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EFFECT OF NONACHLAZINE ON THE CARDIAC COMPONENT OF THE BARORECEPTOR REFLEX IN UNANESTHETIZED CATS

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KEY WORDS: nonachlazine; pressor response of arterial pressure; Mayer's waves; baroreceptor reflex.

After intravenous injection of the new Soviet antianginal drug nonachlazine a phase of elevation of the arterial blood pressure (BP) lasting 20-30 min is observed [2]. No conclusions regarding the mechanism of onset of the pressor response can yet be drawn from the results of electrophysiological investigations [1], for we do not know how the function of the baroreceptor reflex changes during this period.

Accordingly the investigation described below was undertaken to study the structure of the pressor response and to analyze changes in the cardiac component of the baroreceptor reflex following injection of nonachlazine into unanesthetized animals.

EXPERIMENTAL METHOD

Eighteen chronic experiments were carried out on 14 male cats. Under pentobarbital anesthesia (40 mg/kg, intraperitoneally), 3-4 days before the experiments and under sterile conditions, aortic and venous polyethylene catheters connected to a miniature cock were inserted into the cats [7]. In some experiments, to record the cardiac output, the probe of an ultrasonic doppler flowmeter designed by one of the authors [6] or the probe of an electromagnetic flowmeter (MF-6, Nihon Kohden) was placed in the ascending part of the arch of the aorta. To test the baroreceptor reflex, BP was artificially raised by constricting the descending thoracic aorta by means of an implanted silicone occluder [8]. In the course of the experiments BP was measured with an EMT-35 electromanometer (Elema-Schonander), and the momentary cardiac frequency (CF) was recorded periodically by means of a digital cardiotachometer, triggered by the pulse waves of BP. All the hemodynamic parameters studied were recorded in analog form on a Mingograph-81 apparatus and in digital form by means of a SHCH1413 digital voltmeter and CHZ-34A digital frequency meter on a digital printer of the 3512 type (East Germany).

The following drugs were used in the investigation: nonachlazine (Research Institute of Pharmacology, Academy of Medical Sciences of the USSR), propranolol (Obsiden, East Germany); isoproterenol (Euspiran, Czechoslovakia). All the drugs were diluted with sterile physiological saline and injected intravenously.

The results were subjected to statistical analysis by Student's t-test.

EXPERIMENTAL RESULTS

Nonachlazine, in a dose of 1 mg/kg, caused a very small increase in BP in some experiments. The mean values of BP changed from 103.0 ± 3.3 mm Hg in the control to 110 ± 3.5 mm Hg ($P > 0.1$) after injection of the drug. CF remained unchanged at 166 beats/min. An increase

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TABLE 1. Changes in Background Indices of Systemic Hemodynamics in Unanesthetized Cats under the Influence of Nonachlazine (M ±m)

Conditions of recording	BP, mm Hg	CF, beats/min	Cardiac output, ml/min	Stroke volume, , ml
Initial data	103,0±3,3	166,0±13,9	451±58	3,19±0,41
Following nonachlazine, 1 mg/kg	110,0±3,5	166,0±11,2	481±49	3,20±0,44
Initial data	106,0±2,6	162,0±12,2	419±47	3,12±0,53
Following nonachlazine, 6 mg/kg	126,0±5,7*	165,0±8,3	366±57	2,53±0,34

*P < 0.05 compared with control.

