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EFFECT OF LITHIUM COMPOUNDS ON CARDIAC ARRHYTHMIAS INDUCED BY STROPHANTHIN IN CONSCIOUS RATS*

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An important role in the cardiotoxic action of cardiac glucosides is played by the neurogenic component. In particular, one state of strophanthin-induced arrhythmias is connected with hyperactivity of the sympathetic nervous system [8, 9, 11, 13, 14]. The writers showed previously that lithium compounds depress arrhythmias whose genesis is attributable to hyperactivity of the sympathetic nervous system [3, 4]. In the investigations cited, anesthetized cats were used.

Since general anesthesia may affect the control of the cardiac rhythm, in the investigation described below the effects of lithium salts were studied on a model of strophanthin-induced cardiac arrhythmias in unanesthetized animals.

EXPERIMENTAL METHOD

Experiments were carried out on 100 unanesthetized male Wistar rats weighing 140-160 g. The action of strophanthin and of lithium preparations was evaluated on the basis of the ECG which was recorded in standard leads II and III and in a chest lead. The active electrode for the chest lead was located at the level of the cardiac impulse. The ECG was recorded during periods when the animals were resting quietly lying on their back. Toxic doses of strophanthin K, namely 1.4-1.6 ml of a 0.05% solution per 100 g body weight, were used and caused death of the animals in 100% of cases. Lithium chloride and hydroxybutyrate were used in the form of 10% solutions. All drugs were injected into the jugular vein: strophanthin in the course of 2 min, lithium salts in the course of 5-10 min.

EXPERIMENTAL RESULTS

Three stages of changes in cardiac activity could be distinguished in the time course of strophanthin poisoning in most (24 of 30) animals (Fig. 1). In the first stage, which can be called the stage of primary disturbances of the cardiac rhythm, the heart rate slows, and conductivity is disturbed in the form of a high level atrioventricular block, with single or grouped idioventicular contractions (Fig. 1b). The longest duration of this stage was 3 min. The second stage was characterized by disappearance of the above-mentioned disturbances (Fig. 1b). This stage lasted from 1 to 3 min. The third stage, the stage of secondary disturbances of the cardiac rhythm, was characterized by complex changes of rhythm in the form of well-marked ectopic ventricular automatism against the background of A-V dissociation, changing into ventricular tachycardia (Fig. 1d, e). This stage occurred 5-7 min after injection of stro-

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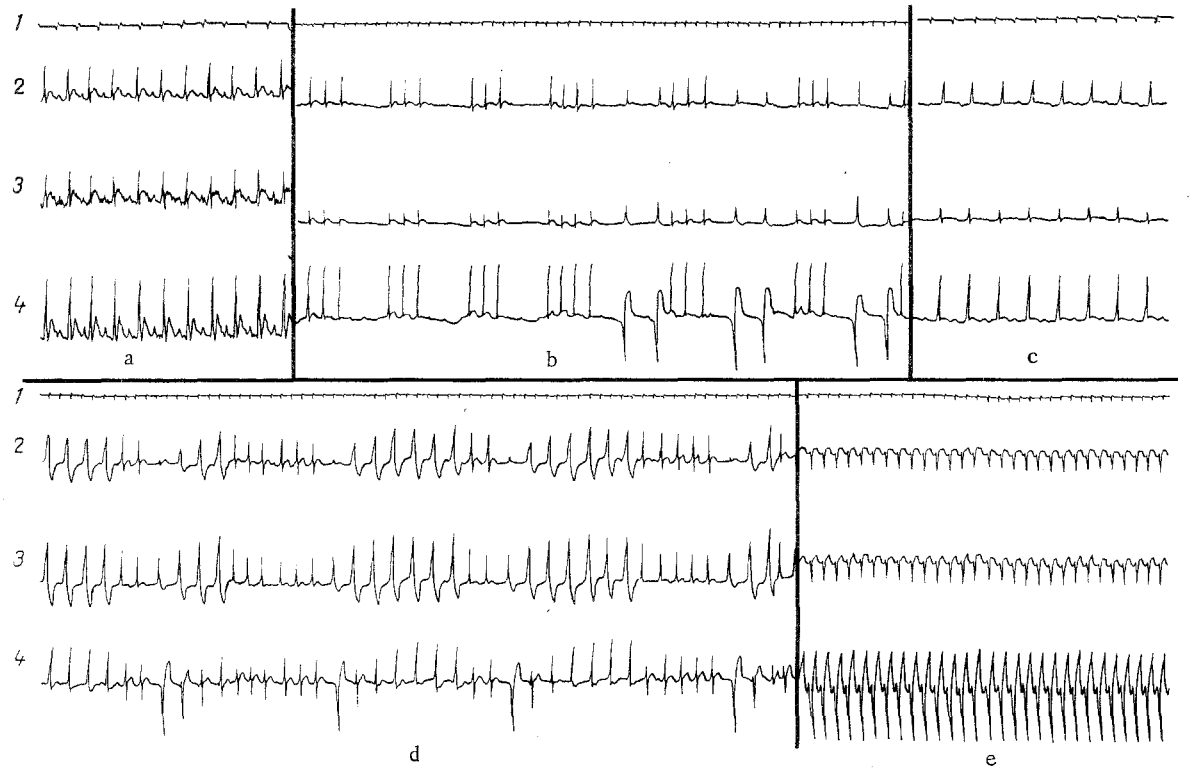

