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Effect of mesenchymal stromal cell transplantation on nitric oxide metabolism in rat cortex during ischemia-reperfusion

Serhii Konovalov
PhD in Medical Sciences, Associate Professor
National Pirogov Memorial Medical University, Vinnytsya
21018, 56 Pirogov Str., Vinnytsia, Ukraine
https://orcid.org/0000-0002-9729-7204

Mykhaylo Yoltukhivskyy
Doctor of Medical Sciences, Professor
National Pirogov Memorial Medical University, Vinnytsya
21018, 56 Pirogov Str., Vinnytsia, Ukraine
https://orcid.org/0000-0001-8733-8247

Nataliia Gadzhula*
PhD in Medical Sciences, Associate Professor
National Pirogov Memorial Medical University, Vinnytsya
21018, 56 Pirogov Str., Vinnytsia, Ukraine
https://orcid.org/0000-0003-0016-2264

Abstract. One of the causes of stroke is acute impairment of cerebral blood flow, which initiates with the formation of acute neuronal energy deficiency, activation of the "ischaemic cascade", and nitrosative stress. Reactive nitrogen species, namely nitric oxide and peroxynitrite, play a central role in tissue damage. The search for new therapeutic strategies to address these processes remains relevant. The objective of this study was to evaluate the effect of transplantation of mesenchymal stromal cells of various origins, their lysates, and citicoline on nitric oxide metabolism in the somatosensory cortex of the eyes using an ischaemia-reperfusion model. An experimental model was established using 126 rats, with bilateral 20-minute occlusion of the internal carotid arteries followed by reperfusion. The animals were divided into groups according to the substances administered: mesenchymal stromal cells extracted from Wharton's jelly of the human umbilical cord, human and rat adipose tissue, rat fetal fibroblasts, lysates of mesenchymal stromal cells from Wharton's jelly, and citicoline. On days 7 and 14 after treatment, indicators of nitric oxide metabolism in the somatosensory cortex following ischaemia-reperfusion were analysed. The results demonstrated that transplantation of mesenchymal stromal cells from Wharton's jelly of the human umbilical cord and rat fetal fibroblasts, as well as administration of citicoline, significantly altered total nitric oxide synthase activity during the observed periods. It was found that mesenchymal stromal cells derived from human Wharton's jelly, particularly when combined with citicoline, reduced nitrosative stress. Thus, the ischaemia-reperfusion model induced an imbalance in the functioning of the nitric oxide system. The greatest protective effect was observed with transplantation of mesenchymal stromal cells from Wharton's jelly of the human umbilical cord, which effectively safeguarded neurons from nitrosative stress, in a manner comparable to citicoline

Keywords: cerebral ischaemia; Wharton's jelly; stromal cells; citicoline; NO synthase

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*Corresponding author

Introduction

Stroke is the most prevalent vascular disease worldwide and one of the leading causes of disability and mortality. Among its various forms, ischaemic stroke is the most common, representing a major global health challenge due to its high incidence, complex pathogenesis, and limited treatment efficacy. The mechanisms of ischaemia-reperfusion (IR) injury, which significantly worsen the prognosis after stroke, have become a focus of intensive research aimed at improving therapeutic outcomes.

