

CORRECTION OF PHYSICAL STAMINA AND METABOLIC CHANGES WITH DIACAMPH HYDROCHLORIDE UNDER CONDITIONS OF IMMOBILIZATION STRESS AGAINST THE BACKGROUND OF MODELLED DIABETES MELLITUS

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Introduction. Diacamph hydrochloride (DH) being a derivative of benzimidazole exerts no effect on normal glucose content in blood however it reduces excessive glucose levels, stimulates regeneration of pancreatic β -cells, decreases insulin resistance, exerts anti-oxidative effect and demonstrates antihypoxic and cerebroprotective features in various models of cerebral lesions. That complex of pharmacologic activity types gives grounds for expectations that the new substance may have actoprotective features particularly under conditions of diabetes mellitus (DM).

The Study Objective The study objective is to make a comparative assessment of actoprotective features of DH and bemithyl under conditions of experimental DM. The assessment to be performed on the basis of physical stamina changes and behavior characteristics of metabolic processes in various organs of rats with a modelled stress induced by chronic immobilization (CIS).

Materials and Techniques. Stress-protective features of DH were assessed in rats with alloxan model of DM against the background of two-week immobilization induced by putting the animals into tight boxes. DH was used in conditionally effective intraperitoneal (i/p) dose of 25 mg / kg and compared with bemithyl used in i/p dose of 50 mg / kg. Actoprotective activity of both drugs was studied using forced swimming test under various temperature conditions (24-27 °C; 10-12 °C and 38-40 °C), rod rotating test (15 rpm) and treadmill run test (42 m /min belt speed and 10° inclination angle). Appropriate biochemical studies were performed upon therapy completion to assess metabolic changes. The animals were narcotized, then decapitated and musculus quadriceps femoris, hepar, heart and brain were isolated. Indices of energy metabolism (glycogen, lactate, pyruvate, adenosine triphosphate (ATP) and adenosine diphosphate (ADP)) and those of oxidative stress (content of TBK-reactants, proteins' carbonyl groups (PCG) as well as activity of NADPH-oxidase and superoxide dismutase (SOD)) were being determined in organs. The results were being statistically processed using Statistika 6.0 software and Student's test.

The Findings. Physical stamina of rats is considerably reduced in alloxan model of DM. DH (25 mg / kg) demonstrates distinct actoprotective features being superior to bemithyl (50 mg / kg). According to results of three exercise tolerance tests DH as actoprotector appeared to be likely superior to bemithyl. Substantial metabolic disorders emerge in skeletal muscles, heart, hepar and brain of rats with CIS against

the DM background. The processes of oxidative phosphorylation and its conjugation with tissue respiration are inhibited, hypoenergy state is being formed (ATP content in brain and heart is being reduced by 25% and 22% respectively while ADP level is being increased by 43% and 41% at the average respectively), reserve of glycogen is being decreased in hepar and skeletal muscles, anaerobic pathway of glucose metabolism prevails and lactate-acidosis is being developed. At the same time balance of prooxidant-antioxidant enzymes is impaired: activity of prooxidant enzyme NADPH-oxidase is being increased (by 16% at the average) and activity of antioxidant enzyme SOD is being decreased (by 21%), processes of free radical type oxidation of lipids and proteins are being activated in hepar, myocardium and brain. DH and bemithyl facilitate activation of oxidative phosphorylation and its conjugation with tissue respiration in brain and myocardium, they also contribute to inhibition of glycogenolysis and increasing of glycogen reserves in skeletal muscles and hepar, activation of aerobic pathway of glucose metabolism and reducing of lactate-acidosis in hepatocytes, restoration of prooxidant-antioxidant balance and inhibition of processes of peroxidation of fat and proteins in brain, myocardium and hepar of rats. Favourable metabolic effects of DH under conditions of CIS against the background of diabetes mellitus are more evident than influence of bemithyl. DH showed antihyperglycemic effect decreasing level of glucose in blood by 39.9% while bemithyl decreased it only by 18.9% ($p < 0.05$). DH facilitated increasing of glycogen content in hepar and skeletal muscles of rats by 68.8% and 46.4% respectively while relevant indices of bemithyl appeared to be likely inferior (by 49.4% and 27.8% respectively). Clear impact on energy metabolism in the brain and myocardium was demonstrated by DH, increasing the level of ADP by 58.2% and 60.4% versus 40.5% and 39.6% respectively against the background of bemithyl. DH also reduced the lactate content and lactate / pyruvate ratio by 69.9% and 70.4% respectively, while bemithyl by 63% and 56%. Levels of TBK-reactants and PCG appeared to be trustworthy lower when compared with control pathology (by 19% and 12% in brain, by 8.3% and 13% in heart and by 15% and 14% in hepar respectively) than in case of treatment with bemithyl. DH inhibited NADPH-oxidase by 26% and increased activity of SOD by 66.1%, activity of the enzymes under study was being changed by 16% and 48% respectively against the background of bemithyl. All differences mentioned above were statistically significant ($p < 0.05$). More evident actoprotective effect of DH correlates with its more powerful corrective influence on energy metabolism and anti-oxidative action as compared with bemithyl.

Conclusions. DH as antihyperglycemic drug used in half dose as compared with bemithyl under conditions of CIS against the background of DM appeared to be trustworthy better than bemithyl in terms of animals' physical stamina enhancement, normalization of indices of carbohydrate metabolism, energy metabolism and prooxidant-antioxidant balance.