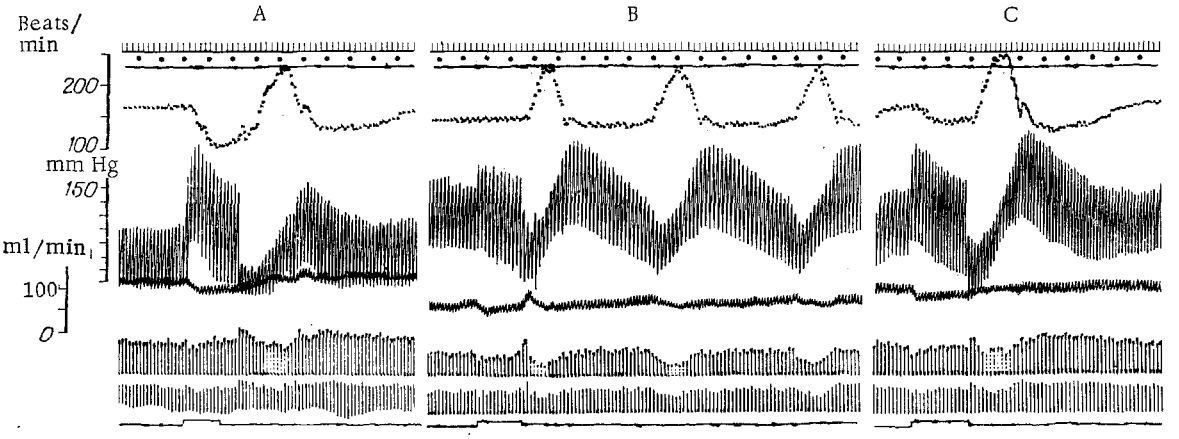

Fig. 1. Effect of nonachlazine in a dose of 6 mg/kg on parameters of systemic hemodynamics in unanesthetized cat. A) Baroreceptor reflex tested before injection of drug, B) Mayer's waves 3 min after intravenous injection of nonachlazine; C) testing of baroreceptor reflex 15 min after injection of drug. From top to bottom: time marker 1 sec, dynamics of frequency of pulse rate, BP, integral cardiac output, stroke volume of blood, phasic ejection of blood into aorta (cardiac output recorded by ultrasonic flowmeter).

in the dose of nonachlazine to 6 mg/kg led to a significant increase in BP by 20 mm Hg ($P < 0.01$), in good agreement with reports of a marked increase in BP in unanesthetized animals [9]. The cardiac output at the peak of the pressor response of BP was 50 ml/min below its initial level, evidence of an increase in peripheral vascular resistance as the main cause of elevation of BP (Table 1). Since the drug does not affect α-adrenergic structures of the aorta [3], it can be postulated that the pressor response arises by virtue of a central mechanism. In the control, 1 mg nonachlazine was injected into the fourth ventricle in a volume of 0.2 ml and this caused elevation of BP typical of the action of this drug. The appearance of well-marked third-order waves of BP (Mayer's waves), with a period of 34.3 ±3.3 sec and an amplitude of 30± 8.2 mm Hg (Fig. 1), was indirect confirmation of the central activating action of nonachlazine. The absence of changes in cardiac output during the phase of elevation of BP confirmed the vascular genesis of this response. The appearance of Mayer's waves has been associated with the functioning of a "central generator" at the bulbospinal level, giving rise to periodic stimulation of activity of preganglionic sympathetic neurons [12].

Preservation of the pressor response to nonachlazine after preliminary injection of propranolol in a dose of 0.3 mg/kg was demonstrated previously [5]. The dose of propranolol used by the authors cited was insufficient to block central β-adrenoreceptors. Accordingly in three experiments nonachlazine was injected after propranolol in a dose of 1-3 mg/kg, which had no effect on the development of the pressor response.

The absence of baroreflex bradycardia during Mayer's waves suggests depression of the function of the baroreceptor reflex. The function of the baroreceptor reflex was analyzed in experiments with occlusion of the thoracic aorta (Fig. 1, Fig. 2). Injection of nonachlazine in a dose of 6 mg/kg induced a sudden decrease in the degree of reflex bradycardia and in the

