PREVENTION OF ARRHYTHMIAS IN CONSCIOUS ANIMALS DURING ACUTE ISCHEMIA WITH THE AID OF A SEROTONIN ANALOG

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Adaptation to brief noninjurious stressors prevents disturbances of electrical stability and also arrhythmias and fibrillation of the heart associated with stress, acute ischemia, myocardial infarction, and postinfarction cardiosclerosis [2, 3]. The study of the protective effect of adaptation has led to the view that a key role in this phenomenon is played by activation of stress-limiting systems: GABA-ergic, opioidergic, serotoninergic, and antioxidant [1]. It has also been shown that, by using the principle of imitation of the body, i.e., using metabolites of stress-limiting systems (synthetic or natural antioxidants, and also the factor of GABA accumulation) disturbances of electrical stability of the heart associated with acute ischemia, myocardial reperfusion, and postinfarction cardiosclerosis can be effectively prevented [2-4].

The aim of the present investigation was to study the state of the serotoninergic system during adaptation to short-term noninjurious stress and to examine the possibility of protection against arrhythmias during acute ischemia in conscious animals, with the aid of the serotonin analog 4-nitro-5-methoxytryptamine, synthesized in the Department of Organic Chemistry, D. I. Mendeleev Moscow Chemical Engineering Institute [5].

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 250-300 g. In the first stage the animals were adapted to short-term stress by brief fixation in the supine position for 15 days: 15 min daily on the 1st day, 30 min on the 2nd, 45 min on the 3rd day, and 60 min on each of the remaining days. At the end of adaptation the control and adapted animals were decapitated, the midbrain was removed, and the serotonin concentration in it was estimated by a fluorescence method [9], involving its condensation with orthophthalic aldehyde. In the second stage the effect of the serotonin analog 4-nitro-5-methoxytryptamine on cardiac arrhythmias associated with acute myocardial ischemia in conscious animals was studied. Ischemia was induced by the method in [7]: initially a ligature was applied beneath the left coronary artery and its free ends were brought out beneath the skin and the wound was sutured in layers, after which a skin incision 0.5 mm long was made and the ends of the ligature drawn tight, producing irreversible coronary occlusion. The ECG was recorded continuously during coronary occlusion.

EXPERIMENTAL RESULTS

The serotonin concentration in the midbrain of animals (13) of the control group was 1061 ± 191 ng/g body weight. Adaptation to stress (eight animals) led to a significant ($p < 0.05$) increase in the serotonin concentration, up to 1696 ± 230 ng/g (by about 70%). Adaptation to stress thus led to activation of the central stress-limiting serotoninergic system, reflected in accumulation of its metabolite, namely serotonin.

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TABLE 1. Prevention of Cardiac Arrhythmias Arising during Acute Ischemia in Conscious Animals by the Aid of a Serotonin Analog

Parameter	Control (n = 10)	Experiment (n = 10)
Number of animals with different types of arrhythmias:		
with extrasystoles	7	4
with ventricular tachycardias	4	2
with ventricular fibrillation	5	1
Total duration of arrhythmias, sec	459	133
Number of dying animals	5	0

Legend. n) Number of animals.

In the modern view of the pathogenesis of arrhythmias associated with acute ischemia, excitation arises in certain zones of the frontal cortex, which is connected through the subthalamus and hypothalamus with the brain stem nuclei that directly control cardiac and circulatory function. This excitation has a powerful adrenergic action on the heart, which plays a role in the genesis of arrhythmias [10].

It seems probable that the antiarrhythmic action of adaptation may be due to activation of central inhibitory stress-limiting systems, especially the serotoninergic system. We know, in fact, that pharmacologically induced accumulation of serotonin, the metabolite of this system, has an inhibitory effect on efferent sympathetic activity [6], and, with a high degree of probability, it can limit the arrhythmogenic action of acute ischemia on the heart.

Lown [8] has already attempted to use serotonin accumulation in the brain as a method of controlling arrhythmias. For this purpose, he injected animals with a large dose of the serotonin precursor, tryptophan, and at the same time blocked conversion of tryptophan into serotonin in all tissues except the brain. As a result, against the background of continuing serotonin accumulation in the brain, an antiarrhythmic effect was obtained in dogs with acute ischemia. This effect can now be achieved by a simpler method and, more importantly, one of greater practical importance, involving the use of stable biologically active serotonin analogs.

