Effects of Ubiquinone-10 on Energy Metabolism and Lipid Peroxidation in Rats with Myocardial Ischemia

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Preventive and therapeutic intraventricular administration of ubiquinone-10 to male rats with epinephrine-induced myocarditis increased the rate of oxidative phosphorylation, elevated the content of ATP, and inhibited lipid peroxidation in ischemic myocardium.

Key Words: *myocardial ischemia; oxidative phosphorylation; lipid peroxidation; ubiquinone-10*

Impaired energy metabolism associated with inhibited tissue respiration and reduced cell content of ATP and phosphocreatine plays a key role in the pathogenesis of myocardial disorders during oxygen deficiency [5, 11]. Lipid peroxidation (LPO) activated under hypoxic or ischemic conditions and damaging membranes is a mechanism of oxygen deficiency-induced injuries [9]. The search for biologically active substances improving myocardial energetics and possessing antioxidant properties is a topical problem in the therapy and prevention of coronary heart disease.

The content of ubiquinone, a component of the mitochondrial respiratory chain, decreases under conditions of oxygen deficiency. Recent clinical and experimental studies indicate that this substance holds much promise as an antihypoxic drug [4,8]. Apart from participation in electron transport in the respiratory chain, ubiquinone also acts as a scavenger of free radicals [8]. The mechanism of antioxidant effects of ubiquinone is similar to that of natural antioxidants, tocopherols [3]. Ubiquinone-9 is widely used as a therapeutic agent; however, human tissues synthesize primarily ubiquinone-10 (Q_{10}) [4].

Here we studied the effects of Q_{10} (Kstovo BVK plant; Sintezbelok Institute, Russian Academy of Sciences) on energy metabolism and LPO in the myocardium of rats under ischemic conditions.

MATERIALS AND METHODS

Experiments were performed on outbred albino rats weighing 200-250 g. Myocardial ischemia was produced by intramuscular injection of 0.5 ml 0.1% epinephrine (epinephrine-induced myocarditis) [1]. As the preventive and therapeutic mean, Q_{10} was administered before and after ischemia, respectively. For the prevention of ischemia, Q_{10} was dissolved in olive oil and administered intraventricularly through a probe in a daily dose of 2 mg/kg for 7 days. Control rats received an equivalent volume of olive oil. Then, all animals were injected with epinephrine. On day 3, when the concentration of macroergic substrates in the heart decreased to a minimum [1], the rats were decapitated, and the heart was removed for biochemical and morphological assays. For the therapy of ischemia, the rats were injected with epinephrine and then received Q_{10} in a daily dose of 0.25 mg/kg for 15 days. Heart samples were examined on day 16 after epinephrine administration (at the peak of myocarditis) [1].

The content of ATP was estimated by the luciferin-luciferase method [10]. Oxygen consumption in heart homogenates was recorded polarographically (open platinum electrode) [6]. The incubation medium contained 0.25 M sucrose, 10 mM KCl, 20 mM KH_2PO_4, 0.5 mM EDTA, 10 mM glutamate, 5 mM malate, and

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10 mM Tris-HCl (pH 7.4). The homogenate (0.2 ml, 5%) was placed into a polarographic cell with the incubation medium, and ADP was added in increasing concentrations. The rate of ADP phosphorylation (ADP/t) in metabolic state III (Chance classification) was estimated. The Michaelis constant (K_M) and V_{max} were calculated as described elsewhere [7]. The intensity of LPO was estimated from the content of malonic dialdehyde (MDA) reacting with thiobarbituric acid [2]. Functional activity of the heart was evaluated by ECG (standard lead II). For histological assay, slices of the heart were stained with hematoxylin and eosin. The results were analyzed by Student's *t* test.

RESULTS

Epinephrine-induced myocarditis was accompanied by a decrease in the content of ATP in rat myocardium. The preventive and therapeutic administration of Q_{10} significantly increased the concentration of macroergic substances in the myocardium compared to the control (Table 1).

In rats with epinephrine-induced myocarditis, the rate of oxidative phosphorylation in the myocardium decreased, especially at low ADP concentrations (Table 2). K_M 3-fold surpassed that in intact animals, while V_{max} remained practically unchanged (Table 3). Thus, epinephrine-induced myocarditis was characterized by inhibition of ADP phosphorylation. Pretreatment with Q_{10} normalized the rate of ADP phosphorylation and decreased K_M for ADP (Tables 2 and 3).

It is known that myocardial ischemia elevates the content of long-chain acyl-CoA in cardiomyocytes suppressing aerobic synthesis of ATP due to the competitive inhibition of adenine nucleotide translocase carrying ADP/ATP across the inner mitochondrial membrane [12,14]. The accumulation of uncleaved acyl-CoA in cardiomyocyte cytoplasm and inhibition of ATP synthesis in mitochondria are the major pathogenetic mechanisms of cardiac dysfunction during myocardial ischemia. The deficiency of electron carriers, cytochrome *c* and ubiquinone due to their efflux from mitochondria [8,14] and inhibition of ubiquinone synthesis [13] also contributes to cardiac dysfunction. The ameliorating effects of Q_{10} are probably associated with its direct influence on the electron transport chain in the myocardium followed by normalization of energy metabolism.

