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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KEY WORDS: strophanthin; myocardial infarction; mediators.

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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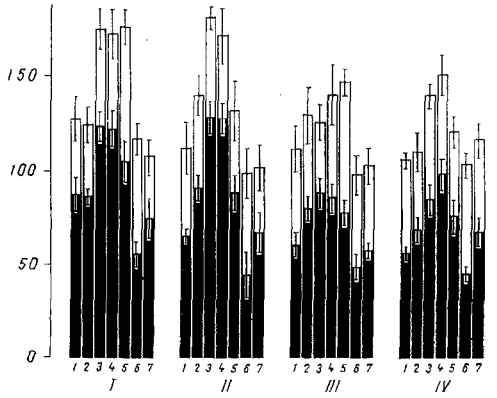

Fig. 1. Effect of drugs with autonomic action on tolerance to strophanthin at different times after OCA. Abscissa: I) intact animals, II) 2 h, III) 24 h, IV) 48 h after OCA; ordinate, dose of strophanthin (in μg/kg). Black columns denote MAD, unshaded columns LD. 1) Animals without premedication; 2) benzohexonium; 3) ornid; 4) propranolol; 5) neostigmine; 6) ephedrine; 7) atropine. Confidence limits given at P = 0.05 level.

EXPERIMENTAL METHOD

Experiments were carried out on 176 cats of both sexes weighing 2-3.1 kg, anesthetized with thiopental sodium (30 mg/kg) and pentobarbital sodium (30 mg/kg). The method of producing experimental myocardial infarction by ligating a branch of the left coronary artery and the method of determining the minimal arrhythmogenic dose (MAD) and the lethal dose (LD) of strophanthin, according to which the tolerance of the animals to the glycoside was judged, were described previously [4].

There were 16 series of experiments: MAD and LD of strophanthin were determined for intact animals (control), after premedication of the intact animals with benzohexonium (1 mg/kg), ornid (bretylium) (40 mg/kg), anaprilin (propranolol) (5 mg/kg), neostigmine (0.05 mg/kg), ephedrine (1 mg/kg), and atropine (0.05 mg/kg), 2, 24, and 48 h after occlusion of the coronary artery (OCA), and after OCA in animals receiving premedication with the drugs mentioned above. Ornid was injected intramuscularly 2 h before, and the other drugs intravenously 5 min before the beginning of biological titration of MAD and LD of strophanthin.

In parallel experiments the sodium and potassium concentrations in the ischemic and boundary zones of the cardiac muscle were determined on the BIAN-140 photometer at the same times after production of myocardial infarction.

EXPERIMENTAL RESULTS

It will be clear from Fig. 1 that the various mediators differed in their action on sensitivity of the animals to the cardiotoxic action of strophanthin.

Pharmacological denervation of the heart at the level of the autonomic ganglia in intact animals by benzohexonium had no effect on the MAD or LD of strophanthin. Blockade of the adrenergic innervation of the heart by the sympatholytic bretylium and the β-adrenoblocker propranolol, and also relative weakening of sympathetic influences by vagotonia induced with neostigmine, led to a marked increase in tolerance to strophanthin. Bretylium and propranolol weakened mainly the arrhythmogenic action of strophanthin, the MAD of which they increased by 41.4 and 39%, whereas neostigmine increased mainly its LD (by 43.2%). Conversely, potentiation of the sympathetic effects by ephedrine, like parasympathetic blockade by atropine, potentiated the cardiotoxicity of strophanthin a little.

These changes in tolerance to strophanthin under the influence of mediators with different directions of action were evidently associated with the fact that potentiation of sympathetic influences on the myocardium increases its concentration of cyclic AMP [6, 14], which is known to participate in the mechanism of the effects of cardiac glycosides [5, 7, 12], and thus to potentiate the cardiotoxicity of strophanthin. Acetylcholine, on the

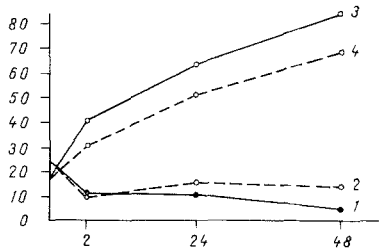

Fig. 2. Changes in myocardial electrolyte balance at different times after OCA. Abscissa, time after OCA (in h); ordinate, electrolyte concentrations (in meq/kg). 1) Potassium in zone of ischemia; 2) potassium in boundary zone; 3) sodium in zone of ischemia; 4) sodium in boundary zone.

other hand, causes accumulation of cyclic GMP in the myocardial cells and a relative decrease in the cyclic AMP concentration [6, 12, 13], thereby evidently weakening the toxicity of strophanthin. Hence it will be clear why antiadrenergic drugs, and also neostigmine, which induces vagotonia, increased the tolerance of the animals to strophanthin whereas the adrenomimetic and cholinomimetic drugs reduced it.

