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ABSTRACT

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THE INFLUENCE OF MESENCHYMAL STROMAL CELLS OF DIFFERENT GENESIS ON ENERGY METABOLISM IN THE RAT SOMATOSENSORY CORTEX DURING ISCHEMIA-REPERFUSION

Introduction. About 60-80% of cerebral circulation disorders are due to ischemia, that leads to high mortality, disability in working age and economic burden on society in developed countries of the world.

Objective: To investigate the effect of ischemia-reperfusion on parameters of carbohydrate and energy exchanges in the rat somatosensory cortex and to determine the cerebroprotective action of mesenchymal stromal cells (MSCs) of various genesis, MSC lysate and the reference drug Citicoline.

Methods. The study was performed on 200 male Wistar rats, divided into 9 groups. Group 1 included intact animals; group 2 – sham-operated rats; group 3 – control pathology (rats were subjected to ischemia-reperfusion by occlusion of the internal carotid arteries and injected with a 0.9% saline solution (2 ml/kg) into the femoral vein); group 4 – immediately after ischemia-reperfusion rats were transplanted with 10^6 MSC cells/animal derived from Wharton's jelly of the human umbilical cord; group 5 – 10^6 cells/animal of rat embryonic fibroblasts; group 6 – 10^6 cells/animal derived from human adipose MSCs; group 7 – 10^6 cells/animal derived from rat adipose MSCs; group 8 – 0.2 ml/animal of lysate derived from Wharton's jelly MSCs; group 9 – the reference drug Citicoline (250 mg/kg). Parameters of carbohydrate and energy metabolism in rat somatosensory cortex under the conditions of cerebral IR and on the background of correction studied on the 7^{th} and 14^{th} day.

Results. It was found that after cerebral ischemia-reperfusion in the rat somatosensory cortex in research periods an increase in the levels of glucose, lactate, lactate/pyruvate ratio and a decrease in the content of pyruvate and succinate dehydrogenase were revealed. In the groups of experimental animals with intravenous transplantation of MSCs of

various origins, MSC lysate and Citicoline, the perturbation in glucose metabolism was reduced, lactate content was decreased and the levels of pyruvate and succinate dehydrogenase were significantly increased ($p<0.05$), compared to rats with control pathology. A more pronounced positive effect in the recovery of disturbed energy processes and elimination of metabolic acidosis was observed with the use of human Wharton's jelly-derived MSCs.

Conclusions. The study demonstrated that experimental 20-minute model ischemia-reperfusion in rats caused a violation of the carbohydrate and energy balance in the somatosensory cortex. Human umbilical cord blood-derived MSCs contributed to the recovery of disturbed energy processes in the somatosensory cortex and eliminated metabolic acidosis at the level of Citicoline or better than it, which is one of the links of the mechanism of the cerebral protective action of MSCs. Embryonic rat fibroblasts were slightly inferior in efficiency to Citicoline and human umbilical cord Wharton's jelly MSCs, which indicates a higher cerebroprotective activity of xenotransplantation.

Keywords: ischemia-reperfusion, somatosensory cortex, glucose, lactate, pyruvate, succinate dehydrogenase, rats.

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ВПЛИВ МЕЗЕНХІМАЛЬНИХ СТРОМАЛЬНИХ КЛІТИН РІЗНОГО ГЕНЕЗУ НА ЕНЕРГЕТИЧНИЙ МЕТАБОЛІЗМ У СОМАТОСЕНСОРНІЙ КОРІ ГОЛОВНОГО МОЗКУ ЩУРІВ ПРИ ІШЕМІЇ-РЕПЕРФУЗІЇ

Вступ. Близько 60-80% порушень мозкового кровообігу припадає на ішемію, що призводить до великої смертності, інвалідизації в працездатному віці та економічному навантаженню на суспільство в розвинутих країнах світу.

