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Morphological Changes in Cortical Neurons and Glia of Rats in the Context of Global Cerebral Ischemia – Reperfusion Injury and its Treatment with p-Tyrosol

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ABSTRACT

Aim. To investigate morphological alterations in neurons and glial cells in the cerebral cortex using a rat model of total transient global cerebral ischemia (GCI) and to evaluate the neuroprotective effects of *p*-tyrosol.

Materials and methods. Experiments were performed on Wistar rats (n = 30), randomly divided into three groups: sham-operated, GCI control, and GCI with *p*-tyrosol treatment. The glioneuronal elements of the cerebral cortex were analyzed by light and transmission electron microscopy combined with a quantitative morphometric assessment.

Results. In the GCI group, a significant reduction in neuron density was observed. Surviving neurons showed a marked decrease in the relative volume of membrane-bound organelles, accompanied by an increase in lipofuscin, lysosomes, and vacuoles. Administration of *p*-tyrosol after GCI enhanced neuronal survival.

Conclusion. For the first time in this rat model of GCI, structural and ultrastructural changes of cortical neurons and glial cells in rats were characterized, confirming the validity of the model. Neuroprotective effects of *p*-tyrosol in the context of GCI were demonstrated at both the light-microscopic and ultrastructural levels.

Keywords: brain, ischemia, light microscopy, electron microscopy, tyrosol, neuroprotection

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Морфологические изменения нейронов и глии коры головного мозга крыс в условиях глобальной церебральной ишемии-реперфузиии их коррекция п-тирозолом

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РЕЗЮМЕ

Цель. Изучить морфологические изменения нейронов и глии коры больших полушарий на модели тотальной транзиторной ишемии головного мозга (ТТИГМ) у крыс и на фоне коррекции *n*-тирозолом.

Материалы и методы. Опыты проведены на крысах линии Вистар (n = 30). Животные были разделены случайным образом на три группы – ложнооперированные, контрольные с воспроизведением ТТИГМ, опытные с моделью ТТИГМ и введением *n*-тирозола. Глионейрональный комплекс коры больших полушарий изучали при помощи световой и электронной микроскопии с применением морфоколичественного анализа.

Результаты. В группе животных с ТТИГМ отмечено значимое снижение численной плотности нейронов. В сохранившихся нейронах происходило значительное уменьшение удельного объема мембранных органелл, а также повышение удельного объема липофусцина, лизосом и вакуолей. У животных, получавших *n*-тирозол после ТТИГМ, отмечалось усиление выживаемости нейронов.

Заключение. Впервые на данной модели ТТИГМ охарактеризованы структурные и ультраструктурные изменения нейронов и глии коры больших полушарий у крыс, которые свидетельствуют о состоятельности модели. В условиях ТТИГМ впервые продемонстрированы нейропротективные эффекты *n*-тирозола на светомикроскопическом и ультраструктурном уровнях.

Ключевые слова: головной мозг, ишемия, световая микроскопия, электронная микроскопия, *n*-тирозол, нейропротекция

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии источника финансирования при проведении исследования.

Соответствие принципам этики. Исследование одобрено комиссией по биоэтике СибГМУ (протокол № 2203201 от 22.12.2014).

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INTRODUCTION

According to the WHO, stroke is the second leading cause of death in Russia and most other countries [1], with ischemic strokes predominating. Acute cerebral ischemia – reperfusion causes massive death of neuronal and glial cells and leads to severe neurological deficits [2], creating a need for neuroprotection [3]. Due to the leading role of oxidative stress during ischemia – reperfusion injury, the use of neuroprotective agents with antioxidant effects is relevant [4]. One such neuroprotective

agent is *p*-tyrosol, a naturally occurring phenol with high bioavailability for brain tissue [5].

To study the pathogenesis of ischemia – reperfusion injury and to carry out a preclinical evaluation of neuroprotection, a total transient global cerebral ischemia (GCI) rat model was used [6]. We developed a modified variant of the model proposed by N.S. Shcherbak et al., with low morbidity and mortality in animals [7]. The pharmaceutical substance *p*-tyrosol (99.5% purity) was provided by the Institute for Problems of Chemical and Energy Technologies, Siberian Branch of the Russian Academy of Sciences (Biysk, Russia).

