http://dx.doi.org/10.35630/2199-885X/2021/11/3/7

THE EFFECT OF PIR-20 COMPOUND ON COGNITIVE DEFICIT REDUCTION IN EXPERIMENTAL GLOBAL CEREBRAL ISCHEMIA IN RATS

Received 03.03.2021
Received in revised form 17 April 2021;
Accepted 27 April 2021

***Natalia Shabanova*[1]✉, *Anastasia Gerashchenko*[1]**
***Andrey Voronkov*[2]**

[1] *Pyatigorsk Medical and Pharmaceutical Institute — Branch of Volgograd State Medical University, Pyatigorsk;*
[2] *The Volgograd State Medical University, Volgograd, Russia*

✉ *vahlushina@mail.ru*

ABSTRACT — A study was conducted to assess the effect of a new pyrimidine derivative PIR-20 (50 mg/kg) on the development of cognitive deficits in the conditions of global cerebral ischemia in rats. The study was performed on 40 male Wistar rats weighing 200–220 g, divided into 4 groups of 10 individuals. False-operated rats and negative control animals were injected with a suspension of purified water and tween-80, the third group of animals received Cavinton (3,2 mg/kg), the fourth — PIR-20 (50 mg/kg). All test subjects were injected intraperitoneally for ten days prior to surgery. The number of dives increased to 100%, while the decision-making time decreased by 55,2% ($p<0,05$) in the extrapolation escape test against the background of the PIR-20 compound administration. 75% of the animals treated with PIR-20 did not re-visit the dark compartment, and the time of entering the dark chamber increased by 172,9% ($p<0,05$) as compared to the group of negative control rats in the test of passive avoidance of the avesir environment. It was confirmed that the studied compound PIR-20 contributes to the improvement of cognitive and mnestic functions, which is confirmed by the results of tests of passive and active aversive environment avoidance. The obtained effect exceeded the results of the control group and the reference drug Cavinton.

KEYWORDS — brain ischemia, cognitive deficits, mnestic deficits, derivatives of pyrimidine, Cavinton.

INTRODUCTION

Cerebral stroke ranks first among the causes of disability in most developed countries as a result of the development of severe neurological and cognitive impairments [1]. Violation of cognitive and mnestic functions is most often one of the major causes ofa high level of disability [2]. Effective correction of disruptions of the memory trace with cerebroprotective drugs is of undoubted interest for this pathology. Some pyrimidine derivatives have previously established themselves as substances that improve motor and behavioral activity against the background of global brain ischemia[3,4], which was the purpose of this study.

Objective:

To study the effect of PIR-20 compound on cognitive deficit reductionin experimental global cerebral ischemia in rats.

MATERIALS AND METHODS

The study was conducted in accordance with the "Guidelines for Preclinical Trials of Drug Products" ed. by A.N. Mironov (a 2012 edition) [5]. The animals were maintained in compliance with current best practices and standards of care in laboratory animals. The experiment was performed on 40 male Wistar rats m=200–220 g, divided into 4 groups (n=10). Rats were kept on a standard vivarium diet, with a natural succession of light and darkness. The first group was represented by falsely operated rats (FO), the second one — by negative control animals (NC). The both groups received an intraperitoneal suspension of Tween-80 in purified water. The third and fourth groups received reference drugs: Cavinton (3,2 mg/kg, LLC Gedeon Richter Pharma) [6]. The fourth group was administered the pyrimidine derivative PIR-20 (50 mg/kg), synthesized at the department of organic chemistry of the Pyatigorsk Medical and Pharmaceutical Institute — branch of Volgograd State Medical University[7]. Global brain ischemia was simulated in the second and subsequent groups by bilateral occlusion of the common carotid arteries (under chloral hydrate anesthesia 350 mg/kg) [8, 9]. All objects were injected intraperitoneally for ten days before the operation. 72 hours before the simulation of irreversible occlusion of the common carotid arteries, the animals were trained in the tests of passive (the conditioned passive avoidance re ex – CPAR) and active (extrapolation discharge test-EDT) aversive environment avoidance. A day after the operation, the preservation of the memorial trace was checked. All findings were processed by means of variation statistics methods using the STATISTICA 6.0 software. The normality of distribution was assessed by the Shapiro-Wilk test. In the case of a normal distribution of the data, a parametric t-test was applied. In the case of abnormal distribution of the data, the statistical processing was

performed using the Mann-Whitney U-test. The difference was considered significant at the significance level of more than 95% (p<0,05).