Ischaemic brain injury triggers a cascade of biochemical events in the affected brain regions, ultimately resulting in oxidative stress that causes irreversible neural tissue damage and cell death following reperfusion. A literature review by V. Chavda *et al.* [1] summarised the powerful molecular mechanisms underlying the development of oxidative stress and its detrimental impact on neural tissue during ischaemic stroke. In a study by S. Arfin *et al.* [2], it was found that after restoration of perfusion in an occluded artery, secondary reperfusion injury occurs in the brain. This is accompanied by increased production of reactive oxygen species (ROS), enhanced inflammation, and an intensified immune response, which disrupt the integrity of the blood-brain barrier (BBB) and eventually lead to cerebral oedema. In another study conducted by A. García-Sánchez *et al.* [3], it was shown that oxidative stress – driven by excessive ROS production from microglia and astrocytes, along with reactive nitrogen species – disrupts synaptic transmission and neuron-glia interactions during ischaemic and reperfusion injuries. Under conditions of elevated ROS production, nitro-oxidative stress arises due to increased nitric oxide (NO) synthesis. Nitric oxide, predominantly produced by enzymatic reactions involving L-arginine and oxygen, is catalysed by three isoforms of nitric oxide synthase (NOS): neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS). Among these, activated nNOS and iNOS are implicated in NO overproduction, which exacerbates damage to the ischaemic brain. During reperfusion, oxygen preferentially reacts with NO to form a potent oxidant, peroxynitrite ($ONOO^-$), which possesses a much stronger oxidising capacity than either NO or oxygen alone. The findings of L. Wu *et al.* [4] indicate that the cytotoxic effect of NO is primarily associated with peroxynitrite, formed through a diffusion-limited reaction between NO and another free radical, the superoxide anion. Data obtained by L. Piacenza *et al.* [5] demonstrated that peroxynitrite interacts with proteins, lipids, and DNA through direct oxidative reactions or indirectly via radical-mediated mechanisms, resulting in significant oxidative damage that leads to either apoptosis or necrosis of cells.

Therefore, there is an urgent need to develop safer and novel therapeutic options for the treatment of IR injury. The management of ischaemic stroke frequently involves a combination of strategies aimed at restoring neurological function. Reviews by C. Li *et al.* [6] and F. Shehjar *et al.* [7] noted that traditional treatment methods based on antithrombotic and neuroprotective therapies are significantly limited due to their low safety profile and limited treatment efficacy. However, ongoing research is focused on developing improved therapeutic strategies to reduce stroke-induced damage and maximise recovery of lost neurological function in patients with acute ischaemic stroke. The therapeutic focus has shifted towards stem cell therapy as one of the most promising approaches for treating a wide range of neurodegenerative diseases. T. Li and G.H. Zhu [8] emphasised that stem cell therapy not only has the potential to promote neuroregeneration, but also to suppress neuroinflammation, enhance angiogenesis, and improve the microenvironment in the ischaemic brain, thereby contributing to functional recovery in patients with ischaemic stroke. M. Chan and Y. Nalapko [9] underlined the potential of regenerative medicine approaches, including stem cell therapy, in restoring neurological functions in stroke patients. Among many types of stem cells, mesenchymal stromal cells (MSCs) are considered the most suitable option for the treatment of ischaemic stroke due to their regenerative and immunomodulatory properties [10-12]. W. Li *et al.* [10] reviewed recent preclinical and clinical data confirming the efficacy of MSCs in modulating post-stroke inflammation and promoting angiogenesis and neurogenesis. Similarly, E.H. Ntege *et al.* [11] highlighted that MSC-based therapies can reduce ROS levels, stabilise the blood-brain barrier, and promote neural repair. X. Wu *et al.* [12] further explained that the therapeutic effects of MSCs are largely mediated by their secretome, which contains anti-apoptotic, trophic, and immunoregulatory factors.

One of the key mechanisms underlying the protective action of modern neuroprotective agents is their modulatory effect on NO metabolism, particularly with respect to the development of nitrosative stress in brain tissues. In light of this, it was appropriate to investigate the modulatory effects of MSCs of different origins, cell lysates from human umbilical cord Wharton's jelly-derived MSCs, and citicoline on the dynamics of NOS activity in the rat somatosensory cortex during experimental IR, as a potential mechanism underlying their cytoprotective properties.

