EFFECT OF TOXIC DOSES OF NORADRENALIN ON SOME INDICES OF MYOCARDIAL METABOLISM

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UDC 615.357.452.015.35:612.173.1

After intramuscular injection of noradrenalin (2.5 mg/kg) into rabbits and electrical stimulation of the aortic arch similar disturbances of metabolism are found in the myocardial tissue: uncoupling of oxidative phosphorylation, accumulation of lactic acid, a decrease in the creatine phosphate level, and an increase in the inorganic phosphorus; the ATP concentration also falls. It is postulated that an important role in the mechanism of these disturbances is played by the deficiency of endogenous noradrenalin developing in both cases.

Catecholamines play an active role in the regulation of metabolism in the myocardium [1, 3, 4]. Experiments in the writers' laboratory have shown that after intramuscular and intraperitoneal injection of toxic doses of catecholamines, just as after extreme stimulation, the balance of the endogenous catecholamines in the tissues of the internal organs is disturbed [1, 5]. A deficiency of sympathetic mediator in the cells may be one of the most important causes of development of degenerative changes of both neurogenic and "catecholamine" origin.

To analyze the changes leading in both cases to the development of similar morphological lesions some indices of metabolism were studied and compared in the early stages of development of these degenerative conditions.

EXPERIMENTAL METHOD

Male rabbits weighing 2.4-3 kg were used. Noradrenalin was injected intramuscularly into the animals of one group in a dose of 2.5 mg/kg. These animals were killed 3 h later and the heart removed for examination. In the animals of a second group the aortic reflexogenic zone was stimulated through a metal electrode implanted previously. Square pulses of alternating current (50 Hz, 5-7 V, 1 msec) were applied for 3 h. The heart tissue was taken for examination immediately after the end of stimulation. Intact rabbits acted as the control. The mitochondria were isolated from the heart muscle [7] and oxidative phosphorylation was determined by a manometric method in Warburg's apparatus. ATP [2], creatine phosphate [6], and lactic acid (by Barker and Summerson's method) also were determined.

EXPERIMENTAL RESULTS

After injection of noradrenaline oxidative phosphorylation was disturbed in the mitochondria of the heart muscle: the oxygen consumption fell by 41%, esterification of phosphorus fell by 63%, and as a result the P/O ratio fell from 2.3 in the control to 1.4 in the experimental series ($P < 0.05$).

In response to stimulation of the aortic arch the P/O ratio in the myocardial mitochondria also fell. The oxygen consumption in the experimental animals differed only a little from the control but the phosphorus transfer fell by 34%. The P/O ratio in the experimental animals was reduced by 35% (Fig. 1). The lactic acid concentration in the heart increased under these experimental conditions: by 70% after injection

Laboratory of Experimental Pharmacology, Department of Pharmacology, Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR S. V. Anichkov.) Translated from Byulleten' Eksperimental'noi Biologii i Meditsiny, Vol. 77, No. 4, pp. 61-63, April, 1974. Original article submitted April 9, 1973.

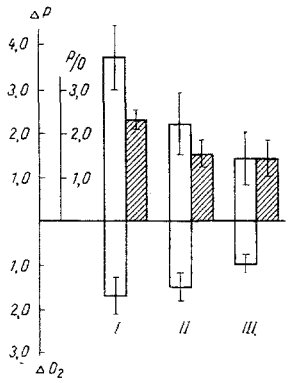

Fig. 1

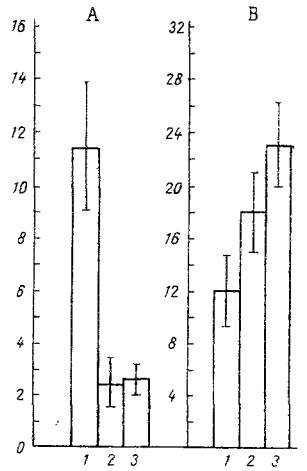

Fig. 2

Fig. 1. Oxidative phosphorylation in mitochondria of rabbit heart muscle: I) intact animals; II) after electrical stimulation of the aortic arch for 3 h; III) 3 h after injection of noradrenalin (2.5 mg/kg, intramuscularly). ΔP) Phosphorus transfer (in μg-atoms/mg protein); ΔO_2) oxygen consumption (in μg-atoms/mg protein); shaded columns represent P/O ratio. Limits of variations in parameters are shown.

Fig. 2. Concentration (in mg %) of creatine phosphate (A) and inorganic phosphorus (B) in rabbit myocardium: 1) intact animals; 2) 3 h after injection of noradrenalin (2.5 mg/kg, intramuscularly); 3) immediately after electrical stimulation of aortic arch for 3 h. Limits of variations in parameters shown.

of noradrenalin and by 40% after extreme stimulation. An increase in the lactic acid concentration in the myocardial tissue is an indication of the predominance of anaerobic over aerobic glycolysis. The uncoupling of oxidative phosphorylation and the accumulation of lactic acid are thus evidence of marked disturbances of oxidation in the myocardium whether in response to the action of toxic doses of noradrenalin or stimulation of the aortic arch.

Since these disturbances could affect the production of high-energy compounds experiments were carried out to determine the creatine phosphate and ATP content.

In all the experimental animals the concentrations of creatine phosphate and ATP were reduced. The creatine phosphate concentration was reduced by 5 times after injection of noradrenalin and this was accompanied by an almost twofold increase in the inorganic phosphorus content (Fig. 2). Similar changes were observed after electrical stimulation of the aortic arch for 3 h. The ATP content in the heart muscle tissue also fell, but by a lesser degree: whereas the ATP content in the control was 1.6 (1.4-1.8) μmole/g wet tissue, under the influence of exogenous noradrenalin it fell to 1.2 (0.9-1.5) μmole/g, while after reflex stimulation it fell to 1.13 (0.8-1.43) μmole/g.

These observations thus show that exogenous noradrenalin, in doses inducing destructive changes in the tissues, disturb energy formation in the heart muscle. Comparison of the biochemical changes induced by noradrenalin with the disturbances arising during the first few hours of development of neurogenic degeneration revealed considerable similarity. In both cases uncoupling of oxidative phosphorylation, accumulation of lactic acid, and a decrease in the content of high-energy compounds were observed. Meanwhile, as was mentioned above, in the animals of both groups the tissue noradrenalin reserves were sharply reduced. The possibility cannot be ruled out that this deficiency of the noradrenalin mediator plays an important role in the mechanism of development of biochemical changes leading ultimately to a disturbance of the structural integrity of the tissues.

LITERATURE CITED

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