RESULTS

Ligation of the common carotid arteries in negative control rats caused the phenomenon of retrograde amnesia, which was manifested in an increase in the number of visits to the dark compartment in the CPAR test and a decrease in the latent period of entry [10]. Repeated entries into the dark compartment were not observed in the falsely operated (FO) group of rats. The number of the animals in the negative control (NC) group that visited the dark chamber was 75%, and the time of the entry relative to the data of the experiment increased minimally (from 28,1±2,3 to 35,3±4,5) (Fig. 1). The numbers of rats receiving reference preparation Cavintonwho revisited the dark compartment of the CPAR was 50%. At the same time, the time of the arrival of the group of rats treated with Cavinton exceeded the value of the NC group by 57,8% (p<0,05). In the group of rats that received the intraperitoneal compound PIR-20, the minimum number of visits to the dark compartment by animals was observed — 25%. The approach time relative to the baseline data increased by 172,9% (p<0,05) in animals treated with PIR-20, which was statistically significant relative to the NC group of rats. In addition, the latent period of visiting the dark chamber by rats against the background of receiving PIR-20 was statistically significantly higher than that of the reference drug Cavinton by 39,1% (p<0,05).

Only 25% of the animals in the negative control group coped with the extrapolation disposal test and the diving time decreased by only 9,3% relative to the data before ischemia (58,4±4,6 sec.), while all the falsely operated subjects again completed the task and the latent period for decision-making decreased by 85,8% from the outcome (57,6±3,8 sec.) (Fig. 2). Of the group of animals that received Cavinton, 60% of subjects did not repeat the extrapolation test, and the time to solve the problem was reduced by 23,5% compared to the data before the operation (58,8±4,6 sec.). All rats treated with the experimental compound PIR-20 intraperitoneally performed the extrapolation disposal test. The latent time to make a decision about the data before the experiment (58,7±4,6) decreased by 55,2% (p<0,05). The diving time in the rats treated with PIR-20 was significantly lower by 50,4% (p<0,05) and 41,6% (p<0,05) compared to the control group and the animals treated with Cavinton.

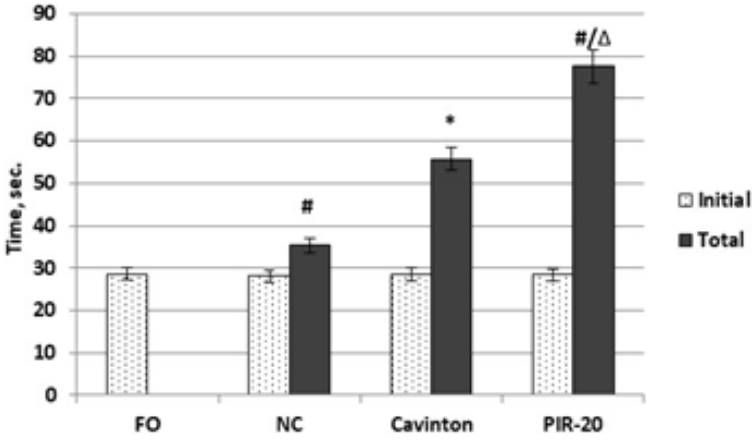

Fig. 1. *Assessment of changes in the latent period of rats entry into the dark compartment in the test of conditioned passive avoidance reflex during the intake of the compound PIR-20 and cavinton in experimental cerebral ischemia*

Note: *FO — false-operated rats ; NC — negative control rats; Cavinton — a group rats treated with Cavinton; PIR-20 — a group of rats treated with PIR-20; # — statistically significant as compared to the FO rats (p<0,05); * — statistically significant as compared to the NC rats (p<0,05); Δ — statistically significant as compared to rats treated with Cavinton (p<0,05).*

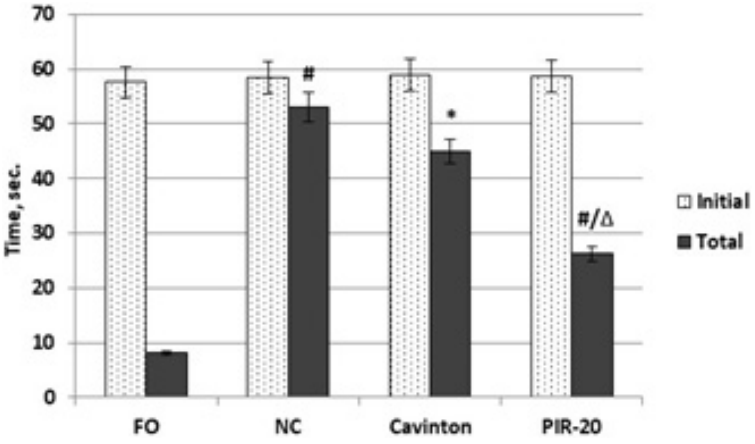

Fig. 2. *Assessment of changes in the latent period of rats' diving in the extrapolation disposal test against during the intake of compound PIR-20 and cavinton in experimental cerebral ischemia*