Мета: дослідити вплив ішемії-реперфузії на показники вуглеводного та енергетичного обмінів у соматосенсорній корі щурів та визначити церебропротекторну дію мезенхімальних стромальних клітин (МСК) різного генезу, лізату МСК та референс-препарату цитиколіну.

Методи. Експеримент проведено на 200 щурах-самцях лінії Вістар, розподілених на 9 груп. 1-а група включала інтактних тварин; 2-а група – псевдооперованих щурів; 3-а група – контрольна патологія (щурам цієї групи проводили ішемію-реперфузію внутрішньої сонної артерії й однократно вводили в стегнову вену 0,9% розчин NaCl із розрахунку 2 мл/кг); 4-й групі тварин одразу після ішемії-реперфузії однократно трансплантували 10^6 клітин/тварину МСК із Вартонових драглів пуповини людини; 5-й групі – 10^6 клітин/тварину ембріональних фібробластів щура; 6-й групі – 10^6 клітин/тварину МСК жирової тканини людини; 7-й групі – 10^6 клітин/тварину стовбурових клітин, отриманих із жирової тканини щура; 8-й групі – одноразово вводили 0,2 мл/тварину лізату МСК Вартонових драглів людини; 9-й групі – референс-препарат цитиколін у дозі 250 мг/кг. Показники вуглеводного та енергетичного обмінів у соматосенсорній корі щурів за умов ішемії-реперфузії мозку й на тлі корекції досліджували на 7 та 14-добу.

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Результати. Встановлено, що після ішемії-реперфузії головного мозку в соматосенсорній корі щурів в досліджувані періоди спостерігалось підвищення рівня глюкози, лактату, співвідношення лактат/піруват та зниження вмісту піруват та сукцинатдегідрогенази. У групах піддослідних тварин, яким була проведена внутрішньовенна трансплантація МСК різного походження, лізату МСК та цитиколіну, достовірно зменшувалась пертурбація в метаболізмі глюкози, знижувався вміст лактату, підвищувались рівні піруват та сукцинатдегідрогенази ($p<0,05$), відносно щурів із контрольною патологією. Більш виражений позитивний вплив у відновленні порушених енергетичних процесів та усунення метаболічного ацидозу спостерігали при застосуванні МСК Вартонових драглів пуповини людини.

Висновки. Проведене дослідження продемонструвало, що експериментальна 20-хвилинна модельна ішемія-реперфузія в щурів спричинила порушення вуглеводного й енергетичного балансу в соматосенсорній корі. МСК Вартонових драглів пуповини людини сприяли відновленню порушених енергетичних процесів у соматосенсорній корі та усували метаболічний ацидоз на рівні цитиколіну або краще за нього, що є однією з ланок механізму церебропротекторної дії МСК. За ефективністю ембріональні фібробласти щура дещо поступалися цитиколіну та МСК Вартонових драглів пуповини людини, що свідчить про більш високу церебропротекторну активність ксенотрансплантації.

Ключові слова: ішемія-реперфузія, соматосенсорна кора, глюкоза, лактат, піруват, сукцинатдегідрогеназа, щури.

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INTRODUCTION / ВСТУП

In recent years, vascular diseases have become the main cause of disability and mortality in mature and elderly people. According to the American Heart Association as of 2023, cerebral infarction is the second leading cause of death among the population [1]. About 60-80% of cerebral circulation disorders are caused by ischemia, which leads to high mortality, disability in working age and economic burden on society in developed countries of the world [1, 2].

