EFFECT OF NONACHLAZINE ON THE SIZE OF AN EXPERIMENTAL MYOCARDIAL INFARCT

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The extent of the area of necrosis is one of the principal factors which determines the severity of the clinical course and the prognosis in acute myocardial infarction.

Recent investigations into the problem of limiting the size of the necrotic focus have shown that β-adrenoblockers [11], calcium antagonists [10], nitroglycerin [6], and various other preparations are effective when used for this purpose. Nonachlazine, widely used in clinical practice as an antianginal agent [5], is interesting in this respect.

The aim of the present investigation was to study the effect of nonachlazine on the size of an experimental myocardial infarct when the drug was administered by different schemes.

EXPERIMENTAL METHOD

Male Chinchilla rabbits weighing 2-2.5 kg were used. Myocardial infarction was induced under pentobarbital anesthesia (30 mg/kg, intravenously) by ligation of the anterior interventricular branch of the left coronary artery, through a trans-sternal approach to the heart maintaining spontaneous breathing.

Nonachlazine was given in accordance with two schemes. The experimental animals of group 1 received the drug starting from 30 min after ligation in a dose of 3 mg/kg five times at half-hourly intervals. Rabbits of group 2 received the drug intravenously, starting from the 2nd day after ligation, for 6 days. Nonachlazine was injected in the last series three times a day at intervals of 4 h. For the first two injections the drug was given in a dose of 3 mg/kg, for the last injection 6 mg/kg.

The animals were killed 7 days after ligation of the coronary artery by rapid intravenous infusion of 10 ml of 2.5% procaine solution and the size of the infarct was determined planimetrically [12]. The size of the lesion was represented as the ratio, in percent, between the weight of necrotic tissue and the total weight of the left ventricle. The ATP concentration also was determined in the left ventricular myocardium of intact animals, of untreated rabbits with coronary occlusion, and in rabbits with ligation of the coronary artery and treated with nonachlazine by the same scheme as the animals of experimental group 1. The investigation was carried out 24 h after ligation, using kits from "Boehringer."

The significance of differences was assessed by Student's t test.

EXPERIMENTAL RESULTS

Injection of nonachlazine by both schemes caused a significant decrease in size of the infarct compared with that in the control animals (Table 1). The infarct in rabbits receiving nonachlazine on the day of ligation was 22.8% smaller in size than in animals of the control group ($P < 0.05$). In the group of animals with long and late administration of nonachlazine the lesion was 39.4% smaller than in the control ($P < 0.01$).

The marked protective action of the drug when given by a 6-day cycle of injections is evidence that compensatory mechanisms inhibiting infarct formation can be mobilized between

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TABLE 1. Effect of Nonachlazine on Size of Infarct

Experimental conditions	n	Size of infarct, in % of weight of left ventricle (M ± m)				
		integral parameter	level	level	level	level
Control	18	12,7±0,9	15,7±1,6	19,0±1,5	14,7±2,5	11.6±2,6 (7)
Injections of nonachlazine						
6-day cycle	14	7,7±0,6	7,2±0,9	11,0±1,9	10,8±1,9	8,1±1,7 (7)
1-day cycle	15	9,8±1,0	10,3±1,9	14,5±2,2	15,4±2,6	10,4±4,5 (10)

Legend. Number of cases in which infarct was absent is given in parentheses.

the second and sixth days after ligation of the coronary artery. Mobilization of the collateral coronary circulation, inhibition of the development and more rapid absorption of perifocal edema, stabilization of membrane structures, and inhibition of the cytotoxic action of myocyte breakdown products in the zone of necrosis must be listed among the leading mechanisms of limitation of the size of the infarct.

Histopathological investigation of the myocardium revealed that after a 6-day course of nonachlazine preserved muscle fibers were more numerous in the zone of necrosis and adjacent areas, and the process of absorption of necrotic myocytes proceeded more rapidly.

Biochemical tests showed that nonachlazine, in a dose of 3 mg/kg given during the first 3 h after ligation, significantly increases the ATP concentration in the left ventricular myocardium from 3.45 to 4.70 μmole/g, close to the initial level of 4.78 μmole/g.

