THE MECHANISM OF INSULIN'S TOXIC EFFECT ON A FROG'S HEART

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The works of many researchers [4, 5, 8, 12, 13] have established that the administration of toxic doses of insulin leads to significant changes in the activity of the cardiovascular system (fall of blood pressure, weakening of cardiac contractions, changes in the electrocardiographic indices, etc.) A series of authors [see 5, 12, 13] consider the results obtained to be a consequence of myocardial injury.

The data presented in the literature do not reveal the intimate mechanism of insulin's negative effect on the action of the heart. The literature does not contain any information on the biochemical structures which take part in the processes of insulin's toxic effect on myocardial activity, nor is the role of the sulfhydryl groups of the protein bodies known.

Recently, much material has been accumulated which indicates the importance of sulfhydryl groups in the chemism of muscle contraction [2, 6, 11], specifically, in the contractile function of the myocardium [6, 7, 9, 10]. For example, the works of Kh. S. Koshtoyants [6], T. M. Turpaev [10] and other authors have shown that blockade of the tissue sulfhydryl groups by thiolic poisons (cadmium chloride) causes sharp depression of the amplitude of the contractions of an isolated frog's heart. Under these conditions, the administration of cysteine (a donator of sulfhydryl groups) or urea, which has the ability to break up the protein molecule and thereby liberate the tissue sulfhydryl groups, restores the contractile function of the myocardium.

We expressed the hypothesis that toxic doses of insulin may affect the activity of the tissue sulfhydryl groups of the protein bodies of the myocardium. In order to prove this proposal experimentally, we decided to conduct a series of experiments which would demonstrate whether the negative effect of insulin on the myocardium can be removed by the action of urea, a substance which can liberate reserve sulfhydryl groups.

METHOD

The experiments were performed on frog's hearts isolated according to Shtraub. The heart action was recorded mechanographically and electrocardiographically. The electrocardiograms (ECG) were recorded with the aid of an EKP-4 electrocardiograph. We used depolarized electrodes ($Zn + ZnSO_4$) with cotton wicks to lead off the action currents of the heart. One electrode was placed on the region of the sinus venosus, the other, at the apex of the heart. We tested the effect of insulin in a concentration of 400 units per 100 ml of solution and the effect of urea in a dilution of $1 : 10^{-2}$. All the experimental preparations were prepared in Ringer's solutions.

RESULTS

In all 22 experiments, the introduction of insulin into the perfusate of the isolated frog's heart caused a rapid and considerable decrease in the amplitude of the cardiac contractions. In 14 experiments, the amplitude of the cardiac contractions was only 16-30% of the original value. The subsequent 3-minute washing out of the ventricle of the heart with a Ringer's solution did not restore normal cardiac activity, but the administration of urea under these conditions caused the amplitude of the cardiac contractions to increase in all the experiments. In 12 experiments, the amplitude of the cardiac contractions was fully restored to the original level, and in 10 experiments, the amplitude was 6-14% lower than before the introduction of insulin into the heart (Fig.1).

The action of insulin on the heart caused typical changes in the ECG. To begin with, the P-Q interval, increased, although the time of the passage of excitation through the auricles did not change. The sharpest changes were observed in the QRS complex, which increased considerably in duration. The R wave became wide, acutely deformed and cloven. In most cases, the T wave dropped or became negative. The changes in the Q and S waves were not stable.

The ECG data, therefore, clearly indicates that the introduction of toxic doses of insulin causes considerable disturbances in the function of the heart's conduction system, primarily affecting atrioventricular and intraventricular conduction.

