium homeostasis, play a significant role in its neuroprotective properties [31, 32]. The results obtained complement existing data, confirming that lithium medications may be a promising means for the therapy of ischemic stroke, especially in combination with other neuroprotective agents.

Conclusion

Lithium chloride demonstrated marked neuroprotective properties in a model of photochemically induced ischemic stroke in rats, which were manifested by:

— a 30% reduction in the volume of the ischemic lesion;

— an increase in the intensity of NeuN-positive neuron signals in the penumbra area;

— a 25% and 58% decrease in the expression levels of caspase-3 and Iba-1, respectively.

The improvement in neurological functions in rats treated with lithium chloride confirms the clinical significance of its neuroprotective effect.

Notably, the favorable safety profile of lithium at the doses used in this experiment, combined with the obtained data on its positive effects, suggests a promising outlook for preclinical studies of its neuroprotective properties.

References

1. *Толпыгина С.Н., Загребельный А.В., Чернышева М.И., Воронина В.П., Кутишенко Н.П., Дмитриева Н.А., Лерман О.В., с соавт.* Отдаленная выживаемость больных, перенесших острое нарушение мозгового кровообращения, в различных возрастных группах в регистре РЕГИОН-М. *Российский кардиологический журнал.* 2023; 28 (2): 5250. *Tolpygina S.N., Zagrebelny A.V., Chernysheva M.I., Voronina V.P., Kutishenko N.P., Dmitrieva N.A., Lerman O.V., et al.* Long-term survival of patients with acute cerebrovascular accidents in different age groups in the REGION-M registry. *Russian Journal of Cardiology=Rossiyskiy Kardiologichesky Zhurnal.* 2023; 28 (2): 5250. (In Russ.). DOI: 10.15829/1560-4071-2023-5250.
2. *GBD* 2016 *Stroke Collaborators.* Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019; 18 (5): 439–458. DOI: 10.1016/S1474-4422(19)30034-1. PMID: 30871944.
3. *Cheng J., Zheng Y., Cheng F., Wang C., Han J., Zhang H., Lan X., et al.* Different roles of astrocytes in the blood-brain barrier during the acute and recovery phases of stroke. *Neural Regen Res.* 2026; 21(4): 1359–1372. DOI: 10.4103/NRR.NRR-D-24-01417. PMID: 40537147.
4. *Yang J., Wu S., He M.* Extracellular vesicle-mediated delivery of mitochondrial circRNA MTCO2 protects against cerebral ischemia by modulating mPTP-dependent ferroptosis. *Redox Biol.* 2025; 86: 103806. DOI: 10.1016/j.redox.2025.103806. PMID: 40768899.
5. *Лихванцев В.В., Мороз В.В., Гребенчиков О.А.* Механизмы фармакологического прекондиционирования мозга и сравнительная эффективность препаратов-ингибиторов гликоген-синтетазы-киназы-3 прямого и непрямого действия. *Общая реаниматология.* 2012; 8 (6): 37–42. *Likhvantsev V.V., Moroz V.V., Grebencchikov O.A.* The mechanisms of pharmacological preconditioning of the brain and the comparative efficacy of the drugs — direct-and indirect-acting glycogen synthase kinase-3 inhibitors: experimental study. *General Reanimatology = Obshchaya Reanimatologiya.* 2012; 8 (6): 37–42. (in Russ.&Eng.). DOI: 10.15360/1813-9779-2012-6-37.
6. *Karati D., Meur S., Roy S., Mukherjee S., Debnath B., Jha S.K., Sarkar B.K., Naskar S., et al.* Glycogen synthase kinase 3 (GSK3) inhibition: a potential therapeutic strategy for Alzheimer's disease. *Naunyn Schmiedebergs Arch Pharmacol.* 2025; 398 (3): 2319–2342. DOI: 10.1007/s00210-024-03500-1. PMID: 39432068.