Fig. 1. Disturbances of cardiac rhythm after injection of strophanthin: a) ECG before injection of strophanthin; b) primary disturbances of cardiac rhythm 2 min after injection of strophanthin (1st stage), c) 5 min after injection of strophanthin (2nd stage), d, e) secondary disturbances of cardiac rhythm 8 and 15 min respectively after injection of strophanthin (3rd stage). Here and in Fig. 2: 1) time marker 0.1 sec; 2-4) standard leads II and III and chest lead of ECG respectively.

phanthin and the animals died after 7-18 min. Six of the 30 animals developed disturbances of cardiac rhythm characteristic of the third stage immediately after injection of strophanthin, and these animals died after 5-10 min.

During control injection of lithium chloride (0.15 and 0.5 ml/100 g body weight, 6 rats) and lithium hydroxybutyrate (0.15 ml/100 g body weight, 5 rats) solutions into normal animals no significant change was observed in cardiac activity, only very mild bradycardia. An increase in the dose to 1 ml/100 g (in the course of 2 min) led to disturbance of the cardiac rhythm and death of the animals (3 rats) after 2-4 min.

Injection of lithium chloride in a dose of 0.15 ml/100 g (5 rats) and lithium hydroxybutyrate in doses of 0.15 ml/100 g which, calculated as the cation, corresponded to a dose of approximately 0.075 ml of lithium chloride, and of 0.38 ml/100 g (in both cases 5 rats were used) at different stages of strophanthin-induced arrhythmias led to temporary (from a few seconds to 7 min) restoration of the sinus rhythm. This effect occurred actually during injection of the lithium salts and could be reproduced 5 or 7 times or more in the same animal (Fig. 2). The duration of action of the lithium compounds was shortened under these conditions. However, the general toxic action of strophanthin was not abolished and the animals died at the same times as in the control.

One-stage injection of lithium chloride in a dose of 0.075 ml/100 g (10 rats) or 0.15 ml/100 g (10 rats) immediately after injection of strophanthin, like its administration by intravenous drip (5 rats), had no significant effect on the appearance of arrhythmias or on the general toxic action of strophanthin: all the animals died after 5-16 min.

Injection of lithium hydroxybutyrate in a dose of 0.15 ml/100 g immediately after strophanthin prevented death of most of the animals (8 of 10); in this case the survival time of animals which died was increased to 30-33 min. In two animals of this group which survived cardiac arrhythmias characteristic of the first stage of strophanthin poisoning occurred, and

