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STUDY OF ENDOTHELIOPROTECTIVE PROPERTIES OF A NOVEL XANTHINE DERIVATIVE – PIPERAZINIUM 3-BENZYL-8-METHYLXANTHINYL-7-ACETATE

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Introduction. A decrease of anti-thrombogenic properties of blood vessel endothelium is one of the main underlying processes of hemostatic activation that accompanies cardiovascular diseases. In recent years the concept of endothelial dysfunction was defined. It is a predictor of a number of diseases, e.g. hypertension, coronary heart disease etc. Our current research aims at investigating the endothelioprotective properties of a novel xanthine derivative – piperazinium 3-benzyl-8-methylxanthinyl-7-acetate (Al-89).

Material and methods. Our study employed an experimental model of cerebral ischemia, which was introduced by bilateral ligation of common carotid arteries in experimental animals (Wistar rats). On the 4th day of experiment we collected the brain homogenate and characterized by: the activity of NO-synthase and glutathione reductase, the content of nitrotyrosine, nitrates, arginine, methionine, cysteine, reduced form of glutathione, and the total level of SH-groups.

Results. We found a marked increase of NO synthesis in the brain tissues of animals with acute ischemia. In particular, our analysis of cytosolic fraction of the brain homogenate from untreated animals revealed an increase of cNOS activity as well as increased production of stable NO-metabolites. Concomitantly the level of L-arginine synthesis decreased compared to the intact animals. At the same time, the content of sulfur-containing aminoacids and activity of glutathionereductase was decreased in comparison with intact group.

Further, we found that the treatment with piperazinium 3-benzyl-8-methylxanthinyl-7-acetate significantly affected the levels of biochemical markers of endothelial dysfunction in animals with acute cerebral ischemia. In particular, injections of the compound Al-89 significantly decreased activity of cNOS and content of stable NO-metabolites without influence the L-arginine level in the brain homogenate of ischemic animals.

The compound Al-89 showed protective properties with respect to the depot of reduced thiols, which in turn increase the availability of NO, thus alleviating the development of endothelial dysfunction. Namely, the brain cytosolic fraction of animals that received a treatment course of Al-89 demonstrated an increase in the content of reduced thiol groups, and sulfur-containing aminoacids - methionine and cysteine.

Conclusion. Piperazinium 3-benzyl-8-methylxanthinyl-7-acetate (compound Al-89) demonstrates potent endothelioprotective properties, most likely conveyed by Al-89's ability to normalize the conjugated system of NO and reduced thiols.