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CEREBROPROTECTIVE EFFECT OF SOME PHENOLIC ACIDS UNDER CONDITIONS OF EXPERIMENTAL BRAIN ISCHEMIA

A.V. Voronkov, S.A. Nigaryan, D.I. Pozdnyakov

Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University
11, Kalinin ave., Pyatigorsk, Russia 357532

E-mail: pozdniackow.dmitry@yandex.ru

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The aim of the study was to evaluate the cerebroprotective effect of some phenolic acids under the conditions of experimental cerebral ischemia in rats.

Materials and methods. The experiment was conducted on male Wistar rats weighing 220–240 g. Focal cerebral ischemia was modeled by irreversible right-sided thermocoagulation of the middle cerebral artery under chloral hydrate anesthesia (350 mg/kg, intraperitoneally). The experimental compounds (4-hydroxy-3.5-di-tert-butyl cinnamic acid, caffeic acid and gallic acid 100 mg/kg each compound) and a reference drug (Mexicor – 100 mg/kg) were administered intragastrically next day after the surgery and then for three daysrunning. The effect of the test-compounds on the cognitive functions of the rats was evaluated by CRPA and TEA tests. The influence of the compounds on the changes in the concentration of lactate, pyruvate, homocysteine, as well as the degree of cerebral edema formation and necrosis of the brain tissue, were studied.

Results. In the study, it has been established that against the background of the focal cerebral ischemia, the administration of caffeic, 4-hydroxy-3,5-di-tert-butylcinnamic and gallic acid, contributed to the preservation of a memorable trace in rats, as well as a decrease in lactate concentration (by 40.37% ($p<0.05$), 151.26% ($p<0.05$), 48.02% ($p<0.05$)) and pyruvate (by 96.6,% ($p<0.05$), 38, 78% ($p<0.05$), 33.3% ($p<0.05$)), homocysteine (by 59.6% ($p<0.05$), 102.18% ($p<0.05$), 28.8% ($p<0.05$)), anecrosis zone (by 122.79% ($p<0.05$), 165.11% ($p<0.05$), 12.38% ($p<0,05$)) and cerebral edema (by 10.47% ($p<0.05$), 11.08% ($p<0.05$), 9.92% ($p<0.05$)) relative to the NC group of rats.

Conclusion. The obtained data indicate the possibility of further detailed investigation of the cerebroprotective effect of 4-hydroxy-3,5-di-tert-butylcinnamic, caffeic and gallic acids.

Key words: cerebral ischemia, an insult to the brain, lactate, pyruvate, caffeic acid, gallic acid, 4-hydroxy-3,5-di-tert-butylcinnamic acid, ethylmethylhydroxypyridine succinate, choline alfoscerate.

Abbreviations: SO – sham-operated animals; NC – negative control**;** M – Mexicor; CA – caffeic acid**;** GA – gallic acid**;** HDTBCA – 4-hydroxy-3,5-di-tert-butylcinnamic acid**;** CRPA – Conditioned Reflex of Passive Avoidance; TEA – extrapolation avoidance test; ATP – adenosine triphosphate; AMP – adenosine monophosphate; ROS – reactive oxygen species.

ЦЕРЕБРОПРОТЕКТИВНОЕ ДЕЙСТВИЕ НЕКОТОРЫХ ФЕНОЛОКИСЛОТ В УСЛОВИЯХ ЭКСПЕРИМЕНТАЛЬНОЙ ИШЕМИИ ГОЛОВНОГО МОЗГА

А.В. Воронков, Д.И. Поздняков, С.А. Нигарян

Пятигорский медико-фармацевтический институт – филиал ФГБОУ ВО
«Волгоградский государственный медицинский университет» Минздрава России
357532, Россия, г. Пятигорск, пр. Калинина, 11

