THE EFFECT OF STROPHANTHIN-K ON THE ACTIVITY OF THE MYOCARDIAL SULFHYDRYL GROUPS

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There have been many works studying the interesting question of how the cardiac glycosides affect the contractility and adenosinetriphosphatase (ATPase) activity of the myocardial actomyosin complex [14]. We know that cardiac glycosides change the ATPase activity of myosin, the contractility of actomyosin preparations and the viscosity of actomyosin, accelerate the conversion of myocardial actin from the globular form into the fibrillar and intensify the contractile function of actomyosin in response to the action of ATP.

However, it is still not clear how the cardiac glycosides react with the myocardial actomyosin complex. We could not find in the literature any information on the effect of cardiac glycosides on the activity of the sulfhydryl groups of the myocardial actomyosin complex.

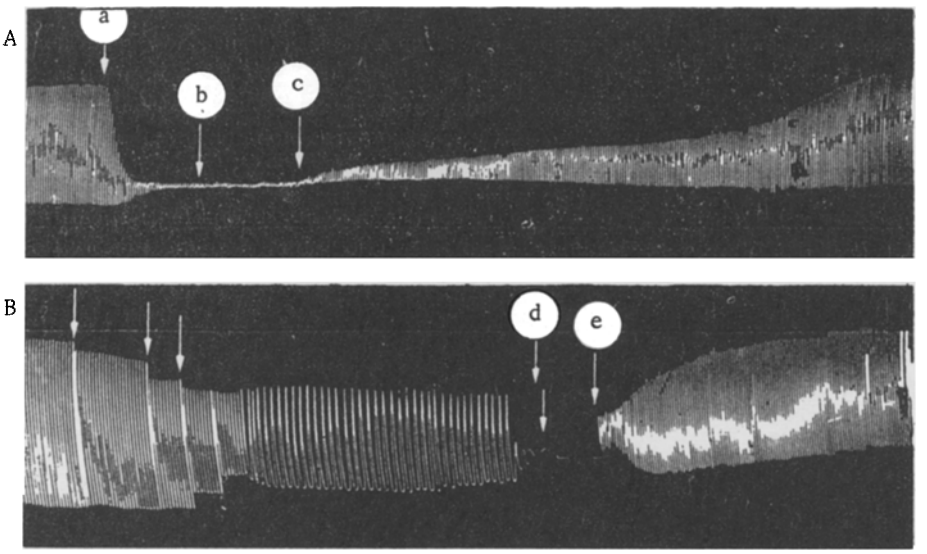

Fig. 1. Effect of strophanthin on contractions of frog's isolated heart under conditions of blocked sulfhydryl groups. a) Effect of cadmium chloride (1.10^{-4}); b) heart ventricle rinsed out with Ringer's solution for 3 min; c) effect of strophanthin (1.10^{-7}); d) heart ventricle rinsed out with Ringer's solution for 3 min; e) effect of ATP (1.10^{-6}). Arrows show points at which kymograph was stopped; duration of mechanogram shows from c to d was 40 min.

Many Researchers [1, 2, 6, 9, 10, 11] have conclusively demonstrated the important part played by sulfhydryl groups in the manifestation of myosin's ATPase activity and its ability to react with actin as well as in the process of its reaction with ATP. Inhibition of the ATPase activity of myosin is known to result from fixation of the sulfhydryl groups by thiolic poisons. The ATPase activity and contractility of myosin can be restored by the action of substances carrying sulfhydryl groups (cysteine or glutathione) or by the action of urea, which liberates reserve sulfhydryl groups [1, 2, 6, 9, 11].

Many authors have established the important role of sulfhydryl groups in myocardial contraction [2, 5, 7, 9]. Fixation of the sulfhydryl groups by thiolic poisons inhibits myocardial contractility; the normal cardiac contractions can be restored by the administration of cysteine or urea. T. M. Turpaev [9] has shown that the heart, which can intensify its contractions in response to the action of ATP, does not react this way under conditions of cadmium chloride fixation of the sulfhydryl groups. The amplitude of the cardiac contractions was not restored until cysteine or urea was introduced into the perfusion fluid.

The fact that isolated preparations of the contractile protein have been employed in most of the investigations studying the effect of cardiac glycosides on ATPase activity and contractility made it important to determine whether the sulfhydryl groups of the myocardial proteins change in activity under the influence of strophanthin.

We studied the effect of strophathin-K on the operation of a frog's isolated heart under conditions of elective blockade of the sulfhydryl groups by cadmium chloride. We proposed that if strophanthin were found to restore the contractile function of the myocardium as well as its sensitivity to ATP, this would be specific evidence to the effect that the sulfhydryl groups play an important part in the realization of strophanthin's effect on the contractile proteins of the myocardium.

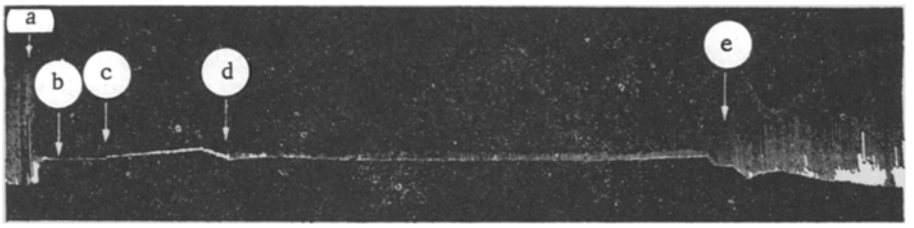

Fig. 2. Effect of ATP on cardiac contractions after preliminary brief strophanthin action on heart muscle under conditions of blocked sulfhydryl groups. a) Effect of cadmium chloride (1.10^{-4}); b) heart ventricle rinsed out for 3 min with Ringer's solution; c) effect of strophanthin (1.10^{-7}) perfused on one minute; d) effect of ATP (1.10^{-6}).