Table 1 shows that preliminary injection of a serotonin analog (4-nitro-5-methoxytryptamine) reduced by two-thirds the total duration of arrhythmias, and by approximately four-fifths, the frequency of onset of fibrillation of the heart and the mortality of conscious animals from acute ischemia.

When this antiarrhythmic effect of serotonin analogs is assessed it must be recalled that arrhythmias associated with acute ischemia were produced in conscious animals. A key role in their genesis was played by the stress reaction. Serotonin is known to limit the stress reaction by blocking the liberation of releasing factors in the hypothalamus [11]. There are thus grounds for supposing that the effect obtained in our own experiments is linked with limitation of adrenergic activity [8] and depression of the stress reaction, both of which play a key role in the pathogenesis of arrhythmias. This hypothesis is in agreement with the data cited above, to show that serotonin accumulation in the brain raises the fibrillation threshold in acute ischemia, and thus increases the resistance of the heart to ischemic arrhythmias.

The experimental results as a whole are in agreement with the view that stress-limiting systems play a role in the prevention of stress-induced and ischemic injuries, and they show that the protective effects of such systems can be successfully reproduced with the aid of synthetic analogs of their metabolites or their activators. As applied to the problem of cardiac arrhythmias this approach affords new prospects in the region of prevention of fibrillation of the heart and subcardiac death.

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PROTECTIVE EFFECT OF THE ANTIOXIDANT IONOL IN TOTAL CARDIAC ISCHEMIA

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Ischemia and, in particular, subsequent restoration of the blood flow are accompanied by activation of lipid peroxidation (LPO), causing damage to cell membrane structures and leading ultimately to disturbance of function of the organ in the postischemic period [1-3, 5, 6]. In myocardial ischemia, inhibition of LPO by antioxidants enables the zone of necrosis in infarction due to coronary occlusion to be reduced, anoxic and reoxygenation damage to the perfused heart to be prevented, and the degree of contractural changes in the myocardium to be diminished [4, 7-9]. Meanwhile, the effectiveness of antioxidants when used during reperfusion of the myocardium after its total ischemia, i.e., under conditions arising during open heart surgery, and also during transplantation of the heart, still awaits investigation.

The aim of the present investigation was to study the effectiveness of the antioxidant ionol when used to maintain the contractile function and prevent the development of contractural changes in the rat heart after total ischemia for 30-60 min, in experiments conducted at different temperatures. A model of perfusion of the isolated rat heart with saline, and also a model of heterotopic transplantation of a donor's heart into recipient rats were used.

EXPERIMENTAL METHOD

Experiments were carried out on Wistar rats anesthetized with hexobarbital (70 mg/kg). Ionol (2,6-di-tert-butyl-4-methylphenol) was injected as a single dose of 240 mg/kg 24 h before the operation and heparin was given in a dose of 3 ml/kg intraperitoneally 1 h before the operation. Ionol was not injected in the control experiments. In series I (20 experiments) the heart was subjected to total ischemia for 30 min at 20°C and reperfused with Krebs–Henseleit solution by the method of Langendorf and Neely [14]. A consequence of the experiment was the following: the heart was removed and placed in cold (4°C) Ringer's solution; then, for 15 min, it was perfused with hydroxy-generated (95% O_2 + 5% CO_2) Krebs–Henseleit solution through the aorta by the Langendorf method, after which it was transferred to a model of the working heart according to Neely. In this model the solution was infused through the left atrium under a pressure of 20 mm Hg, and the left ventricle ejected against a pressure of 70 cm water. Perfusion was stopped after 15 min, and the heart was allowed to stand for 30 min at 20°C. Reperfusion with the same solution was carried out alternately for 15 min by Langendorf's method and 15 min by Neely's method. To assess cardiac function, the pressure developed by the left ventricle (P), its rate of rise (dP/dt), and the end-diastolic pressure (EDP) were recorded. The volume velocity of coronary perfusion (VCP) was determined by measuring outflow. In the experiments of series II and III a model of heterotopic transplantation of the rat heart to the recipient's abdominal vessels by means of cannulas was used. In series II (12 experiments) the heart removed from the donor was kept for

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