Washing out the ventricle of the heart with a Ringer's solution usually did not help restore the ECG indices of a frog's heart poisoned with insulin. After the administra-

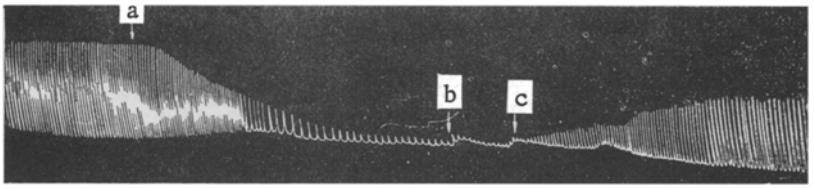

Fig. 1. Effect of urea on the contractions of an isolated frog's heart under conditions of insulin intoxication. a) Introduction of insulin; b) 3-minute washing out of ventricle of heart with a Ringer's solution; c) introduction of urea ($1 \cdot 10^{-2}$).

tion of urea under these conditions, the P-Q interval became shorter and returned to normal. The duration of the QRS complex began to decrease, indicating improved intraventricular conduction. The original direction of the T wave was restored, as was, in most cases, its original amplitude (Fig. 2).

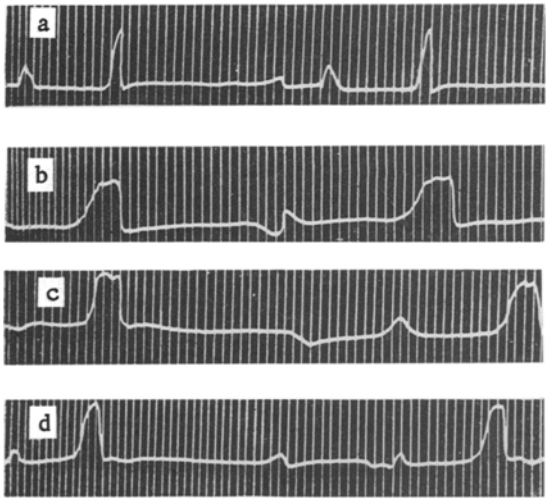

Fig. 2. Change in the ECG of a frog's isolated heart under the influence of urea administered on a background of insulin. a) Normal ECG of the isolated heart; b) ECG one minute after the action of insulin; c) ECG after 3-minute washing out of heart ventricle with a Ringer's solution; d) result of urea's effect after two minutes.

The mechanographic and electrocardiographic data obtained allow the conclusion that insulin has a considerably stronger effect on the function of the atrioventricular node and the intraventricular conduction system of the heart than on the contractile ability of the myocardium.

On the basis of the data obtained, we believe it possible to express the hypothesis that the negative effect of toxic doses of insulin on myocardial contractility and bio-electric activity may be due to a certain extent to depression of the activity of the tissue sulfhydryl groups of the protein molecules. This proposal is based on the fact that, under conditions of acute disturbance of myocardial contractility and bio-electric activity, the administration of urea helps restore these indices to normal.

The explanation of this effect evidently lies in the fact that urea, which a series of authors [1, 3, 6, 7, 10] believe to possess the ability to break up the protein molecule and liberate the tissue sulfhydryl groups, brings about the restoration of the disturbed metabolic processes in the myocardium. As indirect corroboration of this notion, we offer the fact that the changes which we observed insulin to cause in the ECG are very like the data obtained by K. S. Logunova and E. Z. Kipershlak [7] in their study of the ECG of a frog's isolated heart under conditions of cadmium chloride blockade of the sulfhydryl groups.

The opinion we have expressed as to the character of insulin's negative effect on the heart is in no way an attempt to simplify the nature of the problem by reducing the mechanism of this substance's toxic effect to change in the activity of the tissue sulfhydryl groups. Our experimental results rather suggest that the change in the reactivity of the sulfhydryl groups is of great significance in the mechanism of insulin's toxic effect on a frog's heart. Further research is needed to approach an understanding of the nature of the biochemical changes in the myocardium which occur with the action of toxic doses of insulin.

SUMMARY

The author suggests that the negative effect of toxic doses of insulin on cardiac activity is possibly caused by depression of the activity of the tissue sulfhydryl groups. To obtain experimental verification of this suggestion, the author studied the action of urea on the work of the isolated frog's heart under conditions of insulin intoxication. Following the arrest of the cardiac activity caused by toxic doses of insulin, urea administration helped restore the contractile myocardial function and the ECG indices. Such an effect is evidently due to the fact that urea, which has the ability to loosen the protein molecule and liberate the tissue sulfhydryl groups, brings about the restoration of disturbed processes in the cardiac muscle.

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