The aim of the study was to investigate morphological changes in cortical neurons and glia using a rat model of GCI and after treatment with *p*-tyrosol.

MATERIALS AND METHODS

The study involved 30 outbred Wistar rats weighing 220–240 g. The animals were divided into three groups (10 each): a sham-operated group (sham control), a group with GCI induction (control), and a group with GCI induction and *p*-tyrosol administration (experimental). The GCI model was reproduced using the three-vessel occlusion method [7]. Shamoperated animals underwent the same surgical procedure, but without application of arterial occluders. Rats in the experimental group received *p*tyrosol intraperitoneally at a dose of 20 mg/kg body weight for 5 days starting from the time of GCI induction. Rats in the control group received distilled water according to the same regimen.

At the end of the experiment, the animals were euthanized under isoflurane anesthesia, and the brains were removed. All procedures complied with the Directive 2010/63/EU. The study was approved by the Bioethics Committee at Siberian State Medical University (Minutes No. 2203201 dated).

For morphological studies, the brains of the experimental animals were fixed by transcardial perfusion with a mixture of 4% paraformaldehyde and 1% glutaraldehyde for 15–20 minutes at 90 mm Hg. After fixation, the brains were removed and post-fixed in a similar fixative mixture. For light microscopy, the material was embedded in paraffin. Thin serial frontal sections of the whole brain at the level of the sensorimotor cortex were then obtained and stained with hematoxylin – eosin and Nissl stain (cresyl violet). The sections were viewed and photographed using the Carl Zeiss Axiostar plus microscope.

For electron microscopy, the sensorimotor cortex (areas Fpa and Fpp) was isolated using stereotaxic atlases. Slices of the sensorimotor cortex (five from each hemisphere) were then post-fixed in 2% OsO_4, dehydrated in graded alcohols, and embedded in the Epon – Araldite mixture. Semithin sections were cut on the LKB4 ultratome (Sweden) and stained with 0.1% toluidine blue. Ultrathin sections were mounted on copper grids and contrasted with uranyl acetate and lead citrate.

In the paraffin sections stained with cresyl violet, we counted the percentage of neurons with focal and total chromatolysis, hyperchromic and pycnomorphic neurons in layers II, IV, and V of the cerebral cortex per 500 neurons in each layer from each animal. We also determined the numerical density of neurons per section plane (Ns), the mean number of neurons, and the total number of glial cells and perineuronal glia within an ocular frame of 0.029 mm² and calculated the glia-to-neuron ratio (GNR). Using the ImageJ software (NIH, USA) and electron micrographs, we calculated the specific total area of mitochondria, endoplasmic reticulum, Golgi complex (GC), vacuoles, and lipofuscin in layer V neurons.

The statistical significance of differences between the groups was assessed using the nonparametric Kruskal – Wallis test, followed by pairwise comparisons with the Mann – Whitney test. A Bonferroni correction was applied to account for multiple comparisons; the adjusted significance level was 0.01, with a baseline significance level of 0.05. Differences were considered statistically significant at $p < 0.01$. Results were presented as the median and the interquartile range Me (Q_1–Q_3).

RESULTS

Due to ischemia, the numerical density of neurons in cortical layers IV and V decreased by 29 and 22%, respectively ($p < 0.01$) compared to the sham-operated animals. The numerical density of total glial cells also significantly decreased, but the numerical density of perineuronal glia remained at the control level, indicating a pronounced progressive proliferative glial response. The analysis of glial – neuronal interactions revealed a significant increase in the GNR in cortical layers IV and V in the control group by 19 and 35%, respectively ($p < 0.01$; Table 1).

Table 1

Quantitative Characteristics of Glial and Neuronal Elements in Layers II, IV, and V of the Rat Occipital Cortex after Experimental Global Cerebral Ischemia – Reperfusion with and without *p*Tyrosol Treatment, *Me* (Q_1–Q_3)