E-mail: pozdniackow.dmitry@yandex.ru

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Цель исследования – изучить церебропротективную активность некоторых фенолокислот в условиях экспериментальной ишемии головного мозга у крыс.
Материалы и методы. Эксперимент был проведен на крысах-самцах линии Wistar, массой 220–240 г. Фокальную ишемию головного мозга моделировали путем необратимой правосторонней термокоагуляции средней мозговой артерии под хлоралгидратным наркозом (350 мг/кг, интарперитонеально). Экспериментальные соединения (4-гидрокси-3,5-ди-трет-бутилкоричная кислота, кофейная кислота и галловая кислота 100 мг/кг каждое соединение) и референтные препараты (Мексикор – 100 мг/кг, Холина альфосцерат – 150 мг/кг) вводили на следующие сутки после операции интрагастрально и далее в течении трех дней. Влияние соединений на когнитивные функции крыс оценивали в тестах «условная реакция пассивного избегания» (УРПИ) и тесте экстраполяционного избавления (ТЭИ). Изучалось влияние данных соединений на изменение концентрации лактата, пирувата, гомоцистеина, а также степень формирования отека и некроза мозговой ткани.
Результаты. Установлено, что на фоне фокальной ишемии головного мозга применение кофейной, 4-гидрокси-3,5-ди-трет-бутилкоричной и галловой кислот способствовало сохранению памятного следа у крыс, а также снижению концентрации лактата (на 40,37% ($p<0,05$), 151,26% ($p<0,05$), 48,02% ($p<0,05$)) и пирувата (на 96,6,% ($p<0,05$), 38,78% ($p<0,05$), 33,3% ($p<0,05$)), гомоцистеина (на 59,6% ($p<0,05$), 102,18% ($p<0,05$), 28,8% ($p<0,05$)), зоны некроза (на 122,79% ($p<0,05$), 165,11% ($p<0,05$), 12,38% ($p<0,05$)) и отека (на 10,47% ($p<0,05$), 11,08% ($p<0,05$), 9,92% ($p<0,05$)) относительно группы крыс негативного контроля (НК).
Заключение. Результаты экспериментальных данных свидетельствуют о возможности дальнейшего углубленного изучения 4-гидрокси-3,5-ди-трет-бутилкоричной, кофейной, галловой кислот на предмет церебропротективной активности.
Ключевые слова: ишемия головного мозга, инсульт, лактат, пируват, кофейная кислота, галловая кислота, 4-гидрокси-3,5-ди-трет-бутилкоричная кислота, этилметилгидроксипиридина сукцинат, холина альфосцерат.
Список сокращений: Л/О – ложнооперированные животные; НК – негативный контроль; М – Мексикор; КК – кофейная кислота; ГК – галловая кислота; ГДТБКК – 4-гидрокси-3,5-ди-трет-бутилкоричная кислота; УРПИ – условная реакция пассивного избегания; ТЭИ – тест экстраполяционного избавления; АТФ – аденозинтрифосфат; АМФ – аденозинмонофосфат; АФК – активные формы кислорода.

INTRODUCTION

Due to ischemic events, brain damage remains the leading cause for death and primary disability in the whole world [1, 2]. Social and economic consequences of an insult to the brain require the development of effective pharmacotherapeutic approaches, in connection with which the targeted search for new compounds used for the treatment and prevention of this pathology, becomes relevant. For the world scientific and medical community improving the pharmacological correction and rehabilitation of people who have suffered acute cerebrovascular accident, this is still an acute problem [3].

However, to date, the problem of pharmacological correction of an insult to the brain, remains an elusive goal, despite various major studies on the pathogenesis of cerebrovascular diseases and new compounds that can affect it [4, 5].

Based on the results of new domestic and foreign studies, it can be assumed that among the compounds that can influence patogenetic elements of an ischemic stroke, a special role is played by plant-origin bioactive substances, which can become an effective treatment of cerebral ischemia. Such assumptions are mainly associated with the positive effects possessed by plant-origin-substances. These include the breadth of the pharmacological activity spectrum, the ability to use these compounds in complex therapy, as well as the minimal risk of undesirable adverse effects [6, 7].

Cinnamic acid is knownto have antioxidant, anti-inflammatory, anti-apoptotic properties [8]. To date, many scientists have also found out a positive effect of various phenolic compounds on the course of neurodegenerative diseases, in particular, Alzheimer's disease [9]. Caffeic acid (3.4-dihydroxycinnamic acid) is a phenolic compound that is widely found in medicinal plants, as well as in fruits, vegetables, wine, coffee and olive oil [10]. Caffeic acid has various types of apharmacological activity: antioxidant [11], antihypertensive [12], antiviral [13], anti-inflammatory [14] and antidiabetic ones [15]. Recently, a cerebroprotective effect of caffeic acid has also been evaluated [16–18]. Gallic acid is a secondary metabolite present in most plants. This metabolite is known to have a number of pharmacological properties, including antioxidant, antimicrobial, anti-inflammatory and antitumor ones [19].

THE AIM of this study is to evaluate the cerebroprotective effect of caffeic, gallic and 4-hydroxy-3.5-di-tert-butylcinnamic acid under the conditions of experimental cerebral ischemia.

