EXPERIMENTAL STUDY OF THE CEREBROPROTECTIVE PROPERTIES OF NEW OLIGOPEPTIDES HOMOLOGOUS TO PRIMARY SEQUENCE OF AKTH 15-18

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The high prevalence of cerebrovascular pathologies, as well as ansufficient effectiveness of medicines used to correct their consequences, it makes makes it necessary to investigate researches for new neuroprotective agents. Peptidergic drugs have an important place among cerebroprotective agents. In the 80 – 90 the last century the concept of creation of neuroactive substances by chemical modification of the polypeptide chain of cerebral sections of hormones and neurotransmitters - AKTH, vasopressin, etc. was developed and experimentally proved (Л.В. Антонова, 1989). Proceeding from this concept in «State Research Institute of Highly Pure Biopreparations» (St. Petersburg) the panel of conformationally restricted tetrapeptides homologous to primary sequence AKTH 15-18 was established. They all contain the D- or N- methylated form of lysine and arginine . The experimental data show their high resistance to blood peptidases that provides long duration of action. Also the oligopeptides are characterized by the absence of cytotoxic properties.

The purpose of this investigation was to evaluate the cerebroprotective properties of oligopeptides on the models of acute cerebrovascular disease (ACD), normobaric hypoxic hypoxia with hypercapnia (NBHHH), and to determine antagonism with the toxic effects of ethanol.

Experiments were carried out on random white rats (ACD) and white mice of both sexes, which were obtained from the vivarium of the central research laboratory of NUPh. During the investigation "European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes" (Strasbourg, 1986) was used. Peptides were administered intranasally at a dose of

0.02 mg/kg once a day for 4 days (ACD) and prophylaxically at the same dose on the models of NBHHH and antagonism with ethanol .

On the ACD model Acetyl-Lys-Lys-(D-Arg)-Arg-amide (KK-3) peptide demonstrated the highest efficiency, preventing death of animals with ischemia during 3-day postocclusive period. Peptides Acetyl-Lys-Lys-Arg-Arg-amide (NP- 4), Acetyl-(D-Lys)-Lys-Arg-Arg-amide (KK -1), Acetyl-Lys-(D-Lys)-Arg-Arg-amide (KK-2), Acetyl-Lys-Lys-Arg-(D-Arg)-amide (KK-4), Acetyl-(D-Lys)-Lys-(D-Arg)-Arg-amide (KK-5), Acetyl-(D-Lys)-(D-Lys)-(D-Arg)-(D-Arg)-amide (KK-9), Acetyl-(D-Arg)-(D-Arg)-(D-Lys)-(D-Lys)-amide (KK-10) also were effective. All of them showed better results in comparinson with reference drugs mexidol (i/v, 100 mg/kg), piracetam (i/v, 400 mg/kg) and semax (i/n, 0.02 mg/kg), which increased the survival rate to 66.7 - 83.3%.

On the model of NBHHH peptides KK-6, KK-7 and KK-10 exerted prohypoxic properties, reducing the lifetime of mice in the hermetic chamber by 11.1 - 19.4%. Only KK-1 and NP- 4 peptides significantly increased this value by 13.5 and 24.3% respectively, comparing with the control group ($p<0.05$). Other peptides showed only a tendency to antihypoxic action. This dissociation of the results may be explained by different mechanisms of the protective effect on the pathogenetic links of ischemic brain stroke.

Peptides KK-1 and KK-5 showed significant antagonism with ethanol. They demonstrated better results than reference drug semax. These peptides significantly reduced the duration of anesthetic phase of ethanol intoxication by 34 and 34.2% respectively ($p<0.05$ comparing with the control group).

So, the obtained data substantiate the cerebroprotective effect of the neuroactive peptides on the models of ischemia, anoxia and ethanol intoxication. Effectiveness of the peptides KK-6, KK-7 and KK-10 dissociates on the different models of cerebral injury. Investigation of this phenomenon is our aim for the nearest future.