Cerebral infarction is accompanied by a complex pathological process, which begins with the development of acute energy deficiency in neurons with subsequent activation of ischemic cascade response, that leads to an increase in the volume of irreversibly damaged nervous tissue [3]. As a result of the recovery of cerebral perfusion during thrombolytic therapy, in turn, contributes to the deepening of disturbances of metabolic processes in the previously ischemic brain, which leads to the formation of reperfusion injuries [4-6]. During ischemia-reperfusion (IR), the brain undergoes significant fluctuations in constant indicators of homeostasis both at the cellular and tissue levels. In conditions of IR (clinically, this model corresponds to the post-perfusion injury of the brain after thrombolysis), destruction of desmosomes and an increase in the distance between individual neurons occurs, which promotes the spread of free radicals and second messengers, and also leads to the damage of intact cells and the increase of the lesion foci [7]. At first, with ischemic, and then with reperfusion injuries, on the background of the development of experimental IR, fluctuations in the energy balance of brain tissues occur. Considering this, it would be expedient to evaluate the influence of the studied cells and substances on indicators of carbohydrate and energy metabolism in the rat somatosensory cortex in the conditions of model IR.

Objective: to investigate the effect of ischemia-reperfusion in the conditions of model IR on parameters of carbohydrate and energy exchanges in the rat somatosensory cortex and to determine the cerebral protective action of MSCs of different genesis, MSC lysate and the reference drug Citicoline.

MATERIALS AND METHODS

The research was carried out in 200 four-month-old male rats of the Wistar line weighing between 160-190 g. The animals were kept under standard vivarium conditions of National Pirogov Memorial Medical University (Vinnytsya, Ukraine) and had free access to feeder. All manipulations with animals were performed in accordance with the international norms and rules of European Communities Council Directives 86/609/EEC (1986), and according to the principles of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Scientific Purposes" [8] and the Law of Ukraine "On the protection of animals from cruelty" (No. 3447-IV, 2006) [9].

The use of rats as experimental animals is due to the similarity of angioarchitectonics and morphology of the cerebral cortex in rats and humans. The experimental IR model was made by bilaterally occlusion of internal carotid arteries (ICA) lasting 20 minutes under propofol "Propofol-Novo" anesthesia (Novofarm-Biosintez LLC, Ukraine) at the dose of 60 mg/kg intraperitoneally. Experimental rats were divided into 9 groups. Group 1 included intact animals. Group 2 consisted of pseudo/sham-operated rats, which underwent access to the ICA without its subsequent ligation to reduce the impact of the traumatic experimental conditions. Group 3 included rats with control pathology; they were subjected to cerebral ischemia by ligatures placing on the ICA. In 20 minutes the ligatures were removed from the ICA (reperfusion) and a 0.9 % saline solution was injected into the femoral vein (2 ml/kg). The same dose of physiological solution was administered to group 2 rats. In the group 4 the rats were transplanted with 10^6 MSC cells/animal derived from Wharton's jelly of the human umbilical cord (HUC-MSCs) immediately after IR. In the group 5 of animals a single transplantation with 10^6 cells/animal of rat embryonic fibroblasts (REF) was used after IR. Group 6 of rats with IR were transplanted with 10^6 cells/animal derived from human adipose tissue MSCs (HAT-MSCs). Group 7 of rats were injected with 10^6 cells/animal derived from rat adipose MSCs. Group 8 of animals was injected with 0.2 ml/animal of lysate derived from human Wharton's jelly MSCs. Group 9 of rats administered a single dose (250 mg/kg) of the reference drug Citicoline "Neuroxon" (Arterium Corporation, Ukraine). The studied substances were injected intravenously into the femoral vein once immediately after IR, as early MSCs transplantation led to rapid recovery of cognitive impairment and decreased infarct volume, and also required a small amount (1×10^6) of donor cells for a beneficial effect [10]. The method of deriving MSCs is described in our previous study [11].

On the 7th and 14th day of the experiment, the rat brain was removed immediately after decapitation using propofol anesthesia and determined the parameters of carbohydrate and energy exchanges in rat somatosensory cortex under the conditions of cerebral IR and on the background of its correction. Biochemical studies were carried out in the scientific-research and clinical-diagnostic laboratory of our university, certified by the Ministry of Health of Ukraine. Glucose concentration was determined by the glucose oxidase method using standard sets of Filisit-Diagnostika company (Ukraine). The content of pyruvate and lactate was determined by the colorimetric method, succinate dehydrogenase was measured according to the rate of reduction of potassium hexacyanoferrate (III) [12].