MATERIALS AND METHODS

Biological model

The experiment was performed on 42 Wistar male rats weighing 220–240 g, obtained from the «Rappolovo» laboratory animal nursery. All manipulations with animals, as well as their contents, met the requirements of the European Convention for the Protection of Vertebrate Animals used for experimental and other scientific purposes (Strasbourg, 1986). This study was approved by the Independent Ethics Committee of Pyatigorsk Medical and Pharmaceutical Institute. The rats were kept in macrolon cages, where a granular wood fraction was used as litter material at the relative humidity of 60 ± 5% and the air temperature of 22±2°C. The animals received food and water ad libitum. Previously, the rats had been randomized by behavioral activity byCRPA and TEA tests. During the study, seven experimental groups wereformed. The first group of rats wassham-operated (SO) animals (n = 6). The second group of animals (n = 6)

was a negative control group (NC); they received a 0.9% solution of sodium chloride in the equivalent volume. The second and subsequent groups of rats (n = 6in each group) were subjected to the ischemic damage to the brain by irreversible occlusion of the right middle cerebral artery, while the animalsof groups 3–7 received the test-compounds and referebce drugs (Fig. 1).

Reference drug and test compounds

Ethylmethylhydroxypyridine succinate («Mexicor», 100 mg/kg, EcoFarmInvest, Russia) [20, 21] (Fig. 1) was chosen as a reference drug. The reference medicines and test compounds were administered per os next day after the simulation of cerebral ischemia and then for 3 days running. The test compounds-4-hydroxy-3,5-di-tert-butylcinnamic, caffeic, and gallic acids – were administered at the dose of 100 mg/kg (Fig. 1).

Focal cerebral ischemia model

Focal cerebral ischemia was modeled by irreversible right-sided thermocoagulation of the middle cerebral artery under chloral hydrated anesthesia (350 mg/kg). The area below and to the right of the eye was depilated, an incision was made and soft tissues were spread apart, exposing a process us of the zygomatic bone, which was removed. Then, a trepanation hole was madewith a drill and the middle cerebral artery was burned by a thermocoagulator under the place of its intersection with the olfactory tract. After that, if possible, the topography of the soft tissues was restored. The seam was treated with a 5% iodine alcohol solution. The biomaterial was taken outon the 4th day after the reproduction of focal ischemia.

Cognitive tests

Before modeling ischemia, the animals of all groups were skill-trained in the Conditioned Reflex of Passive Avoidance (CRPA) and extrapolation avoidance test (TEA) tests. The essence of the CRPA test is to form a memorial trace in animals, after which the latent entry time into the dark compartment, where electricity is supplied, is lengthened, or the rat does not enter it at all.

The TEA test, also makes it possible to evaluate the cognitive functions of the animals, based on the time of the rat dives from the cylinder. Subsequent reproductions of CRPA and TEA tests, as well as the assessment of the animal's behavioral activity and emotional status, were performed on the fourth day in theCRPA (latent time of the rat entry into the dark compartment was recorded) and TEA tests (the rat diving time was recorded) [22, 23].

Studied laboratory parameters

As biomaterial, the animals' brain and blood were used in the work. The parameters under study were: concentrations of lactic and pyruvic acids in the blood serum, the size of the necrosis zone and the cerebral edema rate. The contents of lactic and pyruvic acids in the blood serum, were determined by an enzymatic colorimetric method using a standard reagents kits, manufactured by SMA«Arbis +» (St. Petersburg, Russia). The necrosis zone was evaluated using the triphenyltetrazolium method, which is based on a change in the absorbance of the formazan chloroform extract between the necrotic and intact parts of the brain [24]. The degree of brain hydration was estimated by the drying method, for which the animal'sbrain was removed and incubated for 24 hours at 60°C. The value of cerebral edema was determined by the difference in the brain masses before and after incubation [23].

Statistical Methods

The experimental data were processed by the variation statistics method using the STATISTICA 6.0 software. (StatSoft, Inc., USA for the Windows). The data obtained, checked the normality of the distribution using the Shapiro-Wilk test. In case the data had been normally distributed, ANOVA with a posteriori Newman-Case criterion was used for statistical average calculation. In case the data of the experiment had been abnormally distributed further statistical processing of the data was carried out using the Wilcoxon test.

RESULTS

In the CRPA test, after the reproduction of ischemia in rats of the NC group, a decrease in the latent time of rat entry into the dark compartment by 10% ($p<0.05$) was registered, the diving time of the animals in the TEA test was increased by 69.6% ($p<0.05$) relative to the SO group. The data of CRPA and TEA tests indicate that all the experimental compounds positively affect the cognitive functions of rats under the conditions of cerebral ischemia.

In the CRPA test, against the background of the administration of all the test compounds, a statistically significant increase in the latent time of entry into the dark compartment was observed. In comparison with the NC group of animals, the maximum effect was observed after the administration of caffeic acid: the latent time of entry into the dark compartment was increased by 239.39% ($p <0.05$), after the administration of gallic acid –by 129.09% ($p<0.05$), after the administration of 4-hydroxy-3,5-di-tert-butylcinnamic acid – by 90.15% ($p<0.05$). The administration of Mexicor to the animals, caused an increase in the time of entry into the dark compartment by 71.2% ($p <0.05$). It is worth noting that all phenolic compounds exceeded the reference drug in thepharmacological effect rate: caffeic acid – by 103.74% ($p <0.05$), gallic acid – by 33.8% ($p<0.05$), 4-hydroxy-3,5-di-tert-butylcinnamic acid –by 11.06 ($p<0.05$) (Fig. 2).