Positive effects of Q_{10} under these conditions also can be explained by its antioxidant properties [3].

It is believed that ischemia is accompanied by marked activation of LPO, which causes structural damages to membranes (membrane labilization and enhanced proton conductance) and inhibits membrane processes, including oxidative phosphorylation. The deficiency of antioxidant Q_{10} [3] under ischemic conditions due to its efflux [8] and inhibition of its synthesis [13] can activate LPO and promote destruction of mitochondrial membranes, which leads to impairment of their conjugating functions. If so, the use of exogenous Q_{10} should normalize LPO. In our experiments, the preventive and therapeutic administration of Q_{10} inhibited LPO (MDA content markedly decreased, Table 1) and promoted the recovery of energy metabolism.

Antihypoxic and antioxidant properties of Q_{10} were also manifested at the structural level. Morphological examination of epinephrine-damaged myocardium revealed irregular eosin staining of the myoplasm, stasis in capillaries, stromal edema, small hemorrhages, and leukocytic infiltration. Dead myofibrils were well defined due to intense eosinophilia of the myoplasm. Circulatory disturbances in the heart appeared as plethora and subendocardial hemorrhages. The capillary bed in damaged myocardium was loosened compared to that in intact animals. Dystrophic changes in the cytoplasm of endotheliocytes were presented by granular degeneration and regions of twisting and hypercontraction of muscle fibers. Medium vessels were often collapsed. Signs of venous plethora were seen in large vessels.

Pretreatment with Q_{10} considerably attenuated histological changes: venous congestion in the heart was insignificant, and regions of twisting and hypercontraction of muscle fibers were found rarely. Transverse striation of cardiomyocyte cytoplasm was preserved.

TABLE 1. Effects of Preventive and Therapeutic Administration of Q_{10} on the Content of ATP and MDA in the Heart of Rats with Epinephrine-Induced Myocarditis (*M*±*m*)

Parameter	Control	Epinephrine-induced myocarditis		
		without Q_{10}	pretreatment with Q_{10}	therapy with Q_{10}
ATP, μmol/g heart	4.01±0.09	2.17±0.14*	3.12±0.26+	3.19±0.28+
MDA, nmol/g heart	1.07±0.08	1.95±0.10*	1.38±0.14+	1.58±0.09+

Note. Here and in Tables 2 and 3: $p<0.05$: *compared to the control and +compared to epinephrine-induced myocarditis without Q_{10} pretreatment.

TABLE 2. ADP/t (μmol/min/g Heart) in Rats with Epinephrine-Induced Myocarditis Pretreated with Q_{10} (*M*±*m*)

ADP concentration, μmol/g heart	Control	Epinephrine-induced myocarditis	
		without Q_{10}	pretreatment with Q_{10}
60	15.9±0.6	11.4±0.2*	15.4±0.8+
90	17.7±0.7	14.2±0.6*	18.7±0.8+
150	20.7±0.9	18.6±1.3	20.8±0.9
300	23.2±1.2	22.7±1.4	24.9±1.3

TABLE 3. Kinetic Parameters of Oxidative Phosphorylation in the Heart of Q_{10}-Pretreated Rats with Epinephrine-Induced Myocarditis (*M*±*m*)

Parameter	Control	Epinephrine-induced myocarditis	
		without Q_{10}	pretreatment with Q_{10}
K_M, μmol	35.5±3.4	105.3±12.6*	47.7±4.7+
V_{max}, μmol ADP/g heart/min	25.3±1.4	31.0±3.2	27.8±1.1

Moderate plethora, minor edema enlargement of perivascular and pericellular spaces were sometimes seen. This indicates that Q_{10} prevents structural changes in the myocardium induced by toxic doses of epinephrine.

These cardioprotective properties of Q_{10} also concerned functional activity of the heart and animal survival. In the control, 10% animals with myocarditis died 2 days after epinephrine administration, while there was no mortality in rats pretreated with Q_{10}. ECG in rats with epinephrine-induced myocarditis was characterized by low-amplitude, widened, and flat QRS complex. Q_{10} administration to rats with myocarditis improved ECG parameters: the amplitude of QRS increased by 1.5 times and approached that in intact animals.

Thus, preventive and therapeutic administration of synthetic Q_{10} to rats with epinephrine-induced myocarditis considerably inhibited LPO and improved energy metabolism in the myocardium. These data indicate that Q_{10} produces correcting effects on the respiratory chain and attenuates morphofunctional changes in the heart under hypoxic conditions. Therefore, Q_{10} can be used as an antihypoxic agent characterized by a direct energizing action [8]. Antihypoxic properties of exogenous Q_{10} normalizing energy metabolism in ischemic myocardium can be also related to its antioxidant activity.

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