EFFECT OF LITHIUM PREPARATIONS ON THE TOXIC EFFECTS OF ADRENALIN

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Lithium preparations have been shown to have an antiarrhythmic action in those cardiac arrhythmias in whose pathogenesis sympathetic hyperactivity is involved [1, 2]. Accordingly, and because of the role of catecholamines in the development of arrhythmias and, in particular, the ability of adrenalin in high doses to cause the appearance of a heterotopic rhythm [7-9], the investigation described below was devoted to a study of the action of lithium compounds on arrhythmias induced by intravenous injection of adrenalin.

EXPERIMENTAL METHOD

Experiments* were carried out on 64 male Wistar rats weighing 150-200 g. The effects of the toxic action of adrenalin were studied in the animals of group 1. Lithium preparations and sodium hydroxybutyrate were injected into animals of groups 2, 3, and 4 after injection of adrenalin. Lithium hydroxybutyrate was injected into the animals of group 5 before adrenalin. The action of the substances was assessed by studying the ECG which was recorded without anesthesia in standard leads II and III and in a chest lead. When the ECG was recorded in the chest lead the active electrode was located at the level of the apex beat. The animals were fixed on their back. A 0.1% solution of adrenalin hydrochloride and 10% solutions of lithium chloride, lithium hydroxybutyrate, and sodium hydroxybutyrate were injected intravenously in all cases.

EXPERIMENTAL RESULTS

Injection of adrenalin in a dose of 0.3-0.4 mg/kg caused disturbances of the cardiac rhythm, pulmonary edema, and death of all the animals of group 1 (20 rats) 2-3 min after injection. Pulmonary edema was accompanied by a profuse discharge of pink frothy fluid from the nose. Morbid anatomical examination of the dead animals showed that the lungs were dark brown in color and a little enlarged. On section of the large bronchii and lungs a frothy pink fluid escaped. Pieces of the lungs sank in water.

On analysis of the changes in cardiac activity reflected in the ECG three stages of manifestation of adrenalin poisoning could be distinguished. The first stage (the first 30 sec after injection of adrenalin) was characterized by the appearance of a slow nodal rhythm and ectopic contractions, and atrial ventricular dissociation was frequently observed; the second stage was characterized by disappearance of the above-mentioned disturbances and the appearance of a sinus rhythm in the form of sinus bradycardia; in the third stage (1-1.5 min after the injection of adrenalin) ectopic pacemaker activity again was enhanced and some animals showed signs of damage to the myocardium (elevation of the S-T interval). At this stage (secondary arrhythmias) the animals developed symptoms of pulmonary edema and died.

Lithium chloride (0.075 ml of the 10% solution/100 g body weight), injected into the animals (10 rats) of group 2 immediately after adrenalin, prevented the development of secondary cardiac arrhythmias and death

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of the animals in 50% of the cases. One rat developed symptoms of incipient pulmonary edema (a discharge of frothy fluid from the nose), but did not die. Cardiac arrhythmias characteristic of the first stage of adrenalin poisoning were observed in all the animals. They appeared immediately after the injection of adrenalin and continued during injection of lithium chloride. In the animals which survived, recovery of the sinus rhythm in the second stage was stable and arrhythmias did not subsequently recur. A second injection of adrenalin into these animals caused death of three of the five rats (after 4-7 min), but one rat did not die even after a third injection of adrenalin.

Animals of group 3 (10 rats) were given an injection of lithium hydroxybutyrate, as a control of the action of Li^+, in a dose of 0.1 ml of the 10% solution/100 g body weight. Lithium hydroxybutyrate, like lithium chloride, did not affect the development of the first stage of adrenalin poisoning but prevented the development of the third stage and all the animals of this group survived. A second injection of adrenalin into seven rats caused death of four of them (after 3, 4, 5, and 7 min respectively); three rats died after a third injection of adrenalin (after 3, 4, and 7 min).

In group 4 (10 rats), as a control of the action of the hydroxybutyrate anion, instead of lithium hydroxybutyrate the animals were given an injection of sodium hydroxybutyrate in a dose of 0.17 ml/kg body weight. These experiments showed that sodium hydroxybutyrate has no antiarrhythmic action and does not prevent the development of pulmonary edema. Eight of the 10 rats in this group developed arrhythmias and died after 2-5 min.