Animal groups		Neuron density (per 1 mm² of slice)	Total glia density (per 1 mm² of slice)	Numerical density of perineuronal glia (per 1 mm² of slice)	Gliato-neuron ratio
Sham-operated animals	Layer II	2,142.39 (2,095.67–2,151.71)	1,040.54 (1,025.03–1,133.89)	385.24 (377.46–409.11)	0.18 (0.18–0.19)
	Layer IV	2,149.61 (2,140.12–2,171.22)	1,195.64 (1,195.58–1,208.57)	352.37 (348.87–371.53)	0.17 (0.16–0.17)
	Layer V	1,972.8 (1,872.8–2,041.46)	975.17 (969.45–982.54)	294.44 (259.73–316.58)	0.13 (0.13–0.19)
Control	Layer II	2,028.16 (1,916.77–2,132.14)	922.28* (902.26–944.47)	373.29 (351.54–374.49)	0.18 (0.17–0.20)
	Layer IV	1,506.50 (1,449.76–1,675.83)*	844.18* (827.38–881.27)	329.14 (311.58–331.59)	0.21 (0.19–0.24)*
	Layer V	1,338.67 (1,330.65–1,338.81)*	976.68 (793.98–893.59)	276.30 (221.87–278.91)	0.20 (0.17–0.21)*
p-Tyrosol	Layer II	1,992.51 (1,991.98–2,132.18)	999.29 (914.94–1,171.46)	396.22 (373.93–429.14)	0.19 (0.18–0.22)
	Layer IV	2,116.55 (2,092.19–2,126.80)^	931.87 (931.53–966.87)	338.84 (325.37–369.45)	0.17 (0.15–0.18)
	Layer V	1,743.45 (1,642.22–1,748.28)^	1,071.07 (1,007.17–1,078.49)	316.44 (316.43–316.45)	0.18*^ (0.18–0.19)

Here and in Table 2, 3: * $p < 0.01$ compared to the sham-operated animals; ^ $p < 0.01$ compared to the control group.

p-Tyrosol (20 mg/kg) promoted normalization of the cytoarchitecture in the examined cortical regions, as evidenced by preservation of the numerical density of neurons and glial cells in cortical layers IV and V at levels comparable to those in the sham-operated rats, along with normalization of the GNR (Table 1).

Among the surviving neurons in cortical layers II, IV, and V in the GCI group, a substantial proportion exhibited chromatolysis of varying severity, as well as dark-stained changes with nuclear pyknosis and a decrease in cytoplasmic volume.

Quantitative analysis showed that chromatolysis was more pronounced in cortical layers II and IV of the control group, whereas dark-stained neuronal changes with nuclear pyknosis and increased osmiophilic cytoplasmic inclusions predominated in layer V (Table 2).

Administration of *p*-tyrosol after ischemia attenuated the development of reversible and irreversible changes in cortical neurons compared to the rats in the control group. Moreover, neuronal integrity was approximately equal in all studied layers; the indices of neuronal damage were 1.5–2-fold lower than in the control group ($p < 0.01$), but they remained significantly higher than in the sham-operated group (Table 2).

Table 2

Morphological Changes in Cortical Neurons of Rats from Different Experimental Groups, %, *Me* (Q_1–Q_3)

Animal groups		Neurons with focal chromatolysis	Neurons with total chromatolysis	Hyperchromic neurons without shrinkage	Hyperchromic neurons with shrinkage
Sham-operated animals	Layer II	0.82 (0.82–0.88)	0.97 (0.83–1.11)	1.23 (0.94–1.34)	1.40 (1.02–1.57)
	Layer IV	1.2 (0.39–1.26)	0.78 (0.42–0.88)	1.39 (1.32–1.41)	1.34 (1.31–1.62)
	Layer V	2.23 (2.15–2.29)	0.47 (0.45–0.57)	10.06 (9.82–10.23)	4.66 (3.31–5.10)
Control	Layer II	58.22* (54.27–59.36)	7.84* (7.17–10.23)	7.15* (6.88–8.91)	3.43* (2.57–3.85)
	Layer IV	58.21* (58.11–58.40)	10.67* (9.15–11.81)	7.04* (6.94–8.45)	2.78* (2.36–3.04)
	Layer V	12.91* (11.42–15.16)	3.36* (3.31–4.44)	13.88 (12.40–14.21)	7.41* (7.41–7.54)
p-Tyrosol	Layer II	42.57 *^ (27.44–43.98)	3.45 *^ (3.13–3.81)	7.77 (7.31–8.70)	2.67 (2.53–2.69)
	Layer IV	35.02*^ (34.43–37.42)	4.94* (4.18–5.16)	9.11 (8.07–9.64)	1.90^ (1.65–2.12)
	Layer V	10.63*^ (10.62–11.29)	2.55*^ (2.41–2.86)	6.59*^ (6.50–6.90)	4.94^ (4.53–5.76)