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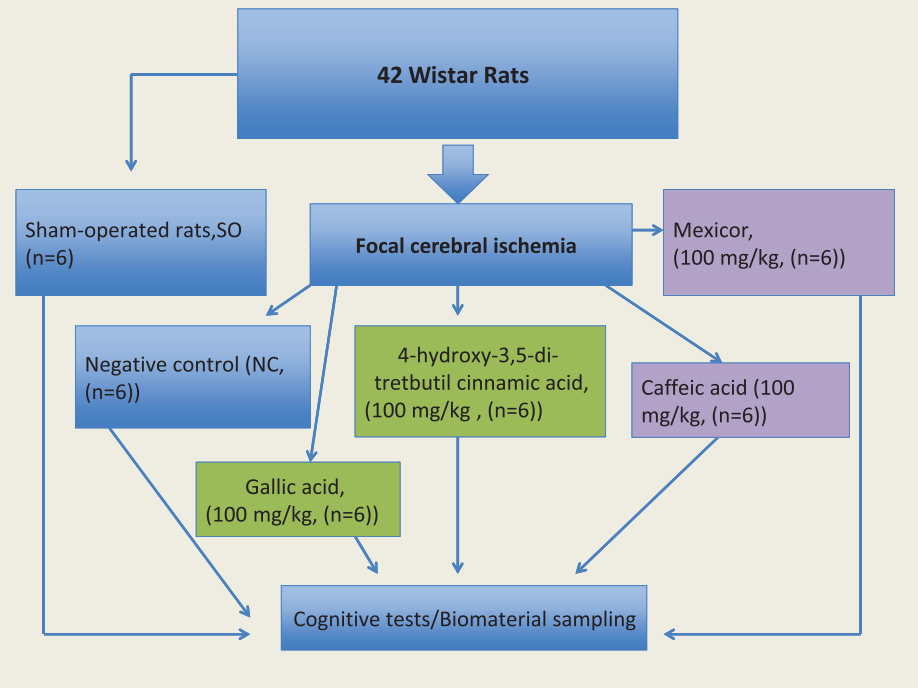

Figure 1 – Model of the study

Table 1 – Study of the effect of experimental compounds on the concentration of lactate, pyruvate and homocysteine

Investigated parameter	SO	NC	Mexicor	Caffeic acid	Gallic acid	4-hydroxy-3,5-di-tert-butyl cinnamic acid
Lactate, mmol/l	1.08±0.1	2.99±0.024#	2.57±0.16*	2.13±0.040*	2.02±0.079*	1.19±0.043*
Piruvate, mmol/l	100.38±1.1	200.68±15.664#	116.89±5.82*	102.07±3.48*	150.51±3.787*	144.60 ±7.357*
Homocysteine, ng/ml	10.27±0.675	46.44±1.054#	26.75±1.617*	29.07±1.303*	36.0±0.86*	22.95±1.342*

Note: * – statistically significant relative to the NC group of rats (Newman-Keulse test; p<0.05);
– statistically significant relative to the SO group of rats (Newman-Keulse test; p<0.05)

In the TEA test, the latent diving time was evaluated. In this test, in comparison with the NC group of animals, a decrease in diving time by 1042.2% (p <0.05) was notedin the rats treated with 4-hydroxy-3,5-di-tert-butylcinnamic acid, whereas, when caffeic and gallic acids were used, this parameter decreased by 358.9% (p <0.05) and 229.48% (p <0.05), respectively. Under the same conditions, the administration of Mexicor reduced the diving time relative to the group of the NC rats by 96.69% (p <0.05). Therefore, in this test,4-hydroxy-3,5-di-tert-butylcinnamic, caffeic and gallic acids exceeded the reference drug effect by 477.7% (p <0.05), 132.14% (p <0.05) and 66.6% (p <0.05), respectively (Fig. 2).

The reproduction of focal cerebral ischemia in rats, caused the development of edema and necrosis of the brain tissue (52.38±3.03), which corresponds with the published data [25]. There was a significant increase in lactate (176.8% (p<0.05)), pyruvate (99.9% (p<0.05)), as well as homocysteine (352.2% (p<0.05)) in the NC group of animals (Tab. 1).

The administration of the reference drug contributed to a decrease in the concentration of lactate, pyruvate and homocysteine. Thus, in the group of the animals treated with Mexicor, a decrease in lactate by 16.3% (p<0.05), in pyruvate – by 71.68% (p<0.05), and in homocysteine content – by 73.45% (p<0.05) relative to the NC group of rats, was noted. (Tab.1).