In group 5, lithium hydroxybutyrate was injected into the rats before adrenalin. The results of this series of experiments showed that lithium hydroxybutyrate has no prophylactic antiarrhythmic action. Of the 14 rats of this group 12 died 2-18 min after injection of adrenalin.

The experiments showed that lithium preparations completely (lithium hydroxybutyrate) or in a certain proportion of cases (lithium chloride) prevent the onset of secondary cardiac arrhythmias in the third stage of adrenalin poisoning. Two questions accordingly require an answer: 1) what is the mechanism of the antiarrhythmic action of lithium; 2) why does preliminary injection of lithium preparations not prevent the development of adrenalin arrhythmias.

Lithium activates monoamine oxidases and potentiates intraneuronal destruction of catecholamines [14], disturbs their secretion [3], and stimulates reassimilation [4, 11]. All these effects relate to presynaptic mechanisms of depression of synaptic activity. They take place in adrenergic structures of the CNS, in the extracardiac adrenergic system and, evidently, in the region of synaptic endings in the heart itself. However, in this case we are concerned with the effects due to the appearance of exogenous adrenalin in the blood. Adrenalin is known to act directly on myocardial cells and cells of the conducting system are most sensitive to it [7-9]. It has been shown that lithium reduces the sensitivity of receptors to catecholamines [6, 10] and inhibits adenylate cyclase activity [5, 13]. These data explain the effects of lithium preparations in arrhythmias induced by adrenalin.

Meanwhile a considerable increase in the circulating blood level of adrenalin causes significant changes in the hemodynamics in connection with peripheral vasoconstriction. The latter gives rise to a reflex increase in parasympathetic activity and potentiates the vagus effect on the heart [15]. Arrhythmias arising in the first stage of adrenalin poisoning thus have a complex pathogenesis: They are due, on the one hand, to the direct action of adrenalin on myocardial adrenoreceptors and, on the other hand, to potentiation of the vagus effect on the heart. This may explain why lithium does not abolish arrhythmias in the first stage of poisoning. The same phenomenon – absence of the antiarrhythmic effect of lithium – was described by the writers previously [1] in cats with strophanthin arrhythmias in cases when no increase took place in sympathetic activity, but potentiation of the effect of the vagus nerves was clearly manifested. Another fact which must be recalled is that lithium effectively acts on excitable membranes, in which it replaces sodium and prevents the inflow of calcium into the cell during depolarization [12]. That is why the prophylactic effect of lithium may be minimal under normal conditions.

Yet another effect of lithium preparations was found in this investigation: their ability to alleviate or to prevent the development of adrenalin-induced pulmonary edema. The mechanism of pulmonary edema caused by intravenous injection of adrenalin is complex.

The data described above on the mechanism of action of lithium suggest that its therapeutic effect is connected with depression of the adrenergic receptor apparatus of the lungs and of central adrenergic structures.

Both effects observed with lithium compounds – the antiarrhythmic action and prevention of the development of pulmonary edema – are evidently due to the action of lithium itself, because they were produced by the use of both lithium hydroxybutyrate and lithium chloride, and they were not found after injection of sodium hydroxybutyrate. Of the lithium compounds used, the hydroxybutyrate was more effective.

The results thus suggest that there is a future for the use of lithium preparations and, in particular, of lithium hydroxybutyrate in clinical practice for the treatment of cardiac arrhythmias and pulmonary edema, in the pathogenesis of which an important role is played by hyperreactivity of adrenergic structures.

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CORRECTION OF HYPERSENSITIVITY TO STROPHANTHIN IN EXPERIMENTAL MYOCARDIAL INFARCTION BY THE ACTION OF DRUGS ON THE EXTRACARDIAL INNERVATION

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According to experimental data [4, 15] and clinical observations [10, 11], myocardial infarction is a factor which provokes poisoning by cardiac glycosides, and the safety of their use is largely dependent on the existence of effective methods of correcting hypersensitivity to these cardiac stimulants by means of drugs.

It was shown previously that pharmacological blockade of the cardiac β-adrenoreceptors by alfeprol (alprenolol) increases tolerance to strophanthin in intact animals and in animals sensitized with homocardial antigen, and also enables increased sensitivity to the cardiac glycoside in acute myocardial ischemia to be abolished [2-4].

The investigation described below was undertaken to study how the action of different kinds of mediators on different levels of the extracardial innervation can affect tolerance to strophanthin in intact animals and at various times after production of experimental myocardial infarction.

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