Electron microscopy of the cerebral cortex in the rats with GCI revealed a marked reduction in the number of rough endoplasmic reticulum (RER) cisternae throughout the cytoplasm, with only isolated polysomes and free ribosomes remaining. A significant reduction in the number of mitochondria was noted; the remaining mitochondria were swollen, with matrix clearing and destruction of cristae. Increased vacuolization was observed in a substantial proportion of neurons. The nuclei of surviving neurons often had an irregular outline, with deep invaginations of the karyolemma and localized expansion of the perinuclear space. In some neurons, the nucleolus was enlarged, which may be interpreted as a compensatory and adaptive response of neurons to injury (Fig. 1, *a*).

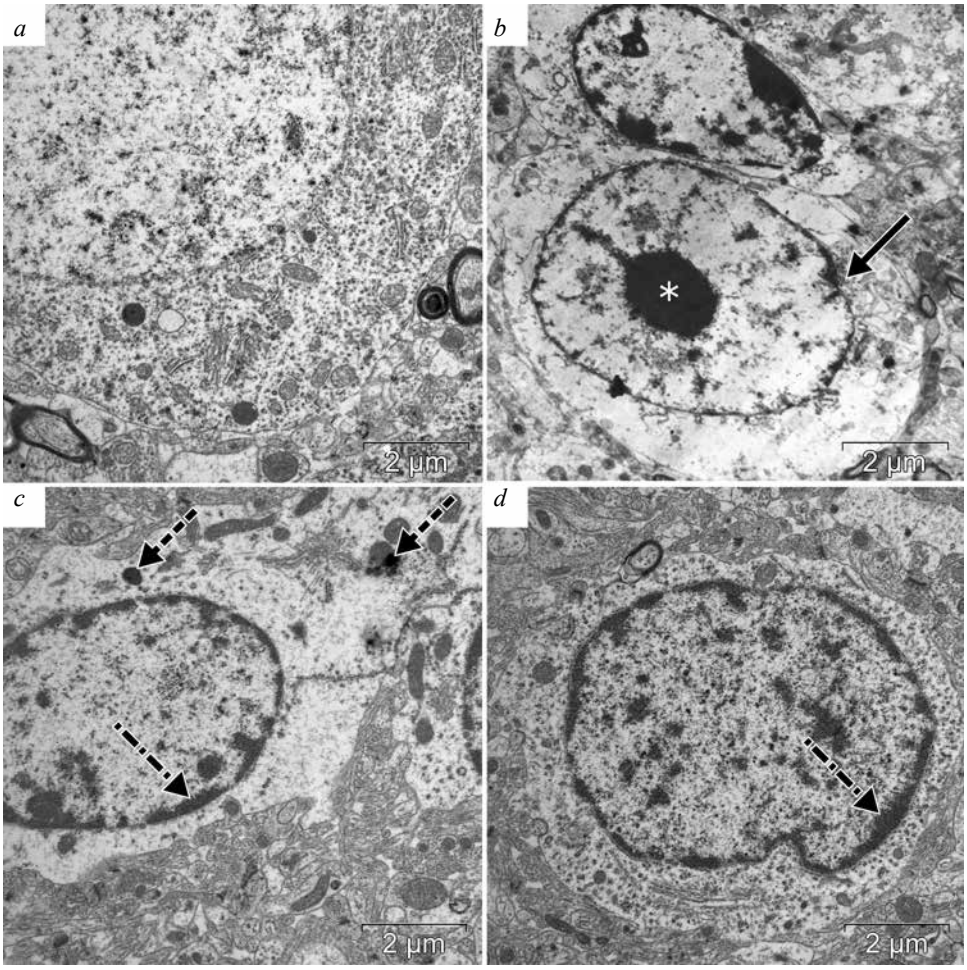

Fig. 1. Layer IV of the cerebral cortex of rats from different experimental groups: *a* – unchanged cortical neuron from a sham-operated rat; *b, c* – cortical neurons from rats in the control group. Disintegration of RER, with isolated RER fragments in the cytoplasm (black arrows), the appearance of lipofuscin granules (dashed arrow), condensation of the neuron nucleolus (asterisk), and peripheral chromatin fragmentation in the nucleus (dotted – dashed arrows); *d* – cortical neuron from a rat in the experimental group. Preservation of organelles, marginal condensation of chromatin in the nucleus (dotted – dashed arrows). Electron micrographs, × 4,500

