Experimental Substantiation for the Use of Mexidol and 3-Hydroxypyridine Fumarate in Chronic Myocardial Injury

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We studied the cardioprotective properties of mexidol and 3-hydroxypyridine fumarate in rat model of chronic myocardial injury. We found that 3-hydroxypyridine fumarate (25 mg/kg) produced more pronounced antioxidant and cardioprotective effects than mexidol (25 mg/kg).

Key Words: *3-hydroxypyridine fumarate; mexidol; chronic myocardial injury*

According to National guidelines for the diagnosis and treatment of chronic heart failure (CHF), β-adrenoblockers and inhibitors of angiotensin-converting enzyme are the basic drugs for the treatment of CHF [7]. At the same time, unfavorable prognosis calls for new approaches to CHF treatment [7] improving clinical course, prognosis, and quality of life of the patients. In this case, myocardial metabolism can be regarded as the object of therapeutic interventions aimed at improving the effectiveness of treatment [1]. Activation of free fatty acids oxidation under conditions of reduced oxygen supply to cardiomyocytes is one of the pathogenetic mechanisms responsible for the progression of heart failure. This mechanism is accompanied by excessive activation of lipid peroxidation (LPO) and is oxygen consuming [3,10], which impairs myocardial energy metabolism and contributes to impairment of myocardial contractility [6,9]. Optimization of energy metabolism in the myocardium with metabolic drugs [2] the produce no direct inotropic effect and provide cytoprotective action [8] seems to be a promising approach to the treatment of heart failure.

Here we studied the effectiveness of mexidol and 3-hydroxypyridine fumarate during experimental chronic myocardium injury.

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MATERIALS AND METHODS

The work was carried out on outbred albino rats (n=28) kept under standard vivarium conditions and divided into four groups (7 animals per group): intact rats (group 1); controls with chronic myocardial injury modeled by intraperitoneal administration of 1 mg/kg epinephrine hydrochloride and 5 U/kg oxytocin (3 times with 48-h intervals) without correction (group 2); mexidol correction (25 mg/kg; group 3); 3-hydroxypyridine fumarate correction (25 mg/kg; group 4). The preparations were administered for 10 days after simulation.

Plasma levels of AST, potassium, and MDA were measured on a BIOSCIENCE biochemical analyzer. AST activity was measured routinely using optimized optical test. The method is based on different absorption of reduced and oxidized form of nicotinamide adenine dinucleotide at 340 nm. The plasma potassium level was determined by nephelometric method without deproteinization (potassium ion concentration is proportional to turbidity of the stable suspension formed by potassium ions introduced into the reaction mixture). MDA plasma levels were assessed by the method [4] based on the reaction between MDA and TBA yielding a colored trimethine complex with absorption maximum at 532 nm at a high temperature and acid pH.

Statistical analysis of the data was performed using Excel statistical software. Significance of the

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TABLE 1. Biochemical Parameters in Experimental Chronic Myocardium Injury in the Studied Animal Groups

Parameter	Group 1	Group 2	Group 3	Group 4
AST, U/liter	0.55±0.11	0.73±0.11*	0.76±0.12*	0.50±0.07+
Potassium, mmol/liter	5.06±0.30	13.1±2.0*	14.66±3.70*	8.5±0.9*+
MDA, mmol/liter	2.86±0.80	7.3±0.7*	6.8±1.6*	4.83±2.3*

Note. $p<0.05$ in comparison with *group 1, +group 2.

differences between the means was calculated by Student's *t* test at the 5% level.

RESULTS

AST activity was significantly increased by 33 and 38%, respectively, in groups 2 and 3 compared with group 1; in group 4, decreased by 9.1% compared with group 2. Potassium concentration in groups 2 and 3 was significantly elevated by 160 and 190%, respectively; in group 4 this parameter increased by 68% in comparison with that in group 1. MDA concentration in groups 2 and 3 was significantly increased by 155 and 138%, respectively; in group 4 this parameter was elevated by 69% in comparison with that in group 1.

AST is an endogenous enzyme belonging to transferases, aminotransferase (transaminase) subgroup, it is synthesized intracellularly; normally, only a small fraction of this enzyme enters the bloodstream. Under conditions of myocardial injury, this enzyme leaks into the blood as a result of cytolysis (cell destruction), which was detected in our experiment by laboratory methods. Mexidol did not normalized increased AST activity against the conditions of chronic myocardial injury; 3-hydroxypyridine fumarate significantly reduced it in comparison with control and brought to baseline. It is well known that potassium is the major intracellular cation. Under conditions of chronic myocardial tissue injury (destruction of its cellular elements), potassium ions leak from the damaged tissues into the bloodstream producing hyperkalemia. In contrast to 3-hydroxypyridine fumarate, mexidol did not correct hyperkalemia. Not only primary endogenous prooxidant, but also secondary products of free radical lipid oxidation formed during oxidative degradation of lipid hydroperoxides, play a damaging role, primarily, aldehydes (MDA), which serves as a measure of LPO activity. MDA content was significantly increased in all experimental groups in comparison with the intact group. However, in the group of animals treated with 3-hydroxypyridine fumarate, MDA level was lower than in the control and mexidol-treated groups.

LPO activation and insufficiency of the endogenous antioxidant system in chronic myocardial injury are important pathogenetic factors of disease development and complication severity. Treatment with of 3-hydroxypyridine fumarate more effectively reduced the plasma concentration of myocardial damage markers, corrected hyperkalemia, and inhibited LPO. On the contrary, mexidol showed low cytoprotective efficacy in experimental chronic myocardial damage. Succinate, a component of mexidol, being a ligand of GPR91 receptor, produces a neurotransmitter effect and stimulates catecholamine release [5], which is an unfavorable factor in CHF and probably explains low mexidol efficiency under the our experimental conditions.

Thus, further investigation of the efficacy of 3-hydroxypyridine fumarate in chronic myocardial injury is required.

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