CHOLINESTERASE AND MONOAMINE OXIDASE ACTIVITY OF ISCHEMIC AND NONISCHEMIC PORTIONS OF THE HEART IN THE ACUTE STAGE OF MYOCARDIAL INFARCTION

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Signs of disturbances of the autonomic nervous system can be distinguished in the clinical picture of acute myocardial infarction in man and in reproductions of the disease in animals. In some cases, for instance, myocardial infarction is accompanied by disturbances of rhythm in the form of atrioventricular block, the appearance of Samoilov–Wenckebach's periods [8, 12], bradycardia [1, 5, 6], an increase in parasympathetic reflex reactions [3], dilatation of the peripheral blood vessels [4, 16], and other signs which may be associated with an increase in vagal tone.

However, there is some evidence that disturbances of the sympathetic nervous system may play a definite pathogenetic role in the development of myocardial infarction. Restoration of the normal cardiac rhythm has been observed after pharmacological block of the sympathetic nerves [9, 17].

A result of the disturbances of the function of the sympathetic nervous system is evidently the change observed by some authors in the concentration of catecholamines, while a disturbance of the function of the parasympathetic division may be demonstrated by changes in the concentration of acetylcholine in the heart during myocardial infarction. An increase in the concentration of catecholamines in the ischemic zone has been observed in the first 2 h after occlusion of the coronary artery [4, 19], although other authors [5, 21, 22, 24] found a decrease in the noradrenalin level in the infarct focus at the same times and also somewhat later. An increase in the concentration of acetylcholine in the heart after ligation of the coronary artery was demonstrated by U. A. Kuz'minskaya [2].

It was considered that a satisfactory method of detecting predominance of the influence of the parasympathetic or sympathetic nervous system in the acute stage of myocardial infarction was by studying the state of the mediator metabolism in the heart.

Changes in the concentration of mediators in the heart may be associated with a disturbance either of the rate of synthesis or of the rate of breakdown of the substances by enzyme action.

In the acute period of myocardial infarction in man, the plasma cholinesterase activity has been found to be reduced [18, 20], returning to normal in the recovery period. In experimental myocardial infarction, a decrease in cholinesterase activity has been discovered in the heart tissue [10]. A decrease in monoamine oxidase activity in the ischemic and nonischemic portions of the heart has been reported [13] after ligation of the coronary artery.

In the present investigation the activity of monoamine oxidase (MAO) and cholinesterase (CE) in the myocardium was studied after ligation of the coronary artery.

EXPERIMENTAL METHOD

Experiments were carried out on 49 cats anesthetized with a mixture of urethane and chloralose (0.8 and 0.08 mg/kg respectively). Myocardial infarction was induced by ligation of the anterior descending branch of the left coronary artery. To detect changes in the pH of the myocardium before and after development of the infarct, glass electrodes were implanted in the wall of the right and left ventricles using a method developed in the author's laboratory [7].

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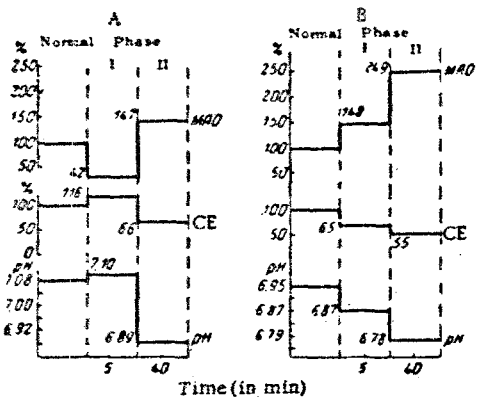

Fig. 1. Dynamics of monoamine oxidase (MAO) and cholinesterase (CE) activity in the ischemic focus in the left ventricle (A) and the nonischemic right ventricle (B) after ligation of the coronary artery

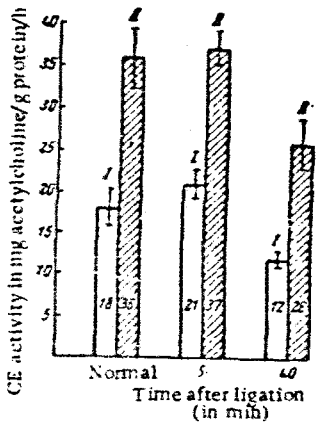

Fig. 2. Relationship between changes in cholinesterase (CE) activity in the ischemic focus and pH at different stages of development of a myocardial infarct. I) CE activity at pH 8.5; II) CE activity at tissue pH.

The MAO* activity was determined from the amount of ammonia liberated during incubation of tyramine (10 μM of 1.7 mg tyramine per sample) in the presence of preparations of mitochondria from the right and left ventricles of the heart for 50 min at pH 7.4 (0.1 M phosphate buffer with 0.23 M sucrose) in an atmosphere of oxygen at 38° with agitation. The ammonia concentration was determined by Conway's isothermic distillation method with subsequent nesslerization. The protein concentration in the suspension of mitochondria was determined by the method of Robinson and Hogden [23]. The MAO activity was expressed in μg NH_3/g protein of the mitochondria/h.