Materials and Methods

The study involved 126 sexually mature male Wistar rats, each weighing between 160 and 190 g. The animals underwent 20-minute bilateral ischaemia of the internal carotid arteries (ICAs) under propofol anaesthesia (Propofol-Novo, LLC "Novofarm-Biosynthesis", Ukraine; 60 mg/kg, intraperitoneally). This investigation is a continuation of previous work assessing the therapeutic effects of mesenchymal stromal cells (MSCs) of various origins on biochemical processes in the somatosensory cortex of rats subjected to induced IR injury [13, 14]. The chosen IR model effectively mimics the clinical presentation of cerebral infarction and serves as an optimal platform for evaluating potential neuroprotective agents. The rats were bred and housed in the vivarium of the National Pirogov Memorial Medical University, Vinnytsya (NPMMU), under standard

laboratory conditions with free access to food and water. The study was conducted in full compliance with international bioethical standards, including the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes [15], and the Law of Ukraine No. 344-IV [16]. MSCs and MSC lysate were obtained from the Institute of Molecular Biology and Genetics (IMBG) of the National Academy of Sciences of Ukraine (NAS), as part of an official scientific cooperation agreement between IMBG NAS and NPMMU. Rats were chosen as experimental subjects due to the morphological and angioarchitectural similarities between their cerebral cortex and that of humans.

For the experiment, the animals were randomly assigned to nine groups, each comprising 14 rats. The first group consisted of intact (untreated) animals. The second group included sham-operated rats, which underwent anaesthesia, skin incision, and vessel preparation, but without placement of silk ligatures on the ICAs, to control for procedural trauma. The third group (pathology control) underwent 20-minute IR of the ICAs followed by a single intravenous injection of 0.9% saline solution (2 ml/kg). The fourth group received a transplantation of 10^6 human Wharton's jelly-derived MSCs (hWJ-MSCs) per animal. The fifth group received 10^6 rat embryonic fibroblasts (REFs) per animal. The sixth group was administered 10^6 human adipose tissue-derived MSCs (AT-MSCs), and the seventh group received 10^6 rat AT-MSCs per animal. The eighth group was given 0.2 ml of lysate derived from hWJ-MSCs. The ninth group received a single dose of the reference drug citicoline ("Neuroxon", Arterium Corporation, Ukraine) at 250 mg/kg. As early MSC transplantation has been shown to promote greater neurological recovery, reduce infarct volume, and require fewer donor cells (1×10^6) to achieve therapeutic effects, intravenous administration of all tested substances was performed immediately after IR [17]. On the 7th and 14th days following treatment, the animals were humanely euthanised by decapitation under propofol anaesthesia (Propofol-Novo, Novofarm-Biosynthesis LLC, Ukraine; 60 mg/kg, intraperitoneally), and the brains were promptly extracted. Biochemical parameters of nitrosative balance in the rat somatosensory cortex were assessed under IR conditions and in the context of therapeutic correction.

Biochemical studies were conducted in the scientific research and clinical diagnostic laboratory of NPMMU, certified by the Ministry of Health of Ukraine. Brains were extracted from decapitated animals, and tissues of the somatosensory cortex were rinsed with cold 1.15% KCl solution before being homogenised at 3,000 rpm (Teflon-glass) in 1.15% KCl (1:3, w/v). The postnuclear fraction was obtained from the homogenates by centrifugation (30 minutes, 600 × g, at -4°C) and stored at -20°C until further analysis. The total activity of NOS was assessed by measuring the concentration of nitrite anion (NO_2^-) following incubation of the postnuclear supernatant for 60 minutes in a reaction medium. Each 1 ml of reaction mixture contained 50 mM KH_2PO_4–NaOH buffer (pH 7.0), 1 mM $MgCl_2$, 2 mM $CaCl_2$, 1 mM NADPH, and 2.2 mM L-arginine (NADPH from Sigma, USA) [18]. Total NOS activity was determined using a spectrophotometric method. Optical density measurements were performed with an APEL PD-303 spectrophotometer (Japan). This method is based on the stereospecific reduction of NADPH during the formation of NO from L-arginine. The decrease in NADPH, which is equimolar to the amount of NO formed, was recorded spectrophotometrically at a wavelength of 340 nm. Total protein content in the postnuclear fraction was determined using the Lowry method [19]. Statistical analysis of the obtained data was conducted using Microsoft Excel 2015 and Statistica 14.0 software. Differences between the studied parameters were evaluated using the non-parametric Mann-Whitney U test, with statistical significance set at $p < 0.05$.