Note: *FO — false-operated rats ; NC — negative control rats; Cavinton — a group rats treated with Cavinton; PIR-20 — a group of rats treated with PIR-20; # — statistically significant as compared to the FO rats (p<0,05); * — statistically significant as compared to the NC rats (p<0,05); Δ — statistically significant as compared to rats treated with Cavinton (p<0,05)*

CONCLUSION

In the experimentally simulated cerebrovascular insufficiency, a pyrimidine derivative under the laboratory code PIR-20 allowed to improve cognitive and

mnestic functions in rats and showed an effect in its strength superior to the comparison drug Cavinton.

REFERENCES

1. **Farokhi-Sisakht F., Farhoudi M., Sadigh-Eteghad S., Mahmoudi J., Mohaddes G.** Cognitive rehabilitation improves ischemic stroke-induced cognitive impairment: role of growth factors //Journal of Stroke and Cerebrovascular Diseases. – 2019. – Vol. 28. – No 10. – P. 104299. DOI: 10.1016/j.jstrokecerebrovasdis.2019.07.015. Epub 2019 Jul 30.
2. **Tyurenkov I.N., Kurkin D.V., Bakulin D.A., Volotova E.V.** Study of the neuroprotective effect of a new derivative of glutamic acid-neuroglutam in focal brain ischemia in rats // Experimental and clinical pharmacology. – 2014. – Vol. 77. – No 9. – P. 8–12. (In Russ.)
3. **Lugovoy I.S., Kodonidi I.P., Voronkov A.V., Shabanova N.B., Kodonidi M.I.** Purposeful synthesis of n-peptide derivatives of pyrimidine-4 (1h)-one with cerebroprotective properties // Journal of scientific articles "Health and Education in the XXI century". – 2017. – Vol. 19. – No 8. – P. 195–199. (In Russ.)
4. **Voronkov A.V., Shabanova N.B., Kodonidi I.P., Shatalov I.S.** Cerebroprotective activity of new derivatives of pirimidine-4-(1H)-one PIR-9 and PIR-10 in irreversible occlusion of the common carotid artery. Pharmacy & Pharmacology. 2018;6(2):167–181. (In Russ.) DOI: 10.19163/2307-9266-2018-6-2-167-181
5. **Mironov A.N.** The guidelines for preclinical studies of pharmaceuticals. Part one. – M.: Grif and K, 2012. – 944 p. (In Russ.)
6. **Nazarova L.E., Dyakova I.N.** Influence of ferulic acid on the necrosis zone resulting from occlusion of the middle cerebral artery //medical Bulletin of Bashkortostan 2011. No. 3. P. 133–135. (In Russ.)
7. **Voronkov A.V., Shabanova N.B., Voronkova M.P., Lysenko T.A.** Study of cerebrotropic dose-dependent effect of pyrimidine derivative under pir-9 code against the background of experimental cerebral ischemia in rats. Pharmacy & Pharmacology. 2018;6(6):548–567. (In Russ.) DOI: 10.19163/2307-9266-2018-6-6-548-567
8. **Yamamoto M., Shima T., Uozumi T., Sogabe T., Yamada K., Kawasaki T.** A possible role of lipid peroxidation in cellular damages caused by cerebral ischemia and the protective effect of alpha-tocopherol administration // Stroke. – 1983. – Vol 14, No 6. – P. 977–982. DOI: 10.1161/01.STR.14.6.977
9. **Ghanbarabadi M., Falanji F., Rad A., Sharahi N.C., Amoueian S., Amin M.,Molavi M., Amin B.** Neuroprotective effects of clavulanic acid following permanent bilateral common carotid artery occlusion in rats // Drug Development Research. – 2019. – Vol. 80. – No 8. – P. 1110–1119. DOI: 10.1002/ddr.21595
10. **Tyurenkov I.N., Kurkin D.V., Volotova E.V., Litvinov A.A., Bakulin DA.** Effect of organic acid compositions of phenibut on neurological, cognitive and behavioral de cit in rats with focal ischemic brain damage // Siberian Medical Journal. – 2012. – Vol. 115 – No. 8. – P. 61–63. (In Russ.)