Statistical analysis of the obtained data was performed with the use of Microsoft Excel 2015 and Statistica 14.0 computer programs. Probability of differences was assessed using the unpaired nonparametric Mann-Whitney U test. The difference between the studied parameters was considered statistically significant at a value $p < 0.05$.

RESULTS

In the study of intact and sham-operated animals, no differences were found between the indicators of metabolic processes in the brain tissues, so we used the group of sham-operated rats as a control.

It was established on the IR model in rats that changes in energy homeostasis of brain tissues developed as a result of ischemic damage, namely glucose imbalance in the somatosensory cortex (Table 1). Thus, on the 7th day of the experiment, an increase in the glucose content was observed in groups 3, 4, 5, 6, 7, 8, 9 of rats, which was 51.2, 20.8, 28.4, 40.3, 40.8, 42.2, 17.5%, respectively ($p<0.05$) compared with sham-operated animals. In the experimental rats under these conditions in group 4 with intravenous transplantation of HUC-MSCs, group 5 with transplantation of REF, and group 9 with Citicoline treatment, the increase in glucose was significantly lower by 20.1; 15.1 and 22.3%, respectively ($p<0.05$) compared to rats with control pathology. Transplantation of HUC-MSCs, similar to Citicoline, contributed to stabilization of the glucose level in the brain of rats with IR, and the glucose concentration was on average 2.55±0.07 and 2.48±0.07 μmol/g of dry tissue. Compared to the group of animals that received the reference drug, in groups 5, 6, 7, 8 the more rise in glucose level was observed on average by 9.3, 19.4, 19.8 and 21.0% ($p<0.05$). On the 14th day of the experiment, an improvement in glucose metabolism in the brain was recorded: the increase in glucose content was 33.9, 10.5, 20.2, 26.6, 27.5, 29.8, 10.1%, respectively ($p<0.05$) compared with the group of sham-operated animals. In animals of groups 4, 5 and 9, the increase in glucose level in the somatosensory

Table 1 – Indicators of carbohydrate and energy metabolism in the somatosensory cortex of rats under conditions of IR of the brain and on the background of correction (M ± m, n=7)