Results and Discussion

No differences were observed in the total NOS activity within the somatosensory cortex between intact and sham-operated animals. Consequently, the sham-operated rats were used as the control group. In this study, nitrosative stress was found to develop in rats on days 7 and 14 following cerebral ischaemia-reperfusion (IR), as evidenced by increased NOS activity. Specifically, the study established that cerebral IR in rats resulted in an average increase in total NOS activity in the somatosensory cortex by 82.4%, 22.0%, 38.5%, 66.5%, 71.0%, 80.7%, and 11.1% ($p < 0.05$) on day 7, and by 72.0%, 19.5%, 33.0%, 55.9%, 59.4%, 62.5%, and 10.0% ($p < 0.05$) on day 14, in comparison to sham-operated animals (Table 1). This increase in NOS activity is likely attributed to the iNOS, whose expression is known to rise during inflammatory responses.

Table 1. Parameters of nitrosative stress in the somatosensory cortex of rats under conditions of cerebral IR and following therapeutic intervention (M ± m, n = 7)

Experimental conditions / Biochemical parameter		Groups of animals								
		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	Group 9
		Intact	Sham-operated	IR (control pathology)	IR + hWJ-MSCs	IR + REF	IR + human AT-MSCs	IR + rat AT-MSCs	IR + MSC lysate	IR + citicoline
NOS, pmol/min·mg protein	7th day	119.3 ± 3.93	122.6 ± 4.66	223.6 ± 9.18* (+82.4%)	149.6 ± 5.11*#$ (+22.0%) [-33.1%]	169.7 ± 3.91*#$ (+38.5%) [-24.1%]	204.1 ± 4.91*$ (+66.5%)	209.6 ± 7.91*$ (+71.0%)	221.4 ± 7.17*$ (+80.7%)	136.1 ± 3.10*# (+11.1%) [-39.1%]

Continued Table 1

Experimental conditions / Biochemical parameter		Groups of animals								
		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	Group 9
		Intact	Sham-operated	IR (control pathology)	IR + hWJ-MSCs	IR + REF	IR + human AT-MSCs	IR + rat AT-MSCs	IR + MSC lysate	IR + citicoline
NOS, pmol/min·mg protein	14th day	116.6 ± 2.36	121.3 ± 3.90	208.6 ± 8.70* (+72.0%)	145.0 ± 3.21*#$ (+19.5%) [-30.5%]	161.3 ± 5.79*#$ (+33.0%) [-22.7%]	189.1 ± 6.18*$ (+55.9%)	193.3 ± 10.54*$ (+59.4%)	197.1 ± 8.06*$ (+62.5%)	133.4 ± 4.35*# (+10.0%) [-36.0%]

Notes: * – $p < 0.05$ in comparison to the corresponding time group of sham-operated animals; # – $p < 0.05$ in comparison to the corresponding time group of animals with control pathology; $ – $p < 0.05$ in comparison to the corresponding time group of citicoline-treated animals. In round brackets – changes of the parameter compared to its level in sham-operated animals; in square brackets – changes relative to the parameter of the control pathology group
Source: created by the authors

The therapeutic interventions applied for IR brain injury in rats during the subacute and recovery phases of acute cerebrovascular insufficiency exerted a positive modulatory effect on the NO cycle, leading to a statistically significant reduction in total NOS activity. The most pronounced decrease in total NOS activity was observed with citicoline treatment, followed by transplantation of hWJ-MSCs, and to a lesser extent with REFs. Specifically, during the experimental period, NOS activity in the somatosensory cortex decreased progressively, averaging 39.1%, 33.1%, and 24.1% by day 7 of follow-up compared to the control group. By day 14, the reductions were 36.0%, 30.5%, and 22.7%, respectively ($p < 0.05$).