Since changes in the tissue pH in myocardial infarction may give rise to disturbances of enzyme activity, the CE activity was determined by means of a method developed in the author's laboratory at the pH of the tissue [11]. The CE activity was investigated by potentiometric titration. Incubation of the samples continued for 1 h at 38°. The CE activity was judged by the volume of 0.01 N NaOH solution used up in titrating the acetic acid set free during hydrolysis of acetylcholine (the final dilution of acetylcholine was 0.5 mg/ml). The CE activity was expressed in μg acetylcholine/g tissue protein/h.

EXPERIMENTAL RESULTS

It is clear from Fig. 1, a that 5 min after ligation of the coronary artery the MAO activity in the ischemic focus situated in the left ventricle fell sharply to 42% of its initial level ($P = 0.021$). Meanwhile the CE activity rose very slightly ($P > 0.1$), parallel with the increase of pH. Changes in the opposite direction took place 40 min after ligation: the MAO activity was increased to 50% above its initial level ($P = 0.02$), while the cholinesterase activity fell to 66% of the initial values ($P = 0.05$) parallel with the decrease in pH.

The changes in the focus of ischemia were thus biphasic in character. The first phase was evidently due to purely local changes in the metabolism of the myocardium. The decrease in MAO activity observed in this phase was probably due to the fact that acute hypoxia leads to depression of oxidative deamination. One result of this was evidently the increase in the concentration of catecholamines discovered [4, 19] in the zone of ischemia. The slight increase in CE activity taking place in this phase and observed in certain experiments may be associated with transient alkalification in the ischemic focus, bringing the conditions for activity of the enzyme close to optimal.

The second phase in the changes in the ischemic focus may have been the result, not only of local, but also of reflex influences. The increase in MAO activity and the decrease in CE activity, resulting in a decrease in the concentration of catecholamines and an increase in the concentration of acetylcholine, may be regarded as compensatory changes directed toward reducing the work of the heart in the conditions of local ischemia.

In the right ventricle (Fig. 1, B), in contrast to the ischemic focus, the MAO activity rose steadily from 148% 5 min after ligation ($P = 0.01$) to 250% 40 min after ligation ($P = 0.001$). The CE activity fell gradually parallel with the fall in pH, reaching 55% 40 min after ligation of the coronary artery ($P = 0.02$).

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Hence, in the nonischemic portions of the right ventricle, where purely local changes in the metabolism of the myocardium were absent, the changes in MAO and CE activity were uniform in direction both 5 and 40 min after ligation.

Further investigations were carried out to verify the hypothesis mentioned above, regarding the relationship between the changes in MAO and CE activity in the focus of ischemia and the conditions of enzyme activity. For this purpose, parallel investigations were made of the CE activity at the optimal pH (8.5) and at the tissue pH, and the MAO activity was studied when the incubation mixture was saturated with 100% oxygen and with a gas mixture containing 50% oxygen and 50% nitrogen. If was found that conditions of relative hypoxia depressed the MAO activity by 54% ($P = 0.001$), and conditions of acidosis depressed CE activity by 57% ($P = 0.001$).

The CE activity in normal conditions and during myocardial infarction is shown in Fig. 2 in the stage of alkalosis (5 min), in the stage of acidosis (40 min), and during transient ventricular fibrillation. The activity was investigated at the natural pH of the tissue and at the optimal pH.

As Fig. 2 shows, the activity of the enzyme was restored to normal 5 min after ligation at the optimal pH. Meanwhile, the CE activity remained lower than normal after 40 min, even at the optimal pH. This was evidently associated with changes in the enzyme structure taking place in this stage.

The results obtained thus show that in the nonischemic portions of the heart the MAO activity is increased after occlusion of the coronary artery, leading to a decrease in the concentration of catecholamines, while the CE activity is depressed, leading to the accumulation of acetylcholine. These changes may be regarded as compensatory, because they create conditions strengthening the influences of the vagus nerve and thereby reducing the activity of the heart in the presence of local ischemia of the myocardium.

Although these changes in mediator metabolism were compensatory in nature, clearly their importance for the state of the heart differed in phases I and II of ischemia. In phase I (5 min after ligation of the artery), when they were opposite in direction, they increased the degree of biochemical and bioelectrical heterogeneity of the myocardium. This was presumably one of the conditions leading to the development of ventricular fibrillation. In phase II (40 min after ligation of the artery) this heterogeneity disappeared. The changes in MAO and CE activity assumed the same direction, thus reducing the work of the heart, and evidently acting as one of the factors reducing its level of activity in myocardial infarction.

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