Periods of follow-up	Biochemical parameters				
	Glucose μmol/g of dry tissue	**Lactate, μmol/g of dry tissue**	**Pyruvate, μmol/g of dry tissue**	**Lactate / Pyruvate**	**SDH, μmol/min•mg protein**
Group 1 – Intact rats					
7th day	2.13±0.08	1.54±0.05	0.287±0.005	5.40±0.21	8.04±0.27
14th day	2.10±0.09	1.44±0.04	0.301±0.011	4.80±0.10	8.27±0.16
Group 2 – Sham-operated rats					
7th day	2.11±0.10	1.61±0.03	0.292±0.009	5.56±0.20	8.15±0.21
14th day	2.18±0.08	1.51±0.05	0.308±0.013	4.91±0.14	8.35±0.17
Group 3 – IR (control pathology)					
7th day	3.19±0.10* (+51.2%)	6.53±0.14* (+305.6%)	0.158±0.008* (-45.9%)	41.67±1.84* (+650%)	3.14±0.17* (-61.5%)
14th day	2.92±0.07* (+33.9%)	5.87±0.13* (+288.7%)	0.187±0.006* (-39.3%)	31.67±1.57* (+545.6%)	3.99±0.22* (-52.1%)
Group 4 – IR + human umbilical cord Wharton's jelly-derived MSCs					
7th day	2.55±0.07*# (+20.8%) [-20.1%]	4.59±0.08*# (+185.1%) [-29.7%]	0.241±0.008*# (-17.5%) [+52.5%]	19.17±0.68*# (+245.3%) [-54.0%]	6.09±0.36*# (-25.3%) [+93.9%]
14th day	2.41±0.05*# (+10.5%) [-17.5%]	3.60±0.12*# (+138.4%) [-38.7%]	0.267±0.011*# (-13.3%) [+42.8%]	13.63±0.62*# (+177.0%) [-57.1%]	7.72±0.14*# (-7.5%) [+93.5%]
Group 5 – IR + rat embryonic fibroblasts					
7th day	2.71±0.06*#$ (+28.4%) [-15.1%] {+9.3%}	5.22±0.13*#$ (+224.2%) [-20.1%] {+17.6%}	0.223±0.010*# (-23.6%) [+41.1%]	23.69±1,18*#$ (+326.3%) [-43.2%] {+20.9%}	5.47±0.18*#$ (-32.9%) [+74.2%] {-14.7%}
14th day	2.62±0.08*#$ (+20.2%) [-10.3%] {+9.2%}	4.17±0.11*#$ (+176.2%) [-29.0%] {+20.5%}	0.237±0.007*# (-23.1%) [+26.7%]	17.73±0.76*#$ (+260.5%) [-44.2%] {+27.0%}	7.44±0.33*#$ (-10.9%) [+86.5%] {-5.6%}
Group 6 – IR + human adipose-derived tissue MSCs					
7th day	2.96±0.09*$ (+40.3%) {+19.4%}	6.21±0.11*$ (+285.7%) {+39.9%}	0.167±0.007*$ (-42.8%) {-26.4%}	37.55±1.54*$ (+576.3%) {+91.8%}	3.51±0.25*$ (-56.9%) {-45.2%}
14th day	2.76±0.08*$ (+26.6%) {+15.0%}	5.63±0.13*$ (+272.8%) {+62.7%}	0.203±0.010*$ (-34.1%) {-19.1%}	28.31±1.89*$ (+476.4%) {+102.1%}	4.29±0.24*$ (-48.6%) {-45.6%}
Group 7 – IR + rat adipose-derived MSCs					
7th day	2.97±0.08*$ (+40.8%) {+19.8%}	6.24±0.15*$ (+287.6%) {+40.5%}	0.162±0.013*$ (-44.5%) {-28.6%}	39.58±2.43*$ (+612.2%) {+102.0%}	3.44±0.29*$ (-57.8%) {-46.3%}
14th day	2.78±0.09*$ (+27.5%) {+15.8%}	5.69±0.17*$ (+276.8%) {+64.4%}	0.199±0.008*$ (-35.4%) {-20.7%}	28.99±1.64*$ (+490.6%) {+107.1%}	4.14±0.36*$ (-50.4%) {-47.5%}

Periods of follow-up	Biochemical parameters				
	Glucose µmol/g of dry tissue	Lactate, µmol/g of dry tissue	Pyruvate, µmol/g of dry tissue	Lactate / Pyruvate	SDH, µmol/min•mg protein
Group 8 – IR + lysate of Wharton's jelly-derived MSCs					
7th day	3.00±0.09*$ (+42.2%) {+21.0%}	6.39±0.16*$ (+296.9%) {+43.9%}	0.154±0.006*$ (-47.3%) {-32.2%}	41.92±1.59*$ (+653.6%) {+113.8%}	3.30±0.21*$ (-59.5%) {-48.5%}
14th day	2.83±0.04*$ (+29.8%) {+17.9%}	5.73±0.11*$ (+279.5%) {+65.6%}	0.185±0.006*$ (-39.9%) {-26.3%}	31.09±0.80*$ (+533.4%) {+122.1%}	4.04±0.25*$ (-51.6%) {-48.7%}
Group 9 – IR + Citicoline					
7th day	2.48±0.07*# (+17.5%) [-22.3%]	4.44±0.09*# (+175.8%) [-32.0%]	0.227±0.007*# (-22.3%) [+43.7%]	19.63±0.62*# (+252.5%) [-53.0%]	6.41±0.38*# (-21.4%) [+104.1%]
14th day	2.40±0.06*# (+10.1%) [-17.8%]	3.46±0.16*# (+129.1%) [-41.1%]	0.251±0.012*# (-18.5%) [+34.2%]	13.96±0.96*# (+184.3%) [-55.9%]	7.88±0.12*# (-5.6%) [+97.5%]