When the animals were treated with 4-hydroxy-3,5-di-tert-butylcinnamic acid, a decrease in the serum lactate concentration by 151.26% (p<0.05), in pyruvate – by 38.78% (p<0.05) and in homocysteine – by 102.18% (p<0.05) relative to the NC group of the animals, was observed. It is worth emphasizing that against the background of the use of 4-hydroxy-3,5-di-tert-butyl cinnamic acid, a greater decrease in the formation of lactate – by 115.96% (p<0.05) and homocysteine – by16.5% (p<0,05) compared with the group of the rats treated with the reference drug, was observed (Tab.1).

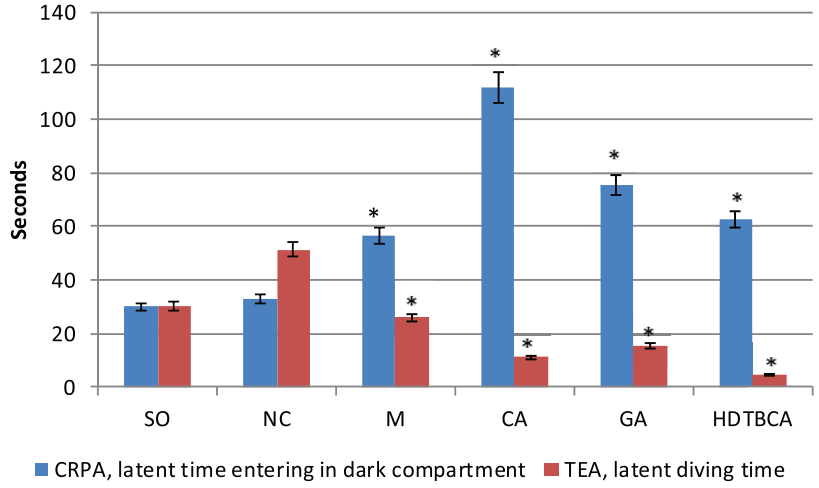

Figure 2 - The influence of the test-compounds on the execution time of tasks in CRPA and TEA tests

Note: * – statistically significant relative to the NC group of rats (Newman-Keulse test; p <0.05); SO – sham- operated animals; NC – negative control; M – Mexicor; CA – caffeic acid; GA – gallic acid; HDTBCA – 4-hydroxy-3,5-di-tert-butylcinnamic acid.

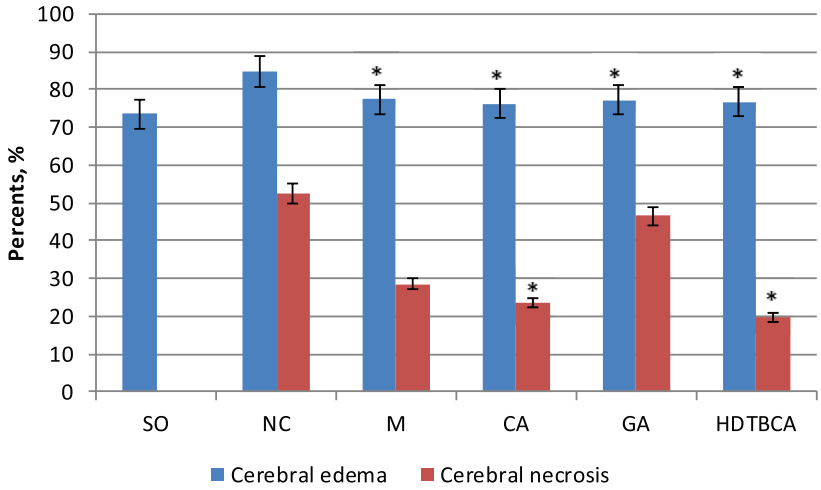

Figure 3 – Influence of caffeic, gallic and 4-hydroxy-3,5-di-tert-butylcinnamic acids on the formation of cerebral edema and necrosis of brain tissue against the background of the experimental focal ischemia

Note: * – statistically significant relative to the NC group of rats (Newman-Keulse test; p<0.05); SO – sham-operated animals; NC – negative control; M – Mexicor; CA – caffeic acid; GA – gallic acid; HDTBCA – 4-hydroxy-3,5-di-tert-butylcinnamic acid

In the group of the rats treated with gallic acid, a decrease in the lactate, pyruvate and a homocysteine content by 48.02% (p<0.05), 33.3% (p<0.05), 28.8% (p<0.05), respectively, relative to the NC group of rats, was noted. Compared with the Mexicor-treated group, gallic acid administration reduced the level of lactate formation by 27.2% (p<0.05) (Tab. 1).