It was shown previously that occlusion of the descending branch of the left coronary artery leads in the course of the first few days to a progressive increase in the sensitivity of animals to the cardiotoxic action of strophanthin [4].

In the study of the effect of mediators on tolerance to strophanthin 2 h after OCA it was found that blocking the extracardial innervation by benzohexonium completely abolished the increase in sensitivity of the animals to the cardiac glycoside.

In acute myocardial ischemia the sympathicoadrenal system is mobilized and its influence on the heart is greatly strengthened [8]. Benzohexonium premedication weakened the sympathetic innervation of the heart, and this determined the protective effect of the ganglion-blocker under these experimental conditions.

Antiadrenergic agents including desympathization at the presynaptic (bretylium) and postsynaptic (propranolol) levels had an even more marked protective action, sharply increasing the resistance of the animal to strophanthin (bretylium increased MAD by 95.4% and LD by 70.4%, propranolol by 86.2 and 58.3% respectively). Neostigmine had approximately the same effect under these conditions as benzohexonium. Potentiation of adrenergic influences by ephedrine, on the other hand, reduced tolerance to the arrhythmogenic action of strophanthin even more (it reduced its MAD by 35.4%).

Benzohexonium 24 h after OCA continued to exert a protective effect, and predominantly weakened the arrhythmogenic action of strophanthin (MAD was increased by 36.2%). Bretylium and propranolol increased resistance to strophanthin at this period by a lesser degree than 2 h after OCA. Neostigmine increased the tolerance of the cats to strophanthin most clearly, and increased its MAD (by 23.8%) and LD (by 28.7%) about equally. Ephedrine, just as previously, reduced tolerance to strophanthin.

At the time of maximal increase in the sensitivity of the animals to strophanthin 2 days after OCA benzohexonium had little effect on tolerance to the cardiac glycoside, whereas bretylium and propranolol significantly increased resistance to strophanthin (its MAD was increased by 52.5 and 64.4% and its LD by 36.3 and 46% respectively). It must be noted, however, that during this period of acute myocardial ischemia the protective effect of the adrenolytics was weaker than 2 h after OCA. Neostigmine mainly increased MAD of strophanthin (by 23.7%; $P < 0.05$). It is an interesting fact that in this stage of myocardial infarction the hitherto similar action of ephedrine and atropine diverged: the former continued to potentiate the arrhythmogenic effect of strophanthin, the latter showed a tendency to increase its LD somewhat.

A study of the electrolyte balance of the heart muscle showed an increase in the sodium concentration in the ischemic and the boundary zones of the myocardium, accompanied by a decrease in their potassium concentration (Fig. 2). These changes reached a maximum in these experiments 48 h after OCA.

The experimental results indicate an important role of the functional state of the extracardial innervation in the genesis of hypersensitivity to strophanthin in acute myocardial ischemia. Under these circumstances the enhanced sympathetic influences play the decisive role, as is shown by the ability of adrenoblockers,

acting on different levels of the extracardial innervation, to increase tolerance significantly to the toxic effects of strophanthin. Neostigmine, which potentiates cholinergic influences on the heart, had an action in the same direction, although it was weaker, whereas ephedrine, on the contrary, potentiated the cardiotoxicity of strophanthin.

It should be noted that the relative contribution of sympathicoadrenal influences to the genesis of hypersensitivity to strophanthin was particularly great during the first few hours of acute myocardial ischemia, when adrenoblockers exerted their strongest protective action.

Besides the adrenergic component, a role of ever-increasing importance was acquired 24 and 48 h after OCA by other factors – disturbance of the ultrastructure and permeability of the myocardial cell membranes, and changes in the electrolyte balance of the heart muscle [1, 9]. The dynamics of the changes in the electrolyte concentrations in the ischemized myocardium reflect this state of affairs in particular.

Hypersensitivity to strophanthin in acute myocardial ischemia is thus successfully corrected by drugs with an antiadrenergic action on the extracardial innervation; they are most effective, moreover, in the early stages of experimental myocardial infarction.

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