THE EFFECT OF CERTAIN ENZYME POISONS ON THE MYOCARDIUM IN DIFFERENT TEMPERATURES

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Many investigations have studied the toxic effect of enzyme poisons on the myocardium as an aid to clearer understanding of the interstitial metabolism of the myocardium. Monoiodoacetic acid (MIA) acutely disturbs myocardial contractility by inhibiting anaerobic glycolysis. This effect of MIA takes longer to become apparent in the heart muscle than in the skeletal musculature [12]. MIA used in combination with cyanide or azide causes immediate cardiac arrest [10]. Adenosine triphosphoric acid (ATP) does not prevent the effect of monoiodoacetic acid [1]. B. P. Ushakov [6] and co-workers [2, 5, 6] have studied the correlations between the monoiodoacetic acid concentration and tissue excitability in detail.

Monofluoroacetate interrupts the Krebs cycle in the isocitric acid phase since the toxic fluorocitric acid is formed. Monofluoroacetate induces rapid myocardial exhaustion [9, 13].

2,4-Dinitrophenol (DNP) acts to inhibit the phosphorylation processes. Under the influence of 2,4-dinitrophenol (DNP), the contractile force and the phosphocreatine content of the myocardium diminish [14]. According to the data of Shapot and Prus [7], ATP prevents the toxic effect of monofluoroacetate, although Ellis [11] does not confirm these data.

Electrocardiography has shown considerable changes in the myocardium attending the action of cyanogen compounds [3, 4].

We performed experiments to study the effect of the above enzyme poisons on the myocardium under different temperature conditions in order to ascertain to what extent and through which energy resources the heart functions under hypothermic conditions.

EXPERIMENTAL METHODS

The experiments were performed on frog's isolated hearts, perfused through the sinus venosus with Ringer's solution 10 or 35° in temperature. The heart contractions were recorded on a kymogram. Monoiodoacetate (in a concentration of 93 mg%), DNP (1 mg%) or KCN (1 mg%) were added to the Ringer's solution during the experiments. In evaluating the experimental results, we considered the time required to reduce the amplitude of the cardiac contractions to 50% of the original level.

EXPERIMENTAL RESULTS

We established that monoiodoacetate induces myocardial exhaustion later at 10° than at 35°. At 10°, the amplitude of the contractions decreased to 50% of the original level in 14.75 min, but in 6 min at 39°. The heart rhythm decreased at 35° and increased at 10°. The results of these experiments are given in the table and in Fig. 1, which shows the mechanograms from two typical experiments at 35 and 10°.

The myocardial exhaustion induced by DNP occurred at the same time at both 35 and 10°, but there was a marked difference in the heart rhythm, which was 27 beats per min at 10°, but 66 beats per min at 35° (see table and Fig. 2).

KCN reduced the amplitude of the contractions 50% after 3.7 min at 35° and after 7.2 min at 10°. A negative chronotropic effect was observed at 35° when DNP and KCN were added at the same time.

Enzyme poisons	Number of experiments	At 35°			At 10°		
		amplitude reduced 50% (in min)	heart rhythm (beats per min)		amplitude reduced 50% (in min)	heart rhythm (beats per min)	
			original	after addition of toxic substances		original	after addition of toxic substances
Monoiodoacetate	10	5	54.6	40.4	14.75	27.2	41.3
Dinitrophenol	10	3.54	66.2	56	3.48	26.8	29.8
KCN	10	3.71	65.2	52.1	7.22	28.8	33.8

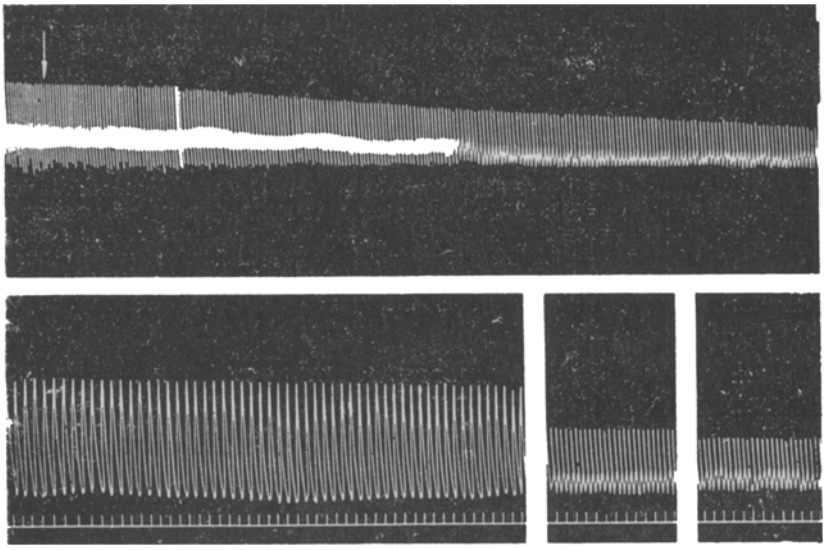

Fig. 1. Effect of monoiodoacetic acid on frog's heart at 35° (top curve) and 10° (bottom curve). Time shown in 6 second marks.

DISCUSSION OF RESULTS

Since monoiodoacetate had little effect on cardiac activity at the low temperature, one can conclude that the myocardium tolerates the decreased amount of energy resulting from inhibition of anaerobic glycolysis better at this temperature.

DNP had a negative inotropic effect after the same time interval at both the low and the high temperature. Exact evaluation of the results, however, is somewhat difficult inasmuch as the work of the heart during this time interval was less at the low temperature because of the bradycardia observed than at the 35° temperature, when tachycardia was present. It would therefore seem that, under the influence of DNP, cardiac exhaustion sets in after a greater load at 35° than at the low temperature. More exact analysis of this phenomenon requires experiments with a constant heart rhythm (artificial stimulation) under different temperature conditions.