*Notes: * – p<0.05 compared to the corresponding group of sham-operated animals; # – p<0.05 compared to the corresponding group of animals with control pathology; $ – p<0.05 compared to the corresponding group of animals treated with Citicoline. In round brackets – changes of the corresponding parameter compared to its level in sham-operated animals; in square brackets – changes compared to the parameter of the control pathology group; in curly brackets – dynamics compared to the parameter of the group of animals treated with Citicoline*

cortex was lower by 17.5, 10.3 and 17.8%, respectively (p<0.05) than in group of animals with control pathology. It should be noted that the use of HUC-MSCs and Citicoline to the greatest extent and almost equally reduced perturbations in glucose metabolism and the average content was 2.41±0.05 and 2.40±0.06 µmol/g of dry tissue. In animals of groups 5, 6, 7, 8 this increase was higher by 9.2, 15.0, 15.8 and 17.9%, respectively (p<0.05), than in group of animals that received the reference-drug.

Lactate is an additional energy substrate for neurons. When analyzing the content of lactate, pyruvate and their ratio, it was established that under conditions of ischemia, the process of aerobic glucose oxidation was inhibited, anaerobic glycolysis was enhanced, which was accompanied by the development of decompensated lactic acidosis in brain tissues (Table 1). Thus, on the 7th day of follow-up, an increase in the lactate level was found in the studied groups 3, 4, 5, 6, 7, 8, 9 by 305.6, 185.1, 224.2, 285.7, 287.6, 296.9, 175.8%, respectively (p<0.05), decrease in pyruvate content by 45.9, 17.5, 23.6, 42.8, 44.5, 47.3, 22.3% (p<0.05) and an increase in the lactate/pyruvate ratio by 650.0, 245.3, 326.3, 576.3, 612.2, 653.6, 252.5% (p<0.05), compared with sham-operated animals. HUC-MSCs, REF and Citicoline caused on the background of IR in the somatosensory cortex of rats a probable decrease in the growth of lactate content on average by 29.7, 20.1 and 32.0%, respectively (p<0.05), an increase in pyruvate level by 52.5, 41.1 and 43.7% (p<0.05) and a decrease in growth of the lactate/pyruvate ratio by 54.0, 43.2, 53.0% (p<0.05), compared with control.

In the case of a general positive direction of the corrective action of the studied MSCs and MSC lysate on the markers of acidosis in the somatosensory cortex of rats, in terms of their ability to reduce the content of lactate, increase the level of pyruvate, and reduce the ratio of lactate/pyruvate, MSCs of Wharton's jelly-derived were not inferior to the reference drug Citicoline. Instead, on the 14th day of follow-up, the changes in the specified parameters were less extensive – the increase in lactate content in the studied groups of animals was 288.7, 138.4, 176.2, 272.8, 276.8, 279.5, 129.1% (p<0.05) and an increase in the lactate/pyruvate ratio by 545.6, 177.0, 260.5, 476.4, 490.6, 533.4, 184.3% (p<0.05), and a decrease in the level of pyruvate by 39.3, 13.3, 23.1, 34.1, 35.4, 39.9, 18.5% (p<0.05) compared with sham-operated animals. The use of HUC-MSCs and REF, as well as Citicoline, contributed to a significant decrease in the lactate content on average by 38.7, 29.0, 41.1% (p<0.05), an increase in the pyruvate level by 42.8, 26.7, 34.2% (p<0.05) and a decrease in the lactate/pyruvate ratio by 57.1, 44.2,

55.9%, respectively ($p<0.05$), compared to the group of animals with control pathology.