The decrease in size of the infarct thus revealed may be due to the effect of nonachlazine on several factors determining survival of the myocardium of the perinecrotic zone. A definite role in limitation of the size of the necrotic focus may be played by the ability of the drug to redistribute the blood flow in the myocardium, demonstrated in [9], and leading to a marked increase of the blood flow in the ischemic zone.

Another possibility is that normalization of the microcirculation in the peri-infarct zone may be aided by depression by nonachlazine of central sympathetic influences on the myocardium [2], as well as its antiaggregating action [1].

Besides improving the energy supply to the perinecrotic zone as a result of improvement of its blood supply, nonachlazine also has a direct action on various stages of energy metabolism. The drug switches cell metabolism to a more economic regime, activates glycogenolysis [3] and also oxidative phosphorylation, which is sharply reduced under ischemic conditions [7], and has a beneficial effect on the lactate dynamics and concentrations of ATP [8] and the oxidized form of NAD in the myocardium [4].

It is difficult at present to state which of the above mechanisms plays the leading role in the action of nonachlazine on limitation of the size of an experimental myocardial infarct. However, analysis of the results suggests that during prolonged administration of the drug the increase in the collateral coronary blood flow, maintained by regular injections of nonachlazine, and the direct action of the drug on myocardial metabolism may be of definite importance.

It can be concluded that nonachlazine has a beneficial effect on the course of experimental myocardial infarction, reduces the area of necrosis, and improves the energy supply to the heart muscle.

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BEHAVIORAL AND RADIORECEPTOR ANALYSIS OF VILOXAZINE STEREOISOMERS

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A study of drugs with antidepressant action showed that isomers of norzimelidine (an active metabolite of zimelidine) differ considerably (by 7-70 times) in their effects [1]. The same property has been found for isomers of amitriptyline and some of its derivatives [1]. Viloxazine (Vivilan, Vicilan) is an atypical antidepressant, marketed as a racemic mixture, and is a weak inhibitor of monoamine reuptake [7, 11]. Experimentally it has a tranquilizing action. Clinically viloxazine has been shown to have an activating effect in patients with depressive illness.

The aim of this investigation was to compare the effectiveness of viloxazine and its R(+) and S(−) stereoisomers on some behavioral models suitable for the study of antidepressants, and also to analyze the affinity of viloxazine racemate and its stereoisomers for various receptors on brain synaptic membranes.

EXPERIMENTAL METHOD

Tetrahybrid male CBWA mice from the Rappolovo Nursery, Academy of Medical Sciences of the USSR, were used. To assess behavior, known models for detection of antidepressant activity were used: the swimming test as in [12] and the "behavior despair" test as described in [3]. The drugs were injected intraperitoneally in the acute experiments and given perorally (in a volume of 0.3 ml) in the chronic experiments. Each dose was tested on at least six animals. The results were subjected to statistical analysis. Unpurified synaptic membranes of whole brain from CBWA mice and P_2 fractions obtained after shock were used for radioligand analysis. Binding of [^{3}H]imipramine was carried out by the method in [2], of [^{3}H]-dehydroalprenolol as in [14], [^{3}H]-mianserin as in [15], [^{3}H]-spiperone as in [6], [^{3}H]5-HT as in [5], [^{3}H]-WB 4101 as in [15], and [^{3}H]-flunitrazepam as in [4]. Molar aqueous solutions of viloxazine racemate (synthesized at the Pharmaceutical Chemical Research Institute of Bulgaria) and viloxazine R(+) and S(−), synthesized at the Institute of Pharmacology, Academy of Medical Sciences of the USSR, were used. The (+) and (−) isomers of viloxazine were separated by a modified method using O,O^1-dibenzole-(+)-tartaric acid, when the (+)-isomer was isolated through the acid tartrate, and the (−)-isomer through the neutral tartrate [10]. Characteristics of the (+)-isomer were: m.p. 164-165°C, $(\alpha)_D^{25}$ +7.9° (c, 1; water), optical purity 74%; (−)-isomer: m.p. 163-164°C, $(\alpha)_D^{25}$ −10.8° (c, 1; water) optical purity 96%.

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