MECHANISM OF ACTION OF NONACHLAZINE ON THE BLOOD SUPPLY AND ACTIVITY OF THE HEART

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Nonachlazine (10 mg/kg, intravenously) has a biphasic effect on cardiac activity. A short phase of weakening of cardiac activity is followed by a marked increase in the cardiac output and contractile function of the myocardium. The increase in the blood supply and activity of the heart coincides in time with the accumulation of noradrenalin in the myocardium and an increase in phosphorylase *a*. β-Adrenoblockers prevent the development of these effects. It is postulated that the effectiveness of nonachlazine in ischemic heart disease is connected with its ability to activate adrenergic mechanisms of glycogenolysis control, leading to switching of metabolism in the myocardium to the anaerobic pathway of energy liberation.

KEY WORDS: heart – blood supply and activity; nonachlazine; noradrenalin; phosphorylase.

Nonachlazine, a new antianginal preparation, was synthesized at the Institute of Pharmacology, Academy of Medical Sciences of the USSR, by A. P. Skoldinov, A. M. Likhosherstov, and L. S. Nazarova and studied pharmacologically by N. V. Kaverina and G. A. Markova [1]. As a result of the first stage in the study of the mechanisms of the positive effect of nonachlazine on the blood supply to the heart it was shown that it affects the adrenergic regulation of the circulation.

In the present investigation the dynamics of changes in cardiac activity was compared with the effect of nonachlazine on phosphorylase activity and the catecholamine concentration in the tissue of the myocardium.

EXPERIMENTAL METHOD

In the experiments of series I the effect of nonachlazine on cardiac activity was studied. These experiments were carried out on anesthetized (urethane 400 mg/kg and chloralose 30 mg/kg) cats. Cardiac activity and the basic indices of the hemodynamics were quantified by analysis of the phasic aortic blood flow, recorded electromagnetically. The systolic output, minute volume, and contractile power of the myocardium were determined.

In the experiments of series II the phosphorylase *a* content in the myocardium was determined [7]. Wistar rats (weighing 200 ± 20 g), anesthetized with amobarbital (100 mg/kg), were used. The percentage of phosphorylase *a* relative to the total phosphorylase was calculated. Samples of myocardial tissue were taken 15 min after injection of nonachlazine (10 mg/kg), propranolol (5 mg/kg), and nonachlazine (10 mg/kg) injected 10 min after propranolol (5 mg/kg). All drugs were injected intravenously. Samples of myocardial tissue from animals receiving 0.9-1.2 ml/kg physiological saline acted as the control.

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TABLE 1. Content of Phosphorylase *a* in Rat Myocardium

Group of rats	Concentration of phosphorylase *a* (in %)
Control	14.41 ± 3.49
Receiving nonachlazine (10 mg/kg)	32.4 ± 5.25
Receiving propranolol (5 mg/kg)	13,00 ± 2.89
Receiving nonachlazine (10 mg/kg) after propranolol (5 mg/kg)	17.23 ± 3.30

Note. Samples taken 15 min after administration of drugs.

TABLE 2. Adrenalin Concentration in Rat Myocardium (in μg/g wet weight of tissue)

Statistical index	Controls	After injection of nonachlazine in a dose of 10 mg/kg		
		after 15 min	after 30 min	after 4 h
$M \pm m$	0,66±0,046	1,15±0,19	1,11±0,22	0,61±0,05
Limits of variations	(0,71—0,61)	(1,34—0,96)	(1,33—0,89)	(0,66—0,56)
n	6	5	7	5

In the experiments of series III the concentration of noradrenalin and adrenalin in the myocardium of rats was determined [2, 9] on the Opton spectrofluorometer. Samples of myocardial tissue were taken from the control animals and also 15 and 30 min and 4 h after injection of nonachlazine in a dose of 10 mg/kg intravenously.

EXPERIMENTAL RESULTS AND DISCUSSION

Nonachlazine has a biphasic action on cardiac activity. Immediately after injection of the preparation a small decrease in the cardiac output and contractile power was observed, as a result of the direct action of the substance on the myocardium. After 3-5 min a prolonged (25-35 min) and clearly marked (23 ± 7.5%) increase in both systolic output and minute volume developed and was accompanied by an increase in the contractile power of the myocardium. The heart rate was substantially unchanged. Practolol (a selective blocker of β-adrenergic structures) and propranolol, in a dose of 5 mg/kg, completely blocked these effects of nonachlazine. The degree of blocking of the cardiac β-adrenoreceptors was checked against their reactions to isoproterenol (3-5 mg/kg).

As Table 1 shows, nonachlazine considerably increased phosphorylase *a* activity. This effect did not take place in the experiments with preliminary injection of propranolol. Since propranolol blocks the stimulant effect of nonachlazine on phosphorylase activity in the heart, its action can be attributed to excitation of cardiac β-adrenergic structures.

As Table 2 shows, the noradrenalin concentration in the heart muscle of the rats increased by 74% 15 min after, and by 68% 30 min after injection of nonachlazine. The adrenalin content in the myocardium of the control rats averaged 0.057 mg/g wet weight of tissue. Its concentration was unchanged 30 min after injection of nonachlazine.

The results show that nonachlazine, by its action on adrenergic processes, increases the noradrenalin concentration in the heart muscle and also increase phosphorylase *a* activity. This coincides in time with an increase in the blood flow in the cardiac vessels, in the cardiac output, and in the contractile function of the myocardium.

The strengthening of cardiac activity is evidently linked with changes in myocardial metabolism. Catecholamines can activate the enzyme adenyl cyclase, in consequence of which cyclic AMP accumulates in the myocardium [8, 10-12]. Substances giving this type of effect have a positive inotropic action [16]. By liberating noradrenalin, nonachlazine can be considered to activate adenyl cyclase, leading to the accumulation of cyclic AMP and to the development of a positive inotropic effect. However, another possibility is that nonachlazine may act directly on β-adrenergic structures. This possibility is supported by the ability of the drug to potentiate the cardiovascular responses to isoproterenol [1].

The increase in the blood supply to the heart produced by nonachlazine is also evidently connected with the effect of the drug on adrenergic processes. Cyclic AMP_3 by activating phosphokinase, leads to the

formation of the active form of phosphorylase, which accelerates glycogen breakdown. According to Wollenberger and Krause's hypothesis [17], under hypoxic conditions the compensatory switching of myocardial metabolism to the anaerobic pathway of energy liberation can take place not only on account of glycolysis (autoregulatory mechanism), but also through the adrenergic regulation of glycogenolysis.

Pharmacological intervention aimed at maintaining these compensatory mechanisms is in fact particularly effective in the treatment of ischemic heart disease [3-6, 13-15]. Presumably the positive effect of nonachlazine also is connected with its ability to activate the adrenergic mechanisms controlling glycogenolysis.

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