

STUDY OF ANTIOXIDANT ACTIVITY OF A NEW STRUCTURAL MELATONIN ANALOGUE ON THE BACKGROUND OF ACUTE HEPATIC ISCHEMIA

Zhurenko D.S., Tsubanova N.A.

The National University of Pharmacy, Kharkiv, Ukraine

zhur@ukrfa.kharkov.ua

It is known that over 30% of adult population suffers from hepatic disorders. One of the most severe hepatic pathologies is hypoxic hepatitis (ischemic hepatitis or liver collapse). Foreign authors consider that hypoxic hepatitis is the most common cause of acute hepatic disorders of intensive care patients, having a prevalence rate of 10%. The level of hospital deaths from hypoxic hepatitis is 61.5%, while the list of medicinal preparations for optimal therapy of this pathology is insufficient.

The actual trend of modern medicine and pharmacy is development, study and introduction of medicinal products with multiple organ action, that is: antihypoxic action, Hepatoprotective action and ability to recover energy metabolism of damaged hepatic cells at treatment and prevention of ischemic and reperfusion damage of hepatic tissue and of microvasculatory bloodstream.

From this point of view, a new preparation can be considered as a perspective compound - 4,3'-spiro[(2-amino-3-nitrile-4,5-dihydropyrano[3,2-c]chromen-5-one)-5-methyl-2'-oxindole] (hereinafter - compound 77), which is a structural analogue of melatonin as of the molecule atomic structure.

The objective is to investigate the antioxidant activity of melatonin structural analogue (compound 77) under acute hepatic ischemia.

Materials and methods. The studies have been performed in white rats of 180-240 g weight. Acute hepatic ischemia has been induced under tiopental-sodium anesthesia (35 mg/kg) by applying a special clamp on the vascular pedicle of liver and on bile passage. Occlusion lasted for 25 minutes. Animals have been separated into the groups as follows: pseudooperated animals; control pathology (25-minute occlusion of the vascular pedicle of the liver and bile canal); animals that received compound 77 in a dose of 5 mg/kg (a dose of maximum antihypoxic effect) intragastrically, daily, during 3 days, last time before ischemia occurrence - 40 minutes; animals that received the comparative preparation melatonin dose of 5

mg/kg in a similar mode. Changes of prooxidant-antioxidant balance verified on the concentration in liver homogenate and serum substances interacting with thiobarbituric acid (TBA-reactants), diene conjugates (DC), glutathione refurbished (GR) and catalase activity.

Results and their discussion. Acute 25-minute hepatic ischemia with subsequent reperfusion was accompanied with significant activation of lipid peroxidation (LPO). Level of TBA-reactants and DC in liver homogenate and blood serum was 1.4-2.6 times more, compared to the one of the pseudooperated animals group, and the activity of the antioxidant system (AAS), as of GR content, was 1.5-1.8 times less.

Melatonin reference product normalizes the imbalance of LPO- AAS system compared to the control pathology group. This way, concentration of TBA-reactants was equal to 172 ± 2.87 mmol/g, DC – 7.57 ± 0.18 mmol/g; GR – 82.9 ± 3.06 ; catalase – 0.27 ± 0.1 mcat/l), which was significantly different from the values in the control pathology indices: TBA-reactants 209 ± 4.95 mmol/g, DC – 8.49 ± 0.21 mmol/g; GR – 72.2 ± 2.80 ; catalase – 0.21 ± 0.02 mcat/l.

Compound 77 showed an expressed antioxidant effect by the way of normalization of LPO-AAS balance. Reduction of LPO processes was verified as of reliable reduction of TBA-reactants (111 ± 4.38 mmol/g) and DC (6.65 ± 0.24 mmol/g). A significant positive aspect of compound 77 antioxidant activity implementation was the restoration of activity and of non-enzymatic link of AAS system (GR 101 ± 1.49 units), and enzymatic (catalase activity: 0.32 ± 0.01 mcat/l). Antioxidant effect of spirocyclic-derived oxindole exceeded the activity of melatonin by all indicators.

Conclusions. On the background of acute 25-minute hepatic ischemia with further reperfusion, a new preparation – compound 77 – has shown an expressed antioxidant activity, which exceeds the effect of melatonin comparative preparation . Pharmacological action of compound 77 has been mainly provided with inhibition of lipid peroxidation together with increase of antioxidant system.