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EFFECT OF NONACHLAZINE ON ATP, ADP, AND LACTIC ACID CONCENTRATIONS IN THE INTACT AND ISCHEMIZED MYOCARDIUM

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Nonachlazine is a new and original drug synthesized in the Institute of Pharmacology, Academy of Medical Sciences of the USSR. The results of clinical trials have shown that nonachlazine is an antianginal agent distinguished by its high efficacy in the treatment of ischemic heart disease [3, 4, 11, 12]. Experimental studies have shown that an important role in the mechanism of the antianginal effect of nonachlazine is played by its effect on adrenergic processes of regulation of the circulation and cardiac activity [5]. Nonachlazine increases the noradrenalin concentration and activity of phosphorylase "a" in the myocardium [6]. These findings suggest that the beneficial effect of nonachlazine is evidently associated with its ability to activate adrenergic mechanisms in the regulation of glycogenolysis.

In accordance with the facts described above, and taking into account data showing that ischemia leads to a decrease in the ATP concentration in the myocardium [2, 14, 15], it was decided to study the effect of nonachlazine on the concentrations of ATP, ADP, and the end product of glycogenolysis – lactic acid – in the intact and ischemized myocardium.

TABLE 1. Concentration of ATP, ADP, and Lactic Acid (in μmoles/g wet weight of tissue) in Cat Myocardium (M ± m)

Series of experiments	Experimental	ATP	ADP	Lactic acid
I	Control	4,49±0,76 5,25÷3,73	1,05±0,33 1,38÷0,72	3,22±0,08 3,30÷3,14
II	Nonachlazine, 6mg/kg	4,31±0,85 5,16÷3,46	1,07±0,47 1,54÷0,60	3,51±0,44 3,95÷3,07
III	Acute ischemia	3,69±0,13* 3,82÷3,56	1,53±0,24* 1,77÷1,29	7,34±3,01* 10,35÷4,33
IV	Acute ischemia + nonachlazine, 6 mg/kg	4,60±1,08† 5,68÷3,52	1,57±0,54 2,11÷1,03	4,25±0,80† 5,05÷3,45

*Results statistically significant compared with control ($P \leq 0.05$).
†Results statistically significant compared with experiments with acute ischemia ($P \leq 0.05$).

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EXPERIMENTAL METHOD

Experiments were carried out on cats weighing 2.5-3.5 kg, anesthetized with a mixture of urethane and chloralose (600 and 400 mg/kg respectively). Thoracotomy was performed on the animals after 3-5 min, the pericardium was opened, and the subsequent investigations in all series of experiments were carried out not before 30 min had elapsed. The EKG was recorded throughout the experiment. Nonachlazine was injected intravenously in a dose of 6 mg/kg and physiological saline was injected into the control animals. The investigations were carried out 15 min after injection of nonachlazine, for this time corresponds to maximal manifestation of the effect of the drug. Tissue for testing (the left ventricle) was frozen in liquid nitrogen. There were four series of experiments. Series I was the control. In the experiments of series II the heart was taken 15 and 30 min after injection of nonachlazine. In series III and IV the left descending coronary artery of the animals was ligated in the middle third; subsequent experiments were performed only on animals with reliable evidence of acute ischemia on the EKG. In the experiments of series III the heart was removed 30 min after ligation of the coronary artery, and in series IV nonachlazine was injected into the animals 15 min after ligation and the heart was removed 15 min after injection of the drug. ATP and ADP were determined by the method in [8] and lactic acid by the method in [13]. The experimental results were subjected to statistical analysis [1].

EXPERIMENTAL RESULTS

In the control series of experiments no significant changes were found in the EKG after thoracotomy and injection of physiological saline. In the experiments of series II, EKG changes after injection of nonachlazine consisted essentially of a very slight reduction in amplitude of the T wave and tachycardia, and they were more marked during the first 3-7 min after injection of the drug; later they showed a tendency to recover. Similar changes in cardiac frequency were observed previously in experiments on anesthetized animals [10]. As Table 1 shows, nonachlazine caused no change in the ATP, ADP, and lactic acid concentrations 15 min after its injection. Similar results were obtained 30 min after injection of the drug. In series III, 3-5 min after ligation of the coronary artery signs of acute myocardial ischemia appeared in the EKG, in the form of elevation of the ST segments above the isoelectric line, a negative T wave, and shortening of the P—P interval. In some animals, starting from the 5th-7th minute after ligation, left-ventricular extrasystoles appeared. The biochemical changes under these circumstances were essentially as follows: The lactic acid concentration was increased by 127%, the ATP level was lowered by 12%, and the ADP level showed a very small increase (Table 1). In series IV, improvement of the EKG was observed in all experiments after injection of nonachlazine: The ST segment was lowered and the configuration of the T wave restored to normal; in 30% of cases the EKG returned to its initial level. Nonachlazine led to a reduction in the lactic acid concentration by 42% and an increase in the ATP concentration by 25% compared with those in the ischemic myocardium, i.e., a tendency was observed for the parameters studied to return to normal (Table 1). The improvement in the EKG was evidently due to a change in myocardial metabolism caused by injection of nonachlazine. The decrease in the lactic acid concentration in the myocardium produced by nonachlazine in myocardial ischemia was not accompanied by its elimination into the blood stream. This is confirmed by results obtained in experiments on dogs using the "Angina Pectoris" model, in which the lactate concentration and lactate/pyruvate ratio were investigated in blood flowing from an area of ischemia [9].

In the modern view, control of the pathway of carbohydrate conversion depends on the oxygen supply to the heart. It was shown previously that nonachlazine increases the coronary blood flow, lowers the arteriovenous oxygen difference and, consequently, increases the oxygen reserve of the myocardium [7]. It can accordingly be suggested that under conditions of myocardial ischemia, nonachlazine improves the oxygen supply to the heart and stimulates oxidative phosphorylation. The possibility cannot be ruled out that the increase in the ATP concentration and the fall in the lactate level in the ischemized myocardium, caused by nonachlazine, depend on stimulation of oxidative phosphorylation by the drug. No unequivocal answer can yet be given to the question of the effect of nonachlazine on the rate of glycolysis and glycogenolysis. Probably by increasing the rate of these processes, nonachlazine at the same time stimulates oxidative phosphorylation. It may be postulated that the intensity of the effect of nonachlazine on each of these processes depends on the extent and severity of the ischemic changes in the myocardium and also on the degree of utilization of the coronary reserves.

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