Thus, the subacute phase of stroke is characterised by an imbalance in the functioning of the nitric oxide system in the somatosensory cortex of the rat brain, associated with a 1.8-fold increase in total NOS activity ($p < 0.05$). Similar changes were observed during the recovery phase of acute cerebral ischaemia. Among the tested treatments, hWJ-MSCs – more so than other MSCs and MSC lysates – along with the reference drug citicoline, contributed most effectively to restoring normal NO cycle functioning in the ischaemic brain during both subacute and recovery phases of stroke. It was also demonstrated that, in terms of modulating total NOS expression, REFs were somewhat inferior to hWJ-MSCs, indicating a higher cerebroprotective potential of xenotransplantation. This effect of hWJ-MSCs may be one of the key mechanisms underlying their protective action in ischaemic and reperfusion injury in the context of cerebral IR in rats.

An important objective of the present study was to elucidate the biochemical mechanisms underlying the cerebroprotective effects of MSCs of different cytological origins, particularly through their influence on nitro-oxidative stress during IR injury in the somatosensory cortex. Numerous studies have highlighted the critical involvement of reactive nitrogen species (RNS) in various pathological processes occurring during reperfusion following ischaemia. Nitric oxide and peroxynitrite are the principal RNS involved in IR injury and are major contributors to nitrosative stress. For example, the study by K. Yatsenko *et al.* [20] demonstrated glial cell activation during ischaemic stroke. In another study, Q. Liu and S.K. Sorooshyari [21] established that microglia become activated within the first hours following ischaemia and act as major sources of cytokine release after stroke. Y. Chen *et al.* [17] showed that microglia and astrocytes are the primary producers of ROS and RNS, which together influence synaptic transmission and play a critical role in neuron-glia communication, contributing to secondary neural damage during IR injury.

A number of experimental studies have also demonstrated the effectiveness of using mesenchymal stromal cells (MSCs) to normalise the functioning of the NO system in the brains of animals with ischaemic stroke. For instance, D. Lapi *et al.* [22] found that bone marrow-derived MSCs increased endothelial NOS (eNOS) expression in rats following transient middle cerebral artery occlusion. S.S. Wang *et al.* [23] demonstrated that extracellular vesicles derived from MSCs exert therapeutic effects in various neurological disorders, including ischaemic stroke and hypoxic-ischaemic brain injury, by suppressing iNOS expression. B. Soria *et al.* [24], using a model of radiation-induced neurological complications, showed that intranasal delivery of human MSCs reduced iNOS expression and oxidative stress biomarkers, ultimately promoting neuronal survival and improving cognitive function in mice. Y. Li *et al.* [25] also reported that MSC transplantation therapy can reduce the number of activated microglia and suppress the expression of pro-inflammatory cytokines, reactive oxygen species (ROS), and reactive nitrogen species (RNS). Thus, MSCs may modulate microglial activation, reducing neuroinflammation and secondary brain injury following ischaemic stroke. Furthermore, Y. Wang *et al.* [26] found that transplantation of hWJ-MSCs increased NO levels and enhanced nNOS activity in a mouse model of Alzheimer's disease. These findings suggest that the antinitrosative effects of MSCs are likely disease-dependent and may vary based on the pathological context.

A distinctive feature of the present study was the use of intravenous transplantation of MSCs of different origins, along with intravenous administration of factors isolated from Wharton's jelly-derived MSCs (WJ-MSCs) and citicoline. An increase in total NOS activity in the brains of experimental animals may indicate NO hyperproduction. At

this stage of cerebral IR, brain injury is primarily associated with excessive NO formation, predominantly due to activation of Ca^{2+}-dependent NOS, which aligns with findings in the literature [1]. These studies support the existence of a temporal pattern in the expression of different NOS isoforms during ischaemic brain injury. During the recovery phase following ischaemia, NO overproduction is mainly driven by iNOS activation.

Thus, the data from this research confirm the therapeutic potential of hWJ-MSC transplantation. It was found that intravenous administration at a dose of 10^6 cells per animal resulted in more pronounced suppression of total NOS expression compared to other types of MSCs and their lysates. Moreover, Wharton's jelly-derived MSCs were not inferior to citicoline (250 mg/kg) in restoring normal functioning of the nitric oxide cycle in the somatosensory cortex. The therapeutic effect of prenatal stem cell transplantation in rats with brain IR injury exceeded that of adult adipose tissue-derived stem cells, as evidenced by a more significant suppression of total NOS expression. These findings expand current knowledge on the therapeutic potential of MSCs for the treatment of IR injury and open new perspectives for the development of effective cell therapy approaches to correct nitric oxide metabolism disorders.