EXPERIMENTAL METHODS

The experiments were conducted on hearts isolated according to Shtraub obtained from frogs in the fall-winter period. We tested the effects of cadmium chloride in a dilution of 1.10^{-4}, strophanthin-K in a dilution of 1.10^{-7}, ATP in a dilution of 1.10^{-6} and urea in a dilution of 1.10^{-3}. All the experimental preparations were prepared in a Ringer's solution before the start of the experiment.

EXPERIMENTAL RESULTS

In the first series of experiments, we studied the effect of strophanthin on the operation of a frog's isolated heart after the preliminary action of cadmium. In all 24 experiments, the introduction of cadmium chloride into the fluid perfusing the frog's isolated heart considerably decreased the amplitude of the cardiac contractions. The amplitude of the cardiac contractions constituted only 10-15% of the original level in five experiments. Normal cardiac activity was not restored when the cardiac ventricle was subsequently rinsed out with a Ringer's solution for 3 min. Under these conditions, the introduction of strophanthin caused an increase in the amplitude of the cardiac contractions in all the experiments. The amplitude of the cardiac contractions was restored to the original level (Fig. 1) in 19 of the experiments and to a level only 18% lower than before the introduction of cadmium chloride in the other 5 experiments.

A striking feature of these experiments was that strophanthin's effect lasted an average of 30 min in a majority of cases, after which the cardiac contractions became retarded and decreased in amplitude to the point of total cardiac arrest.

A second series of experiments was conducted in order to determine the reason for the decrease in the amplitude of the cardiac contractions following prolonged strophanthin perfusion of the heart ventricle. For this purpose, we tested the effect of urea and ATP under conditions of acutely inhibited cardiac activity resulting from prolonged perfusion by the strophanthin solution. Under these conditions, the introduction of urea into the cardiac ventricle usually had no effect; a brief increase in the amplitude of the cardiac contractions was observed in only 2 experiments (out of 11). Under analogous conditions, ATP effected total and durable restoration of the cardiac contractions to their original amplitude in all ten experiments (Fig. 1).

In the third series of experiments, we studied the effect of ATP after the brief preliminary action of strophanthin on a frog's myocardium under conditions of blockade of the myocardial sulfhydryl groups.

A preliminary series of experiments established that brief (one minute) perfusion of the heart ventricle by strophanthin does not in a majority of cases restore cardiac activity disturbed by cadmium chloride.

After the cardiac activity had become acutely inhibited by the action of cadmium chloride, the ventricle of the heart was rinsed out with a Ringer's solution and then perfused with the strophanthin solution for one minute. If the amplitude of the cardiac contractions showed no signs of restoration five minutes after strophanthin was removed from the cannula, ATP was introduced into the heart ventricle.

The experiments conducted showed that myocardial sensitivity to ATP (lost after blockade of the sulfhydryl groups) can be completely restored by the brief action of strophanthin (Fig. 2).

That strophanthin influences the energy metabolism of the myocardium by activating the sulfhydryl groups is indirectly indicated by the results of the above experiments. The fact that, when cardiac activity has been disturbed by elective blockade of the sulfhydryl groups, the introduction of strophanthin into the heart ventricle promotes restoration of the myocardial contractile function supports this hypothesis.

Since thiolic poisons inhibit both the contractility and the ATPase activity of actomyosin filaments simultaneously [2, 6, 8], strophanthin's normalization of the cardiac function may be effected by a simultaneous restoration of the contractility and ATPase activity of the myocardial actomyosin complex. Strophanthin's ability to increase ATPase activity by activating the sulfhydryl groups is indirectly confirmed by the results of the third series of experiments. The restoration of myocardial sensitivity to ATP observed after the short, preliminary action of strophanthin in these experiments was evidently due to restoration of ATPase activity inhibited by the thiolic poison. This agrees with the observations of a number of authors [11, 13] who, working with preparations of the myocardial contractile protein, observed intensified ATPase activity under the influence of strophanthin.

The literature data [12, 15] and the results of the second experimental series allow the conclusion that long contact of strophanthin with the heart tissue depletes the store of energy substances, but does not inhibit ATPase activity. This is confirmed by the fact that the acutely depressed cardiac activity resulting from prolonged perfusion by strophanthin changes, under the influence of ATP, to considerably intensified cardiac contractions.

SUMMARY

The issue deals with the effect of strophanthin-K on the function of the isolated frog heart in conditions of selective blocking of sulfhydryl groups of cardiac muscle proteins by means of cadmium chloride. In such conditions strophanthin restored the cardiac contractions in all the experiments. The effect of urea and ATP was tested during sharp depression of the cardiac activity, caused by prolonged strophanthin perfusion. As a rule urea gave no effect, whereas ATP completely restored the amplitude of cardiac contractions. The ATP sensitivity lost by the cardiac muscle, may be restored by a brief action of strophanthin on the cardiac muscle. A suggestion was put forward that an important role in the mechanism of strophanthin effect on the contractility and the ATP activity of the cardiac muscle is played by an increased sulfhydryl group activity.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
