ROLE OF HISTAMINE IN THE MECHANISM OF ACTION OF CATECHOLAMINES ON THE HEART

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Changes in the biological activity of heart muscle extracts under the influence of catecholamines were studied. The effects of these extracts were investigated on the arterial pressure of cats and on a segment of the small intestine of guinea pigs in acute experiments. The hypotensive action of the extracts was found to be due principally to their content of phosphorus compounds and histamine.

Intravenous injection of noradrenalin (20-40 μg/kg) caused an increase in the vasodilator action of the extracts due to an increase in their content of active histamine, through liberation of histamine from its bond with myocardial tissue proteins.

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Administration of catecholamines raises the arterial pressure (AP), increases the volume velocity of the coronary blood flow, and causes changes in oxidation-reduction processes in the myocardium, reflected in the ECG and in a decrease in the O_2 concentration in blood from the coronary sinus [3, 4, 6, 7, 8, 11]. Some workers have described a vasoconstrictor response also, which they regard as a true catecholamine response; the dilatation of the coronary vessels following it is attributed to an increase in strength of the cardiac contractions and to the appearance of active metabolic products in the myocardium [3, 4, 8, 10]. There is no general agreement concerning disturbances of oxidation-reduction processes as a result of the action of catecholamines [6, 9].

The object of this investigation was to study changes in the content of biologically active substances in the myocardium under the influence of noradrenalin and to determine their nature.

EXPERIMENTAL METHOD

In acute experiments on cats the AP was measured by a direct method, and the volume velocity of the coronary blood flow was determined by Kaverina's method [3]. Alcoholic extracts of myocardium were prepared by Haberland's method as modified by O. A. Stepun. The method of precipitation of phosphoric acids by barium, Stepun's method of acid autolysis, and Code's biological method of estimation of histamine were used in the investigation.

EXPERIMENTAL RESULTS

Injection of noradrenalin (20-40 μg/kg body weight) always led to an increase in volume velocity of the coronary blood flow, developing parallel with elevation of the AP but persisting longer. In experiments with stabilization of AP, injection of noradrenalin also increased the coronary blood flow, although to a much lesser degree. If small doses of noradrenalin were injected in these experiments, a transient decrease in volume velocity was observed, followed by an increase. The heart was removed from the body 2-3 min after injection of noradrenalin, and alcoholic extracts were prepared from the myocardium. The action of these extracts on AP of cats in acute experiments was compared with the action of extracts prepared from the hearts of intact animals. These experiments showed that myocardial extracts lower AP, but against the background of the action of noradrenalin, this effect was stronger (Fig. 1), indicating accumulation of biologically active vasodilator substances in the myocardium under the influence of noradrenalin.

In accordance with the purpose of the experiments, the extent to which strengthening of the hypotensive action could be due to accumulation of acetylcholine in the extracts was next examined. For this

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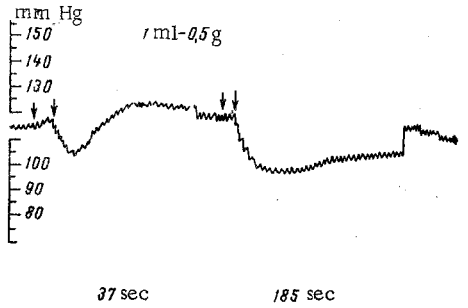

Fig. 1. Effect of myocardial tissue extracts on arterial pressure. Injection (first 2 arrows) of myocardial tissue extract from intact animal (0.5 g in 1 ml physiological saline) and injection (second 2 arrows) of extract obtained from myocardium after injection of noradrenalin (40 μg/kg) into a cat.

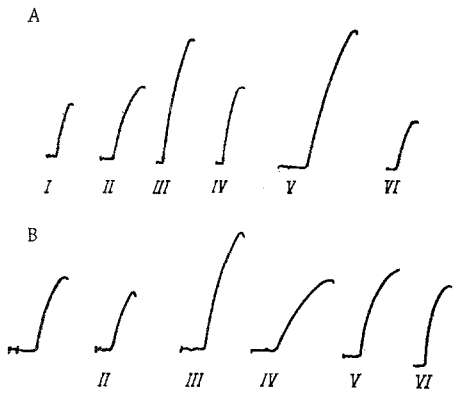

Fig. 2. Curves of contraction of a segment of guinea pig small intestine. In A: I and VI) standard histamine solution (1 μg/1 ml Tyrode solution); II and IV) injection of myocardial tissue extract from intact animal; III and V) injection of myocardial tissue extract obtained after injection of noradrenalin (40 μg/kg) into cats. In B: I and VI) standard histamine solution (1 μg/1 ml Tyrode solution); II) injection of extract of nonautolyzed myocardial tissue; III) injection of extract of autolyzed myocardial tissue from intact animal; IV) injection of nonautolyzed myocardial tissue extract after action of noradrenalin on it; V) injection of the same extract after autolysis.

purpose, acetylcholine was added in vitro to a suspension of myocardial tissue and experiments were carried out on an atropinized animal. Alcoholic extracts were found not to contain acetylcholine (for addition of acetylcholine did not alter their activity), but that the parasympathetic nervous system participates in manifestation of the hypotensive action of the extract, because atropinization of the animal lowered the activity of the extract without addition of acetylcholine. Remembering that phosphorus compounds passing into the extract from the myocardium have a hypotensive action, by precipitating these compounds extracts were obtained which were free from CP and ADP. These extracts possessed the weakest vasodilator action.

The object of the next series of experiments was to examine the connection between the increase in hypotensive action of the alcoholic extracts and accumulation of histamine in the myocardium after injection of noradrenalin. For this purpose, histamine was added to a mince of myocardial tissue, after which the activity of the extracts was tested for their action on the AP of a cat before and after injection of the antihistamine compound theadryl to the animal. Parallel tests of histamine-containing extracts were carried out on an isolated segment of guinea pig intestine (by Code's method). Experiments carried out against the background of theadryl showed that the extracts contained histamine, the amount of which increased after administration of noradrenalin (Fig. 2A). Similar results were obtained also in tests carried out by Code's method.

In the next series of experiments the method of acid autolysis in vitro, leading to rupture of the inactive bond between histamine and proteins [1, 2], was used to study some of the mechanisms of the increase in histamine content in the myocardium. Experiments were carried out by Code's method. Comparison of the action of nonautolyzed and autolyzed myocardial tissue from the same animal showed (Fig. 2B) that bound histamine was present in the myocardium [1], its content falling after injection of noradrenalin until the whole of it had been liberated and transformed into an active state.

Evidently in the presence of changes in oxidation-reduction processes in the myocardium and a relative shift of pH toward the acid side, the inactive histamine–protein (or histamine–polypeptide) complex breaks down with the formation of free, active histamine.

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