7. *Allam E., Abdel Ghafar S.K., Hussein M., Al-Emam A., Radad K.* Lithium chloride rescues dopaminergic neurons in a Parkinson's disease rat model challenged with rotenone. *CNS Neurol Disord Drug Targets.* 2025; 24 (8): 636–647. DOI: 10.2174/0118715273365449250224090655. PMID: 40114566.
8. *Godoy J.A., Mira R.G., Inestrosa N.C.* Intracellular effects of lithium in aging neurons. *Ageing Res Rev.* 2024; 99: 102396. DOI: 10.1016/j.arr.2024.102396. PMID: 38942199.
9. *Шарикадзе Д.Т., Габитов М.В., Редкин И.В., Кузовлев А.Н., Мороз В.В.* Нейропротекторный потенциал хлорида лития при моделировании черепно-мозговой травмы. *Общая реаниматология.* 2025; 21 (5): 44–50. *Sharikadze D.T., Gabitov M.V., Redkin I.V., Kuzovlev A.N., Moroz V.V.* Neuroprotective potential of lithium chloride in a model of traumatic brain injury. *General Reanimatology = Obshchaya Reanimatologiya.* 2025; 21 (5): 44–50. DOI: 10.15360/1813-9779-2025-5-2528.
10. *Черпаков Р.А., Гребенчиков О.А.* Влияние концентрации хлорида лития на его нейропротекторные свойства при ишемическом инсульте у крыс. *Общая реаниматология.* 2021; 17 (5): 101–110. *Cherpakov R.A., Grebencchikov O.A.* Effect of lithium chloride concentration on its neuroprotective properties in ischemic stroke in rats. *General Reanimatology = Obshchaya Reanimatologiya.* 2021; 17 (5): 101–110. (in Russ.&Eng.). DOI: 10.15360/1813-9779-2021-5-101-110.
11. *Шарикадзе Д.Т., Габитов М.В., Лобанов А.В., Гребенчиков О.А., Кузовлев А.Н.* Изучение влияния хлорида лития на уровень провоспалительных цитокинов после черепно-мозговой травмы. *Патологическая физиология и экспериментальная терапия.* 2025; 69 (1): 58–64. *Sharikadze D.T., Gabitov M.V., Lobanov A.V., Grebenshchikov O.A., Kuzovlev A.N.* The effect of lithium chloride on the level of pro-inflammatory cytokines after traumatic brain injury. *Pathological Physiology and Experimental Therapy = Patologicheskaya Fiziologiya i Exsperimentalnaya Terapiya.* 2025; 69 (1): 58–64. (in Russ.). DOI: 10.25557/0031-2991.2025.01.
12. *De-Paula V.J.R., Radanovic M., Forlenza O.V.* Lithium and neuroprotection: a review of molecular targets and biological effects at subtherapeutic concentrations in preclinical models of Alzheimer's disease. *Int J Bipolar Disord.* 2025; 13 (1): 16. DOI: 10.1186/s40345-025-00386-7. PMID: 40348943.
13. *Gildengers A.G., Ibrahim T.S., Zeng X., Aizenstein H.J., Alkhateeb S.K., Anderson S.J., Chu C., et al.* The LATTICE Study: Design of a pilot feasibility randomized controlled trial of lithium to delay cognitive decline in mild cognitive impairment. *Alzheimers Dement (NY).* 2025; 11 (2): e70112. DOI: 10.1002/trc2.70112. PMID: 40501510.
14. *Boll M.C., Alcaraz-Zubeldia M., Rios C., González-Esquivel D., Montes S.* A phase 2, double-blind, placebo-controlled trial of a valproate/lithium combination in ALS patients. *Neurologia.*2025; 40 (1): 32–40. DOI: 10.1016/j.nrleng.2022.07.003. PMID: 36049647.
15. *Puglisi-Allegra S., Ruggieri S., Fornai F.* Translational evidence for lithium-induced brain plasticity and neuroprotection in the treatment of neuropsychiatric disorders. *Transl Psychiatry.* 2021; 11: 1–10. DOI: 10.1038/s41398-021-01492-7. PMID: 34226487.
16. *Gogoleva I.V., Gromova O.A., Torshin I.Y., Grishina T.R., Pronin A.V.* The neurobiological role of lithium salts. *Neurosci Behav Physi.* 2023; 53: 939–945. DOI: 10.1007/s11055-023-01485-7.