The administration of caffeic acid also caused a decrease in the formation of lactate – by 40.37% (p<0.05), pyruvate – by 96.6% (p<0.05) and homocysteine – by 59.6% (p<0.05) relative to the NC group. When compared with the group of the animals treated with Mexicor, it was noted that the concentration of lactate and pyruvate in the blood serum was 20.65% (p<0.05) and 14.52% (p<0.05) higher than in this group of the animals treated with caffeic acid (Tab. 1).

In the rats treated with Mexicor, a decrease in cerebral edema relative to the NC group of rats by 9.36% (p <0.05) was noted. The administration of caffeic, 4-hydroxy-3,5-di-tert-butylcinnamic and gallic acids to the rats, caused a decrease in the hydration of the brain tissue, relative to the NC group, by 11.08% (p<0.05), 10.47% (p<0 05) and 9.92% (p<0.05), respectively (Fig. 3).

According to the effect on the degree of the brain necrosis formation, 4-hydroxy-3,5-di-tert-butylcinnamic was the most effective of the three experimental compounds and the reference drug. So, relative to the NC group of rats, the administration of 4-hydroxy-3,5-di-tert-butylcinnamic acid reduced the degree of cerebral necrosis by 165.11% (p<0.05), caffeic acid – by 122.79% (p<0.05), Mexicor – by

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83.4% (p <0.05). In the rats treated with gallic acid, a decrease in brain tissue necrosis by 12.38% (p<0.05) was observed. It should be noted that 4-hydroxy-3,5-di-tert-butylcinnamic acid exceeded Mexicor by 44.8% (p<0.05) (Fig. 3).

DISCUSSION

Focal cerebral ischemia leads to the depletion of brain energy reserves. In biochemical tests, this is manifested by a decrease in the content of macroergs (ATP, creatine phosphate), an increase in the number of semi-oxidized products (ADP, AMP, lactate, pyruvate, homocysteine), a decrease in the energy charge of the system, and the development of lactic acidosis [26]. Lactate, pyruvate, homocysteine are biomarkers of various neurodegenerative diseases, including an insult to the brain, Alzheimer's disease, as well as pathologies caused by a decrease in the mitochondrial function [27]. The conducted study has shown that against the background of the cerebral ischemia in rats, phenolic acids have a positive effect on theenergy metabolism in the brain decreasing the concentration of lactate; pyruvate and homocysteine in blood serum. Separately, it is worth noting a decrease in the degree of necrotization of the brain tissue when the experimental compounds were administered to the animals. The potential cerebroprotective effect of phenolic compounds may be associated with the chemical structure of these substances and their antiradical effect [28]. The cerebroprotective effect of 4-hydroxy-3,5-di-tert-butylcinnamic, caffeic, and gallic acids, can be also associated with their antioxidant, anti-apoptotic and anti-inflammatory properties [8–19]. It is possible that phenolic compounds improve the functional activity of mitochondria, which are most sensitive to ischemic conditions [29]. Mitochondria are organelles, which are the main producers of reactive oxygen species (ROS). Since ROS play one of the key role in the induction of mitochondrial pores, preventing the development of oxidative stress, is an effective method of stopping the cell death, and antioxidants, in particular phenolic acids, can be used as drugs of pharmacological correction of a mitochondrial dysfunction against the background of the focal cerebral ischemia.

CONCLUSION

Against the background of rats' cerebral ischemia, 4-hydroxy-3,5-di-tert-butylcinnamic, caffeic and gallic acids improved metabolic processes and brain energy exchange, had a positive effect on cognitive functions. Experimental compounds may have a potential cerebroprotective activity against the background of the rat's cerebral ischemia, as evidenced by the experimental data.

This creates prerequisites for a further in-depth study of phenolic compounds, in particular, derivatives of cinnamic acid, in order to confirm cerebroprotective properties, as well as to continue the search for compounds of plant origin that can exert a cerebroprotective effect.