Conclusions

The 20-minute modelled IR of the ICAs induced an imbalance in the functioning of the NO system in the somatosensory cortex of rats, characterised by an increase in total NOS activity. This finding confirms the key role of nitrosative stress in the pathogenesis of ischaemic brain injury and its progression during the reperfusion phase. Therapeutic correction of ischaemic and reperfusion injury in the somatosensory cortex under IR conditions using hWJ-MSCs proved superior to other tested MSCs and MSC lysate, demonstrating a positive modulatory effect on nitrosative stress. Among all options studied, hWJ-MSCs exhibited neuroprotective effects comparable to those of the reference drug citicoline, indicating their potential as an alternative or adjunctive treatment. Specifically, both citicoline (250 mg/kg, i.v.) and hWJ-MSCs (10^6 cells/animal, i.v.) significantly contributed to the normalisation of total NOS activity in the affected brain regions during both the subacute and recovery phases. In contrast, REFs demonstrated lower efficacy, highlighting the advantages of xenogeneic cell therapy with hWJ-MSCs. Despite these promising results, one limitation of the study is the use of a single dose and administration schedule, which may not reflect the optimal therapeutic regimen. Future research should address dose-response relationships, long-term outcomes, and additional mechanisms of action. In conclusion, this study experimentally substantiates the therapeutic potential of hWJ-MSCs in managing IR injury and provides a scientific foundation for the development of an injectable, cell-based pharmaceutical product. These findings support the need for further translational research and clinical trials to evaluate the safety and efficacy of hWJ-MSCs in patients with acute ischaemic stroke.

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Conflict of Interest

None.

References

[1] Chavda V, Chaurasia B, Garg K, Deora H, Umana GE, Palmisciano P, et al. Molecular mechanisms of oxidative stress in stroke and cancer. Brain Disord. 2022;5:100029. DOI: 10.1016/j.dscb.2021.100029

[2] Arfin S, Jha NK, Jha SK, Kesari KK, Ruokolainen J, Roychoudhury S, et al. Oxidative stress in cancer cell metabolism. Antioxidants. 2021;10(5):642. DOI: 10.3390/antiox10050642

[3] García-Sánchez A, Miranda-Díaz AG, Cardona-Muñoz EG. The role of oxidative stress in physiopathology and pharmacological treatment with pro- and antioxidant properties in chronic diseases. Oxid Med Cell Longev. 2020;2020:2082145. DOI: 10.1155/2020/2082145

[4] Wu L, Xiong X, Wu X, Ye Y, Jian Z, Zhi Z, et al. Targeting oxidative stress and inflammation to prevent ischemia-reperfusion injury. Front Mol Neurosci. 2020;13:28. DOI: 10.3389/fnmol.2020.00028

[5] Piacenza L, Zeida A, Trujillo M, Radi R. The superoxide radical switch in the biology of nitric oxide and peroxynitrite. Physiol Rev. 2022;102(4):1881–906. DOI: 10.1152/physrev.00005.2022

[6] Li C, Sun T, Jiang C. Recent advances in nanomedicines for the treatment of ischemic stroke. Acta Pharm Sin B. 2021;11(7):1767–88. DOI: 10.1016/j.apsb.2020.11.019

[7] Shehjar F, Maktabi B, Rahman ZA, Bahader GA, James AW, Naqvi A, et al. Stroke: Molecular mechanisms and therapies: Update on recent developments. Neurochem Int. 2023;162:105458. DOI: 10.1016/j.neuint.2022.105458

[8] Li T, Zhu GH. Research progress of stem cell therapy for ischemic stroke. Ibrain. 2021;7(3):245–56. DOI: 10.1002/j.2769-2795.2021.tb00088.x

[9] Chan MKS, Nalapko Y. Ageing brain and neurodegeneration: Preventive and regenerative medicine. In: Trukhanov A, Chan MKS, editors. Handbook of anti-aging medicine. London: European Wellness Academy; 2023. P. 329–63.