17. *Singulani M.P., Ferreira A.F.F., Figueroa P.S., Cuyul-Vásquez I., Talib L.L., Britto L.R., Forlenza O.V.* Lithium and disease modification: a systematic review and meta-analysis in Alzheimer's and Parkinson's disease. *Ageing Res Rev.* 2024; 95: 102231. DOI: 10.1016/j.arr.2024.102231. PMID: 38364914.
18. *Almeida O.P., Singulani M.P., Ford A.H., Hackett M.L., Etherton-Beer C., Flicker L., Hankey G.J., et al.* Lithium and stroke recovery: a systematic review and meta-analysis of stroke models in rodents and human data. *Stroke.* 2022; 53: 2935–2944. DOI: 10.1161/STROKEAHA.122.039203. PMID: 35968702.
19. *Fan M., Song C., Wang T., Li L., Dong Y., Jin W., Lu P.* Protective effects of lithium chloride treatment on repeated cerebral ischemia-reperfusion injury in mice. *Neurological Sciences.* 2015; 36 (2): 315–321. DOI: 10.1007/s10072-014-1943-x. PMID: 25192664.
20. *Pronin A.V., Gromova O.A., Sardaryan I.S., Torshin I., Stelmashuk E.V., Ostrenko K.S, Aleksandrova O.P., et al.* The adaptogenic and neuroprotective properties of lithium ascorbate. *Neuroscience and Behavioral Physiology.* 2018; 48 (4): 409–415. DOI: 10.1007/s11055-018-0579-3.
21. *Yuan X., Li W., Yan Q., Ou Y., Long Q., Zhang P.* Biomarkers of mature neuronal differentiation and related diseases. *Future Sci OA.* 2024; 10 (1): 2410146. DOI: 10.1080/20565623.2024.2410146. PMID: 39429212.
22. *Green T.R.F., Rowe R.K.* Quantifying microglial morphology: an insight into function. *Clin Exp Immunol.* 2024; 216 (3): 221–229. DOI: 10.1093/cei/uxae02. PMID: 38456795.
23. *De Ryck M., Van Reempts J., Borgers M., Wauquier A., Janssen P.A.* Photochemical stroke model: flunarizine prevents sensorimotor deficits after neocortical infarcts in rats. *Stroke.*1989; 20 (10): 1383–90. DOI: 10.1161/01.str.20.10.1383. PMID: 2799870.
24. *Jolkkonen J., Puurunen K., Rantakömi S., Härkönen A., Haapalinna A., Sivenius J.* Behavioral effects of the alpha(2)-adrenoceptor antagonist, atipamezole, after focal cerebral ischemia in rats. *Eur J Pharmacol.* 2000; 400 (2–3): 211–219. DOI: 10.1016/s0014-2999(00)00409-x. PMID: 10988336.
25. *Ghanaatfar F., Ghanaatfar A., Isapour P., Farokhi N., Bozorgniahosseini S., Javadi M., Gholami M., et al.* Is lithium neuroprotective? An updated mechanistic illustrated review. *Fundam Clin Pharmacol.* 2023; 37 (1): 4–30. DOI: 10.1111/fcp.12826. PMID: 35996185.
26. *Ates N., Caglayan A., Balcikanli Z., Sertel E., Beker M.C., Dilsiz P., Caglayan A.B., et al.* Phosphorylation of PI3K/Akt at Thr308, but not phosphorylation of MAPK kinase, mediates lithium-induced neuroprotection against cerebral ischemia in mice. *Exp Neurol.* 2022; 351: 113996. DOI: 10.1016/j.expneurol.2022.113996. PMID: 35122865.
27. *Wang W., Lu D., Shi Y., Wang Y.* Exploring the neuroprotective effects of lithium in ischemic stroke: a literature review. *Med Sci.* 2024; 21 (2): 284–298. DOI: 10.7150/ijms.88195. PMID: 38169754.
28. *Ghribi O., Herman M., Spaulding N.K., Savory J.* Lithium inhibits aluminum-induced apoptosis in rabbit hippocampus, by preventing cytochrome c translocation, Bcl-2 decrease, Bax elevation and caspase-3 activation. *Journal of Neurochemistry.* 2002; 82 (1): 137–145. DOI: 10.1046/j.1471-4159.2002.00957.x. PMID: 12091474.
29. *King T.D., Bijur G.N., Jope R.S.* Caspase-3 activation induced by inhibition of mitochondrial complex I is facilitated by glycogen synthase kinase-3β and attenuated by lithium. *Brain Research.* 2001; 919 (1): 106–114. DOI: 10.1016/S0006-8993(01)03041-2.
30. *Habib M.Z., Ebeid M.A., Faramawy Y., Saad S.S., Magdoub H.M., Attia A.A., Aboul-Fotouh S., et al.* Effects of lithium on cytokine neuro-inflammatory mediators, Wnt/β-catenin signaling and microglial activation in the hippocampus of chronic mild stress-exposed rats. *Toxicol Appl Pharmacol.* 2020; 399: 115073. DOI: 10.1016/j.taap.2020.115073. PMID: 32454056.
31. *Sakrajda K., Rybakowski J.K.* The mechanisms of lithium action: the old and new findings. *Pharmaceuticals (Basel).* 2025; 18 (4): 467. DOI: 10.3390/ph18040467.
32. *Bortolozzi A., Fico G., Berk M., Solmi M., Formaro M., Quevedo J., Zarate C.A., et al.* New advances in the pharmacology and toxicology of lithium: a neurobiologically oriented overview. *Pharmacol Rev.* 2024; 76 (3): 323–357. DOI: 10.1124/pharmrev.120.000007.

Received 15.08.2025
Accepted 13.05.2026
Online First 02.06.2026