Quantitatively, in the ischemia – reperfusion group, the specific volume of RER, mitochondria, and the GC decreased 4.4-fold, 1.9-fold, and by 21.4%, respectively, compared to the sham-operated animals ($p < 0.01$). In the meantime, a ten-fold increase in the specific volume of lipofuscin and lysosomes and a five-fold increase in the specific volume of vacuoles were detected ($p < 0.01$; Table 3).

Table 3

Specific Area of Organelles in the Cytoplasm of Cortical Pyramidal Neurons of Layer V in Rats from Different Experimental Groups, %, *Me* (Q_1–Q_3)

Animal groups	RER	Mitochondria	Lysosomes	Golgi complex	Vacuoles
Sham-operated animals	24.33 (19.52–27.21)	9.67 (8.72–11.51)	1.38 (1.12–1.72)	2.34 (2.15–3.29)	1.8 (1.6–2.3)
Control	5.48* (4.97–5.86)	5.09* (4.089–5.14)	13.9* (12.15–15.02)	1.84 * (1.7–2.05)	8.82* (8.12–9.91)
p-Tyrosol	10.15*^ (9.58–11.51)	6.85*^ (6.15–7.71)	7.1*^ (6.88–7.65)	1.86* (1.85–2.52)	8.9* (8.1–9.65)

Administration of *p*-tyrosol to the rats after GCI significantly prevented the development of the ultrastructural neuronal abnormalities described above. The specific volume of organelles remained 1.9- and 1.4-fold greater than in the control group, respectively ($p < 0.01$), but was 1.6-fold smaller than in the sham-operated group. *p*-Tyrosol also prevented the accumulation of lipofuscin and lysosomes in the neuronal perikarya: their specific volume value was almost two-fold lower than in the control group ($p < 0.01$; Table 3).

Neuronal death during GCI promoted activation of perineuronal glia, whose cytoplasm contained numerous vacuoles, phagosomes, and myelin-like bodies. Satellite glial cells were frequently observed, indicating the onset of neuronophagia. Activation of microglia was also evident: the cells lost their processes, became rounded, the nucleolus was clearly visible within the nucleus, and there was marked development of the GC and, consequently, of the vacuolar apparatus in the cytoplasm (Fig. 2).

