THE CYCLOPROLYLGLYCINE IS A NEW PROMISING PEPTIDERGIC NEUROPROTECTOR

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Introduction. The amelioration of CNS organic diseases therapy is thought to be high-priority purpose of the modern medicine and pharmacy. The pharmacological neuroprotection is one of directions which means the number of methods to increase survival of neurons, to promote the neuroreparation and neuroplasticity under the conditions of damage caused by the series of pathological factors (ischemia, hypoxia, neuroinflammation etc.). As of today the searching of new neuroprotectors is directed forward the study of pharmacological properties of the brain regulatory peptides and creation on their basis the new high-effectiveness and safe drugs with pleiotropic mechanism of action. It is very interestingly to study the novel diketopiperazines (dipeptides) taking into account their presence throughout neuronal tissue, particularly into brain, and their role of endogenous cognitive enhancers and protective biomolecules. First of all there are dipeptides cycloprolylglycine (cyclo(Pro-Gly)), cyclohistidylproline (cyclo(His-Pro)) and cycloprolylalanine (cyclo(Pro-Ala)). At the present moment the protective properties of both cyclo(Pro-Gly) and cyclo(His-Pro) are additional grounding needed. However, relatively recently it was found out that cyclo(Pro-Ala) exists into the brain as an endogenous product of N-terminal residues of the vascular endothelial growth factor (VEGF) biotransformation. It's highly probably that cyclo(Pro-Ala) provides pronounced neuroprotective properties of VEGF. Consequently, in the State Research Institute of Highly Pure Biopreparations (St. Petersburg) synthetic dipeptide cyclo(Pro-Ala) (laboratory code DKP-9, patent RU 2517209) has been created under the direction of doctor of biological sciences Alexander Kolobov. **The aim of investigation** is to find out neuroprotective and nootropic properties of the cyclo(Pro-Ala).

Materials and methods. The white random bred male mice and rats have been used for the experiment. Peptide DKP-9 was administrated i.n. or i.p. at the doses 0.02 mg/kg, or 0.1 mg/kg, or 1.0 mg/kg, or 10 mg/kg. The models of cerebral ischemia (irreversible bilateral carotid occlusion, iBCO, rats), hypoxia (normobaric hypoxic hypoxia with hypercapnia, NH, mice), anterograde amnesia (conditioned reflex of passive avoidance, CRPA, mice) and extrapolation escape (EE, rats) have been used. As the reference drugs were piracetam and peptidergic neuroprotector semax. The both of them are included in standarts of acute cerebral stroke therapy. Dependent on the variables and the character of their distribution the one-way

analysis of variations (ANOVA), or the Student's t-test, or the Mann-Withney's T-test, or the Fisher's angular transformations φ have been used for statistical analysis.

Results. In the model of iBCO peptide DKP-9 at a dose 0,1 mg/kg has increased rats' survival up to 70% ($p<0,05$ vs control pathology group) for acute period of cerebral ischemia (the first 4 days). According to activity, DKP-9 has exceeded semax (0.02 mg/kg i.n.). Under the same conditions DKP-9 demonstrated inherent to the peptidergic drugs return U-shaped dose-response relationship. Furthermore, DKP-9 reduced neurological and cognitive deficits which had manifested under the conditions of cerebral ischemia. This peptide improved the motility and the exploratory activity of rats in the open-field test, normalized the indices of antioxidant system of their brain tissue. On the model of NH anti-hypoxic properties of DKP-9 have been found out. It has increased the time of mice's life in the hermetic chamber by 17.1% – 20.1% ($p<0,05$ vs intact animals) dependent on the administrated dose (0.1 – 10 mg/kg). According to the activity, reference drug piracetam at a dose 400 mg/kg did not exceed DKP-9 under the conditions of this hypoxia model. Thus, cyclic prolylalanine (DKP-9) protects nervous system against the pathological factors' influence such as hypoxia and ischemia. It characterizes DKP-9 as effective neuroprotective drug.

Pronounced neuroprotective properties of DKP-9 combine successfully with the advantageous nootropic activity. In the model of retrograde scopolamine-induced amnesia DKP-9 (0.1 mg/kg) has demonstrated the high anti-amnestic aactivity (54,8%) and increased the number of animals with the CRPA (up to 57.1%, $p<0,05$ vs control of amnesia group), exceeding the piracetam (400 mg/kg) and semax (0.02 mg/kg) according to activity. According to the results of EE test the ability of DKP-9 to stimulate rats' cognitive function has been found out. The peptide decreased the time of the rats' conclusion to escape the dangerous and difficulty situation. This time has been reduced by 61,7% statistically significant comparing with the control group.

Conclusions. Cycloprolylalanine is a promising peptidergic neuroprotective and nootropic drug. It protects the nervous system against ischemia and hypoxia, which are key the factors of acute stroke pathogenesis. Not less important is that DKP-9 demonstrates the cognitive enhancing properties, complementing in so way itself neuroprotective activity. The intranasal administration of DKP-9 at a dose 0.1 mg/kg is effective. These results confirms the hypothesis about dependence of VEGF neuroprotective activity on its main metabolite, which is cycloprolylalanine. The future experimental such us clinical trials of DKP-9 as the neuroprotective and nootropic drug are expedient.