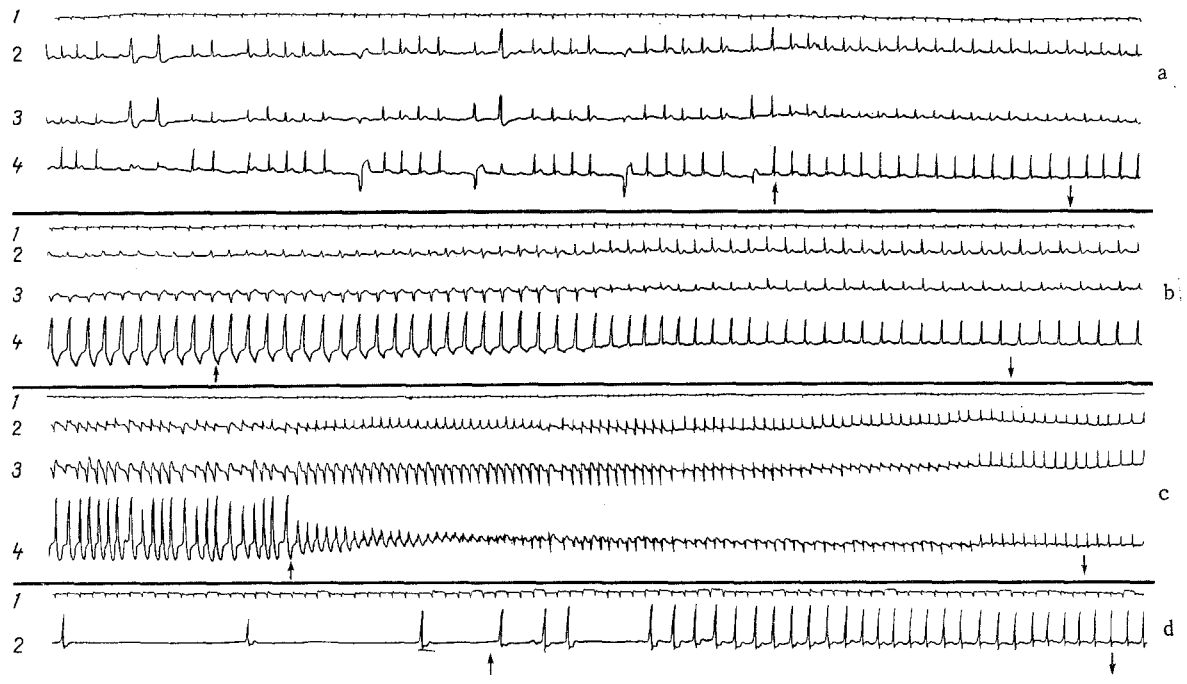

Fig. 2. Effect of lithium hydroxybutyrate on cardiac arrhythmia induced by strophanthin: a-d) various cardiac arrhythmias. Arrows pointing upward and downward denote beginning and end of injection of lithium hydroxybutyrate respectively.

in 5 rats secondary disturbances of the cardiac rhythm also were observed (the 3rd stage of strophanthin poisoning), but they did not progress and after a few minutes the normal cardiac rhythm was restored. An increase in the dose of lithium hydroxybutyrate to 0.38 ml/100 g (5 rats) did not prevent the development of arrhythmias characteristic of the 3rd stage of strophanthin poisoning and did not prevent the toxic action of strophanthin.

Control injection of a 10% solution of sodium chloride in doses of 0.15 ml/100 g and 0.28 ml/100 g which, calculated as anion, corresponds to 0.15 ml lithium chloride (5 rats were used in each case), against the background of various cardiac arrhythmias, had no antiarrhythmic acdion.

The investigations showed that lithium chloride and hydroxybutyrate, given as a single or as repeated injections to animals with various cardiac arrhythmias induced by toxic doses of strophanthin, had a temporary normalizing effect on the cardiac rhythm. It can be tentatively suggested that this effect is associated with the action of the lithium cation and not of the anionic group, which differed in the two compounds. The temporary nature of the antiarrhythmic action of the lithium compounds, observed when they were injected into animals with established arrhythmias, is probably associated with the continuing action of strophanthin, which was given in a lethal dose. This explanation is supported by the fact that lithium did not abolish the general toxic action of strophanthin. It is interesting to note that the antiarrythmic effects of lithium appeared actually during injection of the drug ("on the needle") and they could be repeated many times over in the same animal. These distinguishing features of the antiarrhythmic effects cannot be explained by reflex responses to intravenous injection of hypertonic solution of lithium salts, for hypertonic sodium chloride solution in the same concentration had no antiarrhythmic effect. It must be pointed out that the antiarrhythmic effect of the lithium compounds depends on the rate of their injection. This suggests that the differences in the action of the lithium preparations may be influenced by the rise time of the lithium concentration in the blood.

As already pointed out, a single injection of lithium hydroxybutyrate in a dose of 0.15 ml/100 g immediately after injection of strophanthin depressed its cardiotoxic action and prevented death of most of the animals.

It has been shown, including in our own previous investigations [3-5], that the antiarrhythmic action of lithium salts is connected with both central and peripheral mechanisms.

We also know that in strophanthin arrhythmias the balance between sympathetic and parasympathetic influences on the heart is disturbed [5, 7, 8]. In cases when the arrhythmias developed against the background of enhanced activity in the sympathetic nerves of the heart, inhibition of this activity led to normalization of the cardiac rhythm [3, 4]. Meanwhile antiarrhythmic effects of lithium compounds may be due to the direct action of the lithium cation on the myocardial membrane [7, 12, 15].

Lithium preparations thus exert their antiarrhythmic action in animals not only under general anesthesia, as was shown previously [3-5], but also in the conscious state. Of the two lithium compounds used, the hydroxybutyrate was more effective against the general toxic action of strophanthin. This may evidently be associated with the action of the hydroxybutyrate anion, which gives rise to complex pharmacological and metabolic effects [1, 2, 6, 10] which potentiate the action of lithium.

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