Succinate dehydrogenase (SDH) is a key enzyme of the Krebs cycle for the aerobic oxidation of succinate in the mitochondria and a complex of the electron transport chain. Thus, on the 7th day after IR in the somatosensory cerebral cortex of rats in groups 3, 4, 5, 6, 7, 8, 9, a significant decrease in the SDH level was revealed on average by 61.5, 25.3, 32.9, 56, 9, 57.8, 59.5, 21.4% ($p<0.05$) compared with sham-operated animals (Table 1). Transplantation of HUC-MSCs, REF, and the use of Citicoline increased the SDH content by 93.9, 74.2 and 104.1%, respectively ($p<0.05$), compared to the group of rats with control pathology. On the 14th day of the study, the reduction in the SDH level was on average less extensive compared with sham-operated animals and amounted to 52.1, 7.5, 10.9, 48.6, 50.4, 51.6, 5.6% ($p<0.05$). Therapy with the use of HUC-MSCs, REF, and the reference medicine increased the SDH content by 93.5, 86.5 and 97.5%, respectively ($p<0.05$), compared with control.

DISCUSSION

During our study, in research periods after cerebral IR in the rat somatosensory cortex the increase in glucose, lactate, lactate/pyruvate ratio levels and the decrease in pyruvate and SDH content were observed. In the opinion of many authors, violations of regulatory mechanisms in the endocrine and autonomic nervous systems during IR, as well as the release of pro-inflammatory mediators from the brain, activate the immune response and systemic inflammation. At the same time, the liver, as the main metabolic organ, contributes not only to immunosuppression after a stroke, but also to stress-induced hyperglycemia [13]. Systemic hyperglycemia associated with infarction may contribute to the influx of glucose into ischemic brain tissue. At the stage of energy shifts, this compensatory activates the anaerobic pathway of glucose metabolism and increases the formation of lactate and hydrogen ions, which causes the development of metabolic acidosis [14].

When evaluating the obtained results, it should be noted that human umbilical cord Wharton's jelly-derived MSCs under IR conditions of the brain were not inferior to Citicoline, and in some cases had a more pronounced effect on the processes of aerobic and anaerobic oxidation of carbohydrates and, as a result, more effectively increased the energy fund of neurons. In our studies, it was also established that the therapeutic iv transplantation of Wharton's umbilical cord MSCs into rats with IR brain led to the recovery of disturbed energy processes in the somatosensory cortex and eliminated metabolic acidosis at the level of Citicoline, which is one of the links in the mechanism of cerebroprotective action of MSCs. Embryonic rat fibroblasts were slightly inferior in efficiency to Citicoline and human umbilical cord Wharton's jelly-derived MSCs, which indicates a higher cerebroprotective activity of xenotransplantation. Therefore, our data and the results obtained by other researchers confirm the effectiveness of the use of HUC- MSCs to protect neurons from ischemic and reperfusion damage, which significantly improves neurological function [15].

CONCLUSIONS / ВИСНОВКИ

1. In modelling of ischemia-reperfusion the carbohydrate and energy balance disorders occur in the somatosensory cortex.
2. The use of HUC-MSCs led to recovery of disturbed energy processes in the somatosensory cortex and eliminated metabolic acidosis at the level of Citicoline or better than it, which is one of the links of the mechanism of the cerebral protective action of MSCs.
3. Embryonic rat fibroblasts were slightly inferior in efficiency to Citicoline and human umbilical cord Wharton's jelly-derived MSCs, which indicates a higher cerebroprotective activity of xenotransplantation.

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

The study is preclinical with the further prospect of creating an injectable medicine with pronounced cerebroprotective properties based on the most effective class of MSCs for management of acute ischemic stroke.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

SK – work concept, design, data collection and analysis, writing the article, manuscript preparation.
VM – work concept, design, critical review of manuscript, final approval.
MY – interpretation of results, critical review, final approval.
NG – writing the article, manuscript preparation, review, correspondence with journal.
AS – statistical analysis, review of literature.

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None.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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