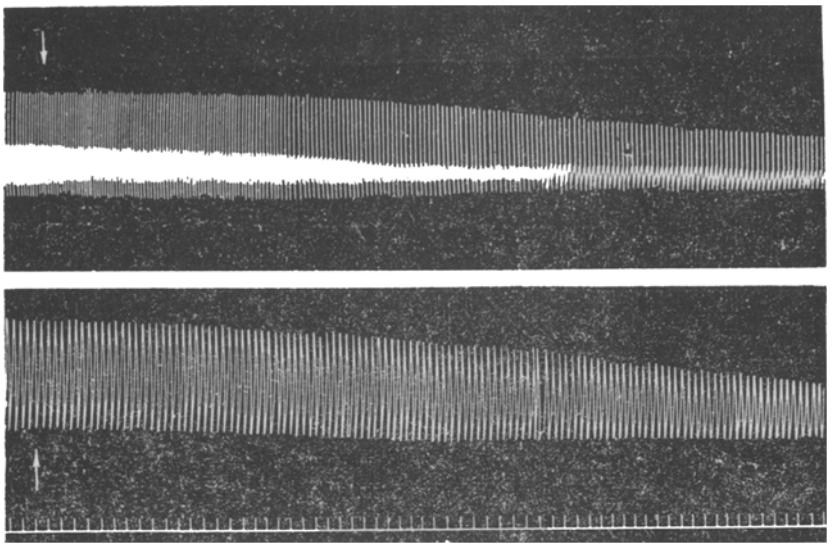

Fig. 2. Effect of dinitrophenol on frog's heart at 35° (top curve) and 10° (bottom curve). Time shown in 6 second marks.

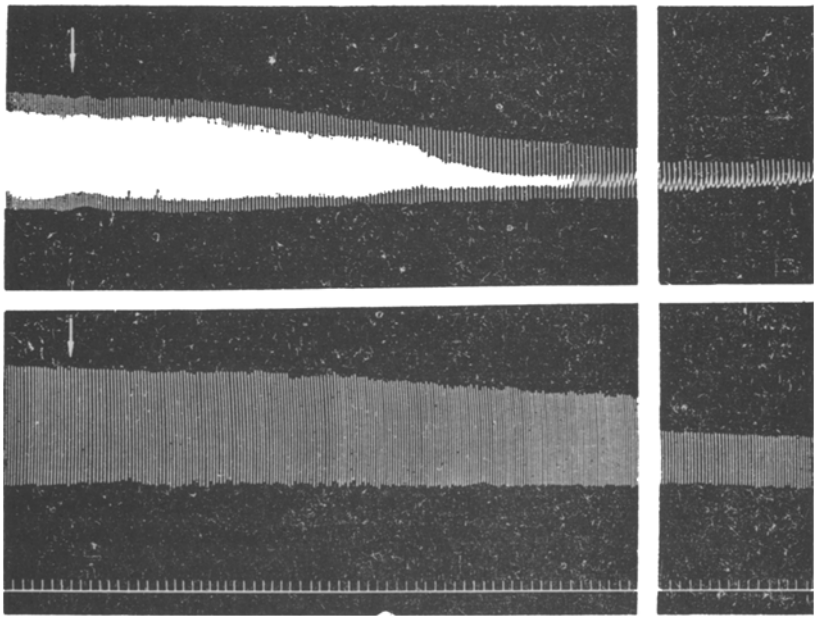

Fig. 3. Effect of potassium cyanide on frog's heart at 35° (top curve) and 10° (bottom curve). Time shown in 6 second marks.

An analogous phenomenon was observed in the case of the inotropic effect of KCN. The amplitude of the cardiac contractions decreased later at the low temperature than at 35°, but bradycardia was observed at the low temperature, so that the work of the heart was approximately equal at both temperatures. All the experimental enzyme poisons had a pronounced negative chronotropic effect at 35°. At 10°, when the heart functions with a slower rhythm due to the lowered temperature of the environment, monoiodoacetate exhibited a positive chronotropic effect, while DNP and KCN did not affect the heart rhythm in any way. The effect of MIA can be explained in a different way. One can assume that monoiodoacetate inhibits the activity of the rhythm leader at the higher temperature and increases it at the lower temperature, but it is more probable that MIA decreases its sensitivity to thermal influences.

As our data to the effect that the positive chronotropic effect of raised temperatures disappears under the influence of DNP and KCN indicate, the biochemical processes inhibited by these substances evidently are also important to the reactivity of the rhythm leader to temperature changes.

SUMMARY

Experiments were staged on isolated dog hearts to investigate the energy resources at the expense of which cardiac activity is provided in hypothermic conditions. Several constituents were added to the Ringer's solution perfusate: monoiodoacetate as a glycolytic poison, 2,-4,-dinitrophenol—as a poison separating the respiration and phosphorylation, and potassium cyanide for blocking cytochromoxidase and excluding respiration.

Isolated frog heart was perfused with one of the mentioned toxic substances at a temperature of 10 and 35°C. As established, at a temperature of 10°C monoiodoacetate had a lesser effect on the cardiac activity than at 35°C. 2, -4,-dinitrophenol provoked myocardial exhaustion at the same time intevals both at 10°C. and at 35°C With KCN added to the perfusate there is a reduction of the contraction amplitude by 50% in 7.2 minutes at 10°C and in 3.7 minutes at 35°C. A negative chronotropic effect is noted at 35°C with a simultaneous addition of 2,-4,-dinitrophenol and KCN.

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