ROLE OF SULFHYDRYL GROUPS IN PREVENTING AND OVERCOMING THE TOXIC EFFECT OF STROPHANTHIN ON THE DOG'S HEART*

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Sulfhydryl (SH) groups play an exceptionally important role in the activity of many enzymes concerned with tissue metabolism, notably in oxido-reduction processes. Blocking of these groups by thiol poisons lowers the ATPase activity of myosin and reduces the contractile power of the heart muscle [1, 2, 5-8]. The activity of myosin and the contractile power of muscle are restored by the action of cysteine, containing free SH-groups.

The cardiac glycosides are known to inhibit the activity of several enzymes containing SH-groups [11], possibly including those concerned in the changes in the cation metabolism in the myocardium. These changes in the cation metabolism in heart muscle are linked with the primary effect of the cardiac glycosides on the myocardium [10]. On the basis of these considerations and of the results of experiments on the isolated frog's heart [4], F. Z. Meerson has postulated that the blocking of the SH-groups of the myocardial enzymes plays an important role in the mechanism of action of the cardiac glycosides.

The further study of this problem on the heart of warm-blooded animals is essential,both to clarify the mechanism of action of the glycosides, and also to determine if it is possible to eliminate the toxic manifestations of these preparations, so frequently encountered in clinical practice.

EXPERIMENTAL

In 25 experiments on a heart-lung preparation (HLP) of dogs weighing 16-18 kg, the minute volume (MN) of the heart was recorded by P. M. Starkov's method, and the arterial (AP) and venous (VP) pressures were determined. In some experiments the volume of the heart was also recorded by means of a cannula introduced into the pericardial cavity. The ECG was recorded in lead II.

In 15 experiments (series I) the effect of strophanthin in a dose of 0.1 mg on the heart was studied. In 10 experiments (series II) cysteine was injected in a dose of 50 mg 5-6 min before administration of the same dose of strophanthin. In 13 of the experiments of series I, SH-groups in the form of cysteine or unithiol were injected in a dose of 2 ml of the 5% solution after the manifestation of the toxic action of strophanthin on the heart. All the substances were diluted in 1-2 ml blood and injected into the venous reservoir of the apparatus.

EXPERIMENTAL RESULTS

In the experiments of series I, after the appearance of fatigue of the heart, as shown by a decrease of MV to 91.6% of its initial level, injection of strophanthin did not produce significant changes in the value of MV. Later, 25±12.8 min after injection of strophanthin, obvious toxic manifestations of the drug on the heart were observed (extrasystoles, ectopic beats, bradycardia). In an experiment on June 12, 1964. (Fig. 1B), for example, loading the heart by a transient increase in the venous inflow (this corresponded to the duration of the increase of venous pressure on the kymogram) after injection of strophanthin,led to an increase in the MV to 1120 ml, whereas before injection of strophanthin, this index reached 1140 ml for a

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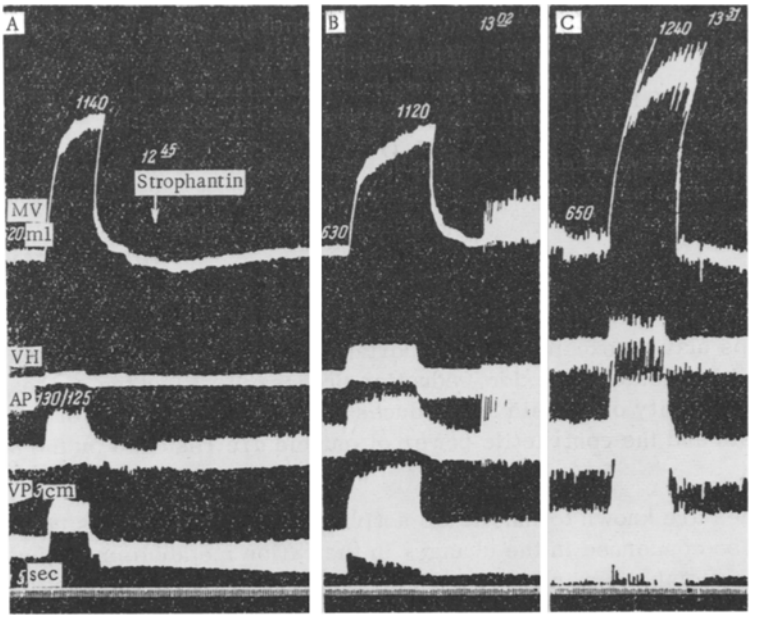

Fig. 1. Changes in the ejection function of the heart during the action of strophanthin followed by administration of cysteine. Experiment on June 12, 1964. MV) minute volume; VH) volume of the heart; AP) arterial pressure; VP) venous pressure; time marker) one division corresponds to 5 sec; A) before injection of strophanthin; B) after injection of strophanthin; C) after injection of cysteine.