[10] Li W, Shi L, Hu B, Hong Y, Zhang H, Li X, et al. Mesenchymal stem cell-based therapy for stroke: Current understanding and challenges. Front Cell Neurosci. 2021;15:628940. DOI: 10.3389/fncel.2021.628940

[11] Ntege EH, Sunami H, Shimizu Y. Advances in regenerative therapy: A review of the literature and future directions. Regen Ther. 2020;14:136–53. DOI: 10.1016/j.reth.2020.01.004
[12] Wu X, Jiang J, Gu Z, Zhang J, Chen Y, Liu X. Mesenchymal stromal cell therapies: Immunomodulatory properties and clinical progress. Stem Cell Res Ther. 2020;11(1):345. DOI: 10.1186/s13287-020-01855-9
[13] Konovalov S, Moroz V, Yoltukhivskyi M, Gadzhula N, Deryabina O, Kordium V. Comparative effects of mesenchymal stromal cells of various origins and sources on biochemical parameters in the hippocampus of rats during cerebral ischemia-reperfusion. Cell Organ Transpl. 2024;12(2):118–25. DOI: 10.22494/cot.v12i2.169
[14] Konovalov S, Moroz V, Yoltukhivskyi M, Gadzhula N, Stelmashchuk A. The influence of mesenchymal stromal cells of different genesis on energy metabolism in the rat somatosensory cortex during ischemia-reperfusion. East Ukr Med J. 2024;12(3):642–50. DOI: 10.21272/eumj.2024;12(3):642-650
[15] European Council. European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes [Internet]. 1986 March 18 [cited 2024 September 10]. Available from: https://rm.coe.int/168007a67b
[16] Law of Ukraine No. 3447-IV. On the Protection of Animals from Cruelty [Internet]. 2006 February 21 [cited 2024 September 10]. Available from: https://zakon.rada.gov.ua/laws/show/3447-15#Text
[17] Chen Y, Peng D, Li J, Zhang L, Chen J, Wang L, et al. A comparative study of different doses of bone marrow-derived mesenchymal stem cells improve post-stroke neurological outcomes via intravenous transplantation. Brain Res. 2023;1798:148161. DOI: 10.1016/j.brainres.2022.148161
[18] Hula NM, Kosiakova HV, Berdyschev AH. (2007). The effects of n-stearoylethanolamine on the NO-synthase pathway of NO generation in the aorta and heart of streptozotocin-induced diabetic rats. Ukr Bioch J. 2007;79(5):153–8.
[19] Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. J Biol Chem. 1951;193(1):265–75. DOI: 10.1016/S0021-9258(19)52451-6
[20] Yatsenko K, Lushnikova I, Ustymenko A, Patseva M, Govbakh I, Kyryk V, et al. Adipose-derived stem cells reduce lipopolysaccharide-induced myelin degradation and neuroinflammatory responses of glial cells in mice. J Pers Med. 2020;10(3):66. DOI: 10.3390/jpm10030066
[21] Liu Q, Sorooshyari SK. Quantitative and correlational analysis of brain and spleen immune cellular responses following cerebral ischemia. Front Immunol. 2021;12:617032. DOI: 10.3389/fimmu.2021.617032
[22] Lapi D, Vagnani S, Sapio D, Mastantuono T, Boscia F, Pignataro G, et al. Effects of bone marrow mesenchymal stem cells (BM-MSCs) on rat pial microvascular remodeling after transient middle cerebral artery occlusion. Front Cell Neurosci. 2015;9:329. DOI: 10.3389/fncel.2015.00329
[23] Wang SS, Jia J, Wang Z. Mesenchymal stem cell-derived extracellular vesicles suppresses iNOS expression and ameliorates neural impairment in Alzheimer's disease mice. J Alzheimers Dis. 2017;61(3):1005–13. DOI: 10.3233/JAD-170848
[24] Soria B, Martin-Montalvo A, Aguilera Y, Mellado-Damas N, López-Beas J, Herrera-Herrera I, et al. Human mesenchymal stem cells prevent neurological complications of radiotherapy. Front Cell Neurosci. 2019;13:204. DOI: 10.3389/fncel.2019.00204
[25] Li Y, Dong Y, Ran Y, Zhang Y, Wu B, Xie J, et al. Three-dimensional cultured mesenchymal stem cells enhance repair of ischemic stroke through inhibition of microglia. Stem Cell Res Ther. 2021;12(1):358. DOI: 10.1186/s13287-021-02416-4
[26] Wang Y, Jiang J, Fu X, Zhang J, Song J, Wang Y, et al. Fe_3O_4@polydopamine nanoparticle-loaded human umbilical cord mesenchymal stem cells improve the cognitive function in Alzheimer's disease mice by promoting hippocampal neurogenesis. Nanomedicine. 2022;40:102507. DOI: 10.1016/j.nano.2021.102507

