

**THE MECHANISMS OF NEUROPROTECTIVE ACTION  
OF NEW OLIGOPEPTIDES-HOMOLOGOUS OF PRIMARY  
ACTH<sub>15-18</sub> SEQUENCE**

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The ischemic stroke is undoubtedly leader among neurological disease, it's prevalent cause of high disability and mortality of working-age population. For the treatment and prevention of it use cerebroprotective agents.

Ideas of peptidergic cerebroprotection have been developing since the 70s of the 20th century. They originated from the work of de Wied [de Wied D., 1977], who has showed protective effect of different sequences of adrenocorticotrophic hormone (ACTH) at various brain diseases. Cerebroprotective drugs have created in particular analogue of ACTH<sub>4-7</sub> semax. The peptidergic mechanism of cerebroprotective effect has established for classical nootropic drug piracetam later [Гудашева, 1985], the most important metabolite of which is native factor of neuronal protect cycloprolylglycine.

The works on the creating of more effective peptidergic cerebroprotectors continue. At State Research Institute of Highly Pure Biopreparations have created number of primary sequence of ACTH<sub>15-18</sub> analogues by Sc.D. A.A. Kolobov, that include D- and N-methylated forms of lysine and arginine. The low toxicity, long-term effect, absence of hormonal and antihormonal action have discovered at the conditions in vitro [Ковалицкая, 2009; Патент RU №2356573 C1, 2012]. The presence of neurotropic properties have suggested for these oligopeptides.

The hypothesis of the presence of such properties was confirmed. The antiischemic and nootropic activity of the peptides Acetyl-(D-Lys)-Lys-Arg-Arg-amide (KK-1), Acetyl-Lys-(D-Lys)-Arg-Arg-amide (KK-2), Acetyl-Lys-Lys-(D-Arg)-Arg-amide (KK-3), Acetyl-(D-Lys)-Lys-(D-Arg)-Arg-amide (KK-5) was established; the improvement of integral mental activity, antihypoxic, actoprotective and antialcoholic activity of tetrapeptides KK-1 and KK-5 was established; elements of sedative and tranquilizing effects of neuropeptides KK-2 and KK-3 was established [Патент RU №2537560 C2, 2015]. Furthermore the investigated

neuropeptides don't influence on the depressive behavior of mice and don't potentiate the exciting action of neuronal toxin penthylettrazole under the experimental conditions. The resulting factual material have been leaving unclear mechanisms of neuronal protect of studied neuropeptides.

Leaders of investigate in terms of neuroprotective and psychotropic action are tetrapeptides KK-1 and KK-5. They have demonstrated synergism of antiischemic and antihypoxic activity among 10 homologous compounds (and too identical in the presence D-lysine in the first position of hydrocarbon chain peptide Acetyl-(D-Lys)-(D-Lys)-(D-Arg)-(D-Arg)-amide (KK-9)). They increase the time of mouse life at hermetic chamber under conditions of normobaric hypoxia with hypercapnia. The results of pulse oximetry and flowmetry have confirmed they beneficial effect on hemoglobin oxygenation (not less than 95 per cent) and hemodynamic parameters: the volume velocity of blood flow in the internal carotid artery, arterial and central venous blood pressure, that on the background of cerebral ischemia restored to physiological level.

Neuropeptides KK-1 and KK-5 correct deferred mechanisms of neuronal death at penumbra (inflammation and apoptosis) beside restore of adequate brain blood perfusion (primary neuroprotection). The ability of peptides KK-1 and KK-5 to normalize the balance of pro- (IL-1 $\beta$ , TNF- $\alpha$ ) and anti-inflammatory (IL-4) cytokines at ischemic brain was detected with the help of immunofluorescence analysis. The ability of peptide KK-1 to reduce to 5.34 and 2.25 times ( $p < 0.05$ ) the expression of neuron specific enolase and protein S-100 (markers of brain injury) have ascertained.

Anti-apoptotic action of KK-1 have confirmed by decrease of 90 per cent of DNA fragmentation level on the background of cerebral ischemia compared to control pathology ( $p < 0.05$ ).

At last, neurotrophic mechanism of protective action of tetrapeptides KK-1 and KK-5 have confirmed. It consists in normalization of nerve growth factor overexpression, which arises on the background of cerebral ischemia.

According investigated indices oligopeptides KK-1 and KK-5 exceed the comparator drug, chemical and pharmacological analog, known peptidergic cerebroprotector semax.

In this way, further experimental and clinical research of oligopeptides KK-1 and KK-5 is perspective.