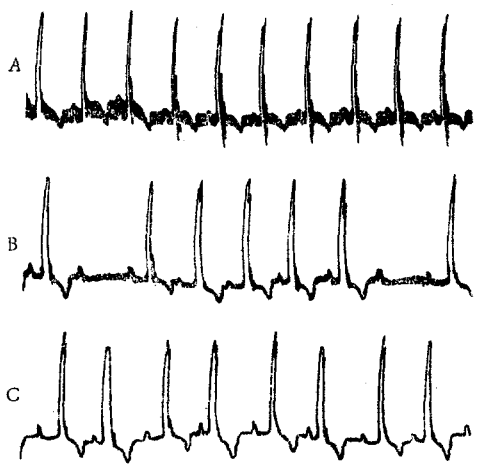

Fig. 2. ECG during the action of strophanthin on the heart followed by administration of unithiol. Experiment on May 6, 1964. A) Before injection of strophanthin; B) after injection of strophanthin; C) after injection of 2 ml of 5% unithiol solution.

load of the same magnitude. The time for the increase in MV was longer than before injection of strophanthin. This was followed by arrhythmia, shown on the kymogram (Fig. 1B) by an increase in the amplitude of the fluctuations of the hemodynamic indices. It may be assumed that these changes were associated with the development of the toxic action of strophanthin on the heart.

To demonstrate the relationship between the onset of arrhythmia and the potassium level, in 5 experiments the concentration of this element in the blood was investigated during the development of arrhythmia. It was found that the toxic action of strophanthin appeared when the plasma potassium concentration was normal (from 16 to 23 mg%).

In the experiments of series II, the mean MV of the heart before injection of strophanthin was 533±149, and after its injection 473±241 ml ($P > 0.2$), i.e., it was practically unchanged and the difference was not statistically significant, just as in the experiments on series I. It follows that administration of SH-groups had no effect on the contractile function of the heart. However, in contrast to the results of the experiments of series I, arrhythmia from the toxic action of strophanthin developed much later, on the average after 71±25.5 min. The difference between the times of onset of arrhythmia in the experiments of series II and I was significant ($P > 0.001$). In 6 of the 10 experiments of series II arrhythmia developed after prolonged working of the heart, and then only as the result of a second injection of strophanthin.

Injection of SH-groups into the blood stream after the appearance of the toxic effects of strophanthin caused an improvement in the electrocardiographic indices on the average after 10±7 min. In 3 of the 13 experiments the arrhythmia was abolished, in 5 it was reduced, in 3 the bradycardia was reduced, and in 2 experiments the conducting function was improved. It is clear from Fig. 1C that the injection of cysteine led to weakening of the developing arrhythmia, and this was shown in the initial part of the kymogram by a decrease in the amplitude of the fluctuations of the MV and other indices. Consequently, in this case, cysteine weakened the toxic action of strophanthin on the heart.

The ECG of one of the experiments (Fig. 2B) showed the presence of an atrioventricular block with periodic omission of the ventricular complex, taking place against the background of the action of strophanthin. Injection of unithiol, a donor of SH-groups, abolished the disturbance of atrioventricular conduction (Fig. 2C).

In these experimental conditions, it must be noted, the injection of SH-groups had no appreciable effect on the contractile function of the heart.

The preliminary injection of SH-groups into the blood thus prevented the toxic effect of strophanthin on the heart in the heart-lung preparation. Injection of SH-groups, after the appearance of the toxic effect of strophanthin, led to weakening or disappearance of these effects. The appearance of the toxic effects of strophanthin is evidently associated with blocking of the SH-groups in the myocardium, and especially in conducting system of the heart. This is demonstrated by signs of strophanthin poisoning such as disturbance of atrioventricular conduction and the development of nodal extrasystoles. It is known that SH-groups are contained in the cytoplasm of the conducting system of the heart [9] and are of great importance to its function [2, 3]. The atrioventricular region of the conducting system is particularly sensitive to blocking of the SH-groups by thiol poison. Injection of an excess of SH-groups in the present experiments evidently had a prophylactic action against these disturbances in the conducting system of the heart.

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