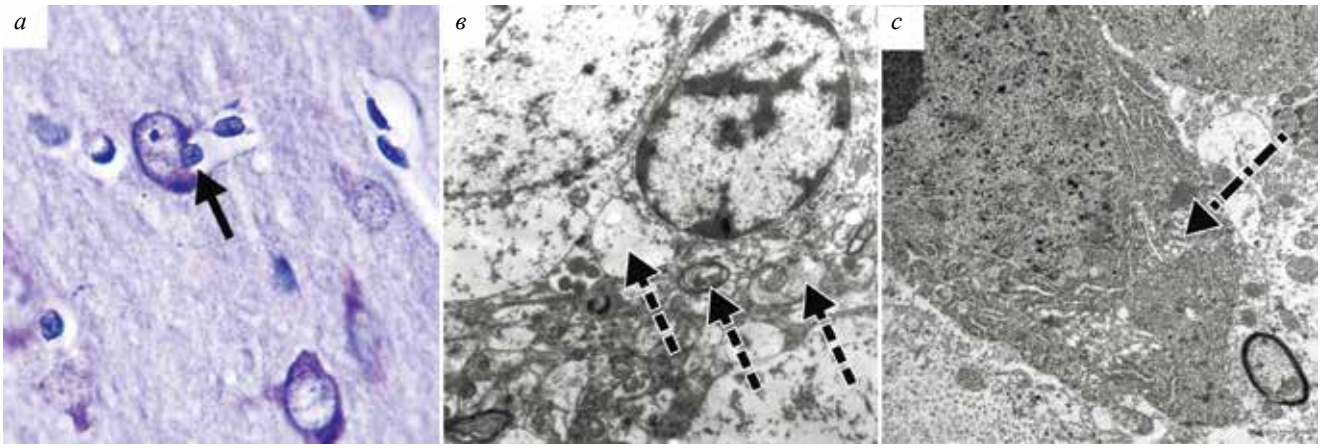

Fig. 2. Glial – neuronal interactions in the cerebral cortex of rats with total transient cerebral ischemia: *a* – neuronophagia: invagination of a satellite glial cell into the neuronal cytoplasm (arrow); Nissl staining with methylene blue; × 1,000; *b* – vacuoles, phagosomes, myelin-like bodies in the cytoplasm of a glial cell (dashed arrows); *c* – activated microglial cell (dotted – dashed arrow). Electron micrographs, × 5,000

DISCUSSION

The comprehensive analysis of layers II, IV, and V of the sensorimotor cortex in the rats subjected to GCI revealed marked alterations in the structure and number of neurons and glial cells during hemodynamic disturbances. Neurons showed hyperchromia and varying degrees of chromatolysis, and postischemic neuronal death was noted. By day 5, focal chromatolysis manifested as peripheral and segmental dissolution of the chromatophilic substance, which is considered as the most typical response to hypoxia [8]. Total chromatolysis was characterized by uniform dissolution of chromatophilic clumps throughout the perikarya and dendrites, and its extreme stage (ghost cells) is regarded as irreversible neuronal destruction [9]. According to various authors, hyperchromia may result either from increased nucleocytoplasmic RNA transport or from suppressed protein synthesis, the latter coinciding with activation of hydrolytic processes and indicating irreversible neuronal damage [8]. Electron microscopy confirmed the morphometric data: after GCI, layer V neurons exhibited degranulation of RER, dilation of RER and GC cisternae, and destruction of membranous organelles with formation of vacuoles. Quantitatively, this was reflected in a decrease in the specific volume of RER, mitochondria, and GC and an increase in the specific volume of lipofuscin, lysosomes, and vacuoles. In surviving neurons, GC cisternae were dilated and fragmented, and the number of lysosomes, lipid inclusions, and lipofuscin granules increased. These findings are consistent with other GCI models [10–12].

Glial – neuronal interactions normally support axonal conduction and synaptic transmission [13]. The study revealed a progressive neuroglial response: increased GNR, more frequent contacts between neurons and glial cell bodies and processes, and an increased number of satellite cells, all of which are characteristic of the early postischemic period [8].

At the same time, the numerical density of glial cells in the GCI control group decreased, reflecting predominant death of astrocytes.

Oxidative stress during ischemia – reperfusion injury damages erythrocyte membranes and vascular endothelium, thereby impairing microcirculation and reducing oxygen availability to tissues [14]. The previously described antioxidant effects of *p*-tyrosol in cerebral ischemia [5] may also explain its neuroprotective effects under GCI conditions. Administration of *p*-tyrosol reduced neuronal loss in all layers, decreased the proportion of neurons with focal and total chromatolysis in layers II and IV, and reduced the proportion of pycnomorphic neurons in layer V. Similarly, in models of focal ischemia, *p*tyrosol was shown to reduce free radical levels, prevent necrosis and apoptosis, decrease the size of the ischemic core, and increase neuronal survival in the prefrontal cortex and hippocampus [15].

At the ultrastructural level, preservation of RER and mitochondria and a smaller number of lysosomes were observed in the *p*-tyrosol-treated animals compared to the GCI control group. In addition to its antioxidant effect, the hemorheological properties of *p*-tyrosol are important: increased erythrocyte deformability, reduced erythrocyte aggregation, and decreased wholeblood and plasma viscosity [16]. These effects probably improve microcirculation and oxygen delivery and thereby limit damage to neurons and glial cells.

CONCLUSION

Therefore, *p*-tyrosol exhibits neuroprotective effects, reducing neuronal loss in the cerebral cortex and decreasing the proportion of neurons with pathomorphological changes after transient total cerebral ischemia – reperfusion. These effects are associated with preservation of neuronal membrane organelles, normalization of neuronal – glial interactions, and improvement of microcirculation. The efficacy of *p*-tyrosol in cerebral ischemia – reperfusion demonstrated in these preclinical trials is an important prerequisite for conducting clinical trials of this drug in the treatment of ischemic lesions of the central nervous system.

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