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AUTHORS' CONTRIBUTION

All authors equally contributed to the research work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Adeloye D. An estimate of the incidence and prevalence of stroke in Africa: a systematic review and meta-analysis. PLoS One. 2014; 9(6): e100724. DOI: 10.1371/journal.pone.0100724.
2. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, Mensah GA, Norrving B, Shiue I, Ng M, Estep K, Cercy K, Murray CJL, Forouzanfar MH. Global Burden of Diseases, Injuries and Risk Factors Study 2013 and Stroke Experts Writing Group. Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurol. 2016; 15(9): 913–24. DOI:10.1016/S1474-4422(16)30073-4.
3. Kuznecov VV, SHul'zhenko DV, Romanyuk TYU, Dovgopola TM. Kombinirovannaya neĭrometabolicheskaya terapiya bol'nyh, perenesshih ishemicheskiĭ insul't. [Combined neurometabolic therapy in ischemic stroke patients] The Journal of Neuroscience of B.M. Mankovskyi. 2016;4(3):69–75. Russian.
4. Mestre H, Cohen-Minian Y, Zajarias-Fainsod D, Ibarra A. (May 15th 2013). Pharmacological Treatment of Acute Ischemic Stroke. DOI: 10.5772/53774. Available from: https://www.intechopen.com/books/neurodegenerative-diseases/pharmacological-treatment-of-acute-ischemic-stroke.
5. Radaelli A, Mancia G, Ferrarese C, Beretta S (Eds.), Current Developments in Stroke, BENTHAM SCIENCE PUBLISHERS. 2017. DOI:10.2174/9781681084213117010l.
6. Woodruff TM, Thundyil J, Tang SC, Sobey CG, Taylor SM, Arumugam TV. Pathophysiology, treatment, and animal and cellular models of human ischemic stroke. Mol Neurodegener. 2011; 6(1):11. DOI:10.1186/1750-1326-6-11.
7. Crupi R, Di Paola R, Esposito E, Cuzzocrea S. Middle cerebral artery occlusion by an intraluminal suture method. Methods Mol. Biol. 2018; 1727:393–401. DOI:10.1007/978-1-4939-7571-6_31.
8. Pontiki E, Hadjipavlou-Litina D. Multi-Target Cinnamic Acids for Oxidative Stress and Inflammation: Design, Synthesis, Biological Evaluation and Modeling Studies. Molecules. 2018;24(1):12. DOI:10.3390/molecules24010012
9. Chandra S, Roy A, Jana M, Pahan K. Cinnamic acid activates PPARα to stimulate Lysosomal biogenesis and lower Amyloid plaque pathology in an Alzheimer's disease mouse model. Neurobiol Dis. 2019; 124:379–395. DOI:10.1016/j.nbd.2018.12.007.