Вплив трансплантації мезенхімальних стромальних клітин на обмін монооксиду азоту в соматосенсорній корі щурів при ішемії-реперфузії

Сергій Коновалов

Кандидат медичних наук, доцент
Вінницький національний медичний університет ім. М. І. Пирогова
21018, вул. Пирогова, 56, м. Вінниця, Україна
https://orcid.org/0000-0002-9729-7204

Михайло Йолтухівський

Доктор медичних наук, професор
Вінницький національний медичний університет ім. М. І. Пирогова
21018, вул. Пирогова, 56, м. Вінниця, Україна
https://orcid.org/0000-0001-8733-8247

Наталія Гаджула

Кандидат медичних наук, доцент
Вінницький національний медичний університет ім. М. І. Пирогова
21018, вул. Пирогова, 56, м. Вінниця, Україна
https://orcid.org/0000-0003-0016-2264

Анотація. Однією з причин інсульту є гостре порушення мозкового кровообігу, яке починається з утворення гострого дефіциту енергії нейронів, активації «ішемічного каскаду» та нітрозативного стресу. Реактивні форми азоту, зокрема оксид азоту та пероксинітрит, відіграють центральну роль у пошкодженні тканин. Пошук нових терапевтичних стратегій для боротьби з цими процесами залишається актуальним. Метою цього дослідження було оцінити вплив трансплантації мезенхімальних стромальних клітин різного походження, їх лізатів та цитиколіну на метаболізм оксиду азоту в соматосенсорній корі очей за допомогою моделі ішемії-реперфузії. Експериментальна модель була створена з використанням 126 щурів, яким проводилась двостороння 20-хвилинна оклюзія внутрішніх сонних артерій з подальшою реперфузією. Тварин було розділено на групи відповідно до введених речовин: мезенхімальні стромальні клітини, отримані з Вартонових драглів пуповини людини, жирової тканини людини та щура, ембріональні фібробласти щура, лізат мезенхімальних стромальних клітин Вартонових драглів, цитиколін. На 7-й і 14-й день після лікування було проаналізовано показники метаболізму оксиду азоту в соматосенсорній корі головного мозку після ішемії-реперфузії. Результати продемонстрували, що трансплантація мезенхімальних стромальних клітин з Вартонових драглі людської пуповини та фетальних фібробластів щурів, а також введення цитиколіну значно змінили загальну активність оксиду азоту синтетази протягом спостережуваних періодів. Було виявлено, що мезенхімальні стромальні клітини, отримані з Вартонових драглів людини, особливо в поєднанні з цитиколіном, зменшували нітрозативний стрес. Таким чином, модель ішемії-реперфузії викликала дисбаланс у функціонуванні системи оксиду азоту. Найбільший захисний ефект спостерігався при трансплантації мезенхімальних стромальних клітин з Вартонових драглів з пуповини людини, які ефективно захищали нейрони від нітрозативного стресу, подібно до цитиколіну

Ключові слова: церебральна ішемія; Вартонові драглі; лізат; цитиколін; NO-синтаза