10. Miles EA, Zoubouli P, Calder PC, Phil D. Differential anti-inflammatory effects of phenolic compounds from extra virgin olive identified in human whole blood cultures. Nutrition. 2005; 21(3): 389–94. DOI: 10.1016/j.nut.2004.06.031.
11. Sánchez-Alonso I, Careche M, Moreno P, González MJ, Medina I. Testing caffeic acid as a natural antioxidant in functional fish-fibre restructured products. LWT-Food Sci Technol. 2011;44(4):1149–55. DOI: 10.1016/j.lwt.2010.11.018.
12. Hudson EA, Dinh PA, Kokubun T, Simmonds MS, Gescher A. Characterization of potentially chemopreventive phenols in extracts of brown rice that inhibit the growth of human breast and colon cancer cells. Cancer Epidemiol Biomarkers Prev. 2000;9(11):1163–70.
13. Ikeda K, Tsujimoto K, Uozaki M, Nishide M, Suzuki Y, Koyama AH, Yamasaki H. Inhibition of multiplication of herpes simplex virus by caffeic acid. Int J Mol Med. 2011;28(4): 595–8. DOI: 10.3892/ijmm.2011.739.
14. Chao CY, Mong MC, Chan KC, Yin MC. Anti-glycative and anti-inflammatory effects of caffeic acid and ellagic acid in kidney of diabetic mice. Mol Nutr Food Res. 2010;54(3): 388–95. DOI: 10.1002/mnfr.200900087.
15. Jung UJ, Lee MK, Park YB, Jeon SM, Choi MS. Antihyperglycemic and antioxidant properties of caffeic acid in db/db mice. J Pharmacol Exp Ther. 2006;318(2): 476–83. DOI: 10.1124/jpet.106.105163.
16. Zhang L, Zhang WP, Chen KD, Qian XD, Fang SH, Wei EQ. Caffeic acid attenuates neuronal damage astrogliosis and glial scar formation in mouse brain with cryoinjury. Life Sci. 2007; 80(6):530–537. DOI: 10.1016/j.lfs.2006.09.039.
17. Altuğ ME, Serarslan Y, Bal R, Kontaş T, Ekici F, Melek IM, Aslan H, Duman T. Caffeic acid phenethyl ester protects rabbit brains against permanent focal ischemia by antioxidant action: a biochemical and planimetric study. Brain Res. 2008; 1201:135–42. DOI: 10.1016/j.brainres.2008.01.053.
18. Zhou Y, Fang SH, Ye YL, Chu LS, Zhang WP, Wang ML, Wei EQ. Caffeic acid ameliorates early and delayed brain injuries after focal cerebral ischemia in rats. Acta Pharmacol Sin. 2006; 27(9):1103–10. DOI: 10.1111/j.1745-7254.2006.00406.x.
19. Fernandes FH, Salgado HR. Gallic Acid: Review of the Methods of Determination and Quantification. Crit Rev Anal Chem. 2016; 46(3): 257–65. DOI:10.1080/10408347.2015.1095064.
20. Voronkov AV, Pozdnyakov DI, Nigaryan SA, Khouri EI, Miroshnichenko KA, Sosnovskaya AV, Olokhova EA. Evaluation of the mitochondria respirometric function in the conditions of pathologies of various geneses. Pharmacy & Pharmacology. 2019;7(1):20–31. DOI:10.19163/2307-9266-2019-7-1-20-31.
21. Voronkov AV, Pozdnyakov DI. Endothelotropic activity of 4-hydroxy-3, 5-di-tret-butylcinnamic acid in the conditions of experimental cerebral ischemia. Research Result: in Pharmacology. 2018; 4 (2):1–10. DOI: 10.3897/rrpharmacology.4.26519.
22. Tushmalova NA, Pragina LL, Mal'ceva EL, Voevodina EB, Burlakova EB. Vliyanie malyh doz Polidana na uslovnyj refleks passivnogo izbeganiya u krys. [The effect of low doses of Polidan on the conditioned reflex of passive avoidance in rats. The effect of small doses of Polidan on the conditioned reflex of passive avoidance in rats]. Moscow University Biological Sciences Bulletin. 2008; (4):3–7. Russian.
23. Voronkov AV, Abaev VT, Oganesyan ET, Pozdnyakov DI. Izuchenie vliyaniya substancii ATACL na fizicheskoe i psihicheskoe sostoyanie zhivotnyh v usloviyah dlitel'nyh istoshchayushchih nagruzok [Studying the effect of ATACL substance on the physical and mental state of animals under conditions of prolonged exhausting loads]. Modern problems of science and education. 2015;(3). Available at: http://www.science-education.ru/ru/article/view?id=20331 (date of the application: 04.01.2019). Russian.
24. Nazarova LE, D'yakova IN. Vliyanie kisloty ferulovoj na zonu nekroza, voznikayushchego v rezul'tate okklyuzii srednej mozgovoj arterii [The effect of ferulic acid on the area of necrosis resulting from occlusion of the middle cerebral artery]. Bashkortostan Medical Journal.2011;(3):133–135. Russian.
25. Lambertsen KL, Finsen B, Clausen BH. Post-stroke inflammation-target or tool for therapy? Acta Neuropathologica. 2018; P. 1–22. DOI: 10.1007/s00401-018-1930-z.
26. Sultanov VS, Zarubina IV, SHabanov PD. Cerebroprotektornye i energostabiliziruyushchie effekty poliprenol'nogo preparata roprena pri ishemii golovnogo mozga u krys [Cerebroprotective and energy-stabilizing effects of the polyprenol preparation of ropren in rat cerebral ischemia]. Reviews on Clinical Pharmacology and Drug Therapy. 2010; 8(3): 31–47. Russian.
27. Saito S, Takahashi Y, Ohki A, Shintani Y, Higuchi T. Early detection of elevated lactate levels in a mitochondrial disease model using chemical exchange saturation transfer (CEST) and magnetic resonance spectroscopy (MRS) at 7T-MRI. Radiol Phys Technol. 2019; 12(1): 46–54. DOI:10.1007/s12194-018-0490-1.
28. Oganesyan ET., Shatokhin SS., Glushko AA. Using quantum-chemical parameters for predicting anti-radical (HO·) activity of related structures containing a cinnamic mold fragment. i. derivatives of cinnamic acid, chalcon and flavanon. Pharmacy & Pharmacology. 2019;7(1):53–66. DOI:10.19163/2307-9266-2019-7-1-53-66.
29. He Y, Jia K, Li L, Wang Q, Zhang S, Du J, Du H. Salvianolic acid B attenuates mitochondrial stress against Aβ toxicity in primary cultured mouse neurons. Biochem Biophys Res Commun. 2018; 498(4): 1066–1072. DOI:10.1016/j.bbrc.2018.03.119.

AUTHORS

Andrey V. Voronkov – Doctor of Science (Medicine), professor, the Head of the department of pharmacology with a course of clinical pharmacology. Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID ID:0000-0001-6638-6223. E-mail: prohor77@mail.ru.

Dmitry I. Pozdnyakov – Candidate of Sciences (Pharmacy), Senior Lecturer of the Department of Pharmacology with a course of clinical pharmacology. Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID ID:0000-0003-0889-7855. E-mail: pozdniackow.dmitry@yandex.ru

Siranush A. Nigaryan – postgraduatestudentof the department of pharmacology with a course of clinical pharmacology. Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID ID: 0000-0001-9898-0518. E-mail: 79682650210@yandex.ru