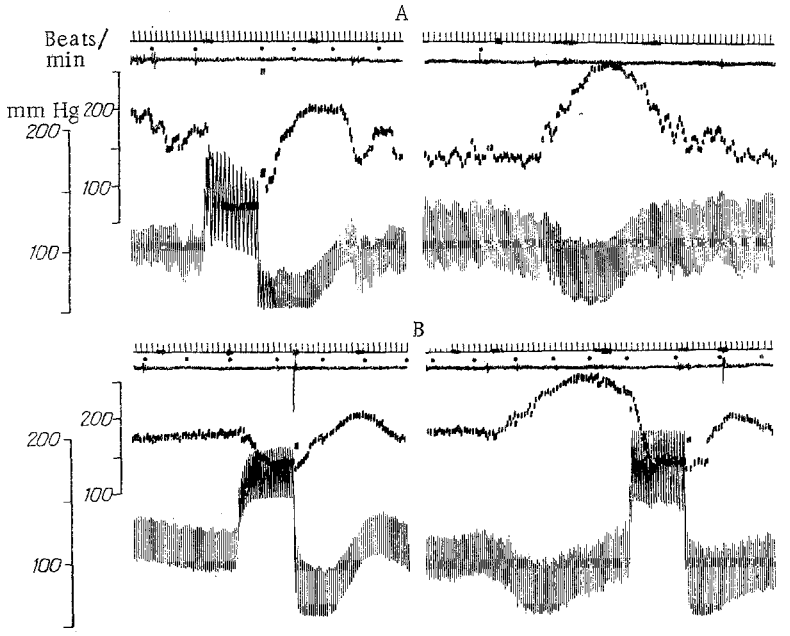

Fig. 2. Effect of nonachlazine in dose of 6 mg/kg and of isoproterenol in dose of 0.05 mg/kg on cardiac component of baroreceptor reflex. A) Descending responses to constriction of aorta (left) and to intravenous injection of isoproterenol (right); B) same test after preliminary administration of nonachlazine. From top to bottom: time marker 1 sec, actogram, cardiac frequency, BP.

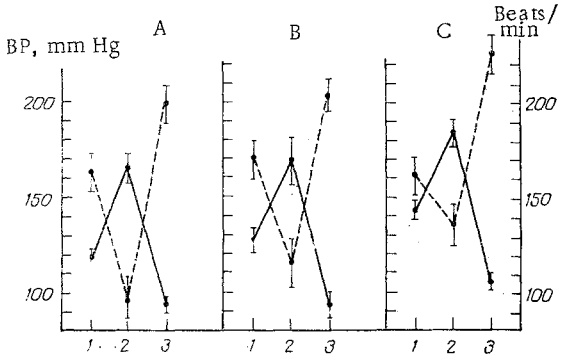

Fig. 3. Averaged data of series of experiments to determine function of baroreceptor reflex in unanesthetized cats. 1) Initial values of BP and CF before occlusion of aorta, 2) maximal values of BP and minimal values of CF during occlusion of aorta, 3) values of BP and CF during first 10 sec after occlusion of aorta. Broken line represents CF, continuous line BP. A) Control, B) nonachlazine, 1 mg/kg; C) nonachlazine, 6 mg/kg.

rate of its development (Figs. 1 and 2, Fig. 3). The observed inhibition of baroreflex bradycardia was not connected with any possible stimulating effect of nonachlazine on β-adrenoreceptors, as was confirmed by testing the baroreflex after preliminary administration of isoproterenol (Fig. 2). Moreover, in a dose of 6 mg/kg, nonachlazine exhibited antagonism against the positive chronotropic action of isoproterenol. In the control, isoproterenol raised CF from 156 ± 13.4 to 246 ± 14.5 beats/min, but against the background of nonachlazine the increase was only from 185 ± 19.7 to 243 ± 23.1 beats/min, confirming Rozonov's observations [9]. There are no grounds for attributing inhibition of reflex bradycardia to strengthening of sympathetic influences on the heart, for activation of the baroreceptors itself leads to strong depression of tonic and reflex activity in the cardiac nerves [4]. Stimulation of the peripheral end of the vagus nerve with a frequency of over 8 Hz, after preliminary stimulation of the inferior cardiac nerve, also is known to reduce the liberation of catecholamines into the coronary blood flow and to cause total suppression of the positive chronotropic reaction [10, 11].

The increase in BP and inhibition of the cardiac component of the baroreceptor reflex under the influence of nonachlazine are thus connected with the central action of the drug, which is evidently effected without the participation of β-adrenergic mechanisms.

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MEMBRANE PERMEABILITY FOR CHLORPROMAZINE AND NONACHLAZINE

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An important role in the mechanism of action of drugs is played by their ability to penetrate through cell membranes and tissue–blood and blood–brain barriers. Investigation of the permeability of biomembranes for each substance is a difficult task. It is much easier to study such problems on model membranes, which can reproduce many of the properties of biomembranes.

The writers compared the ability of two drugs, chlorpromazine and nonachlazine, to penetrate through model membranes, namely liposomes. The two drugs are tranquilizers of the phenothiazine series but they differ in the spectrum of their pharmacological action: whereas chlorpromazine is a psychotropic agent, nonachlazine is an effective antianginal drug of Soviet origin, with a basically new type of action [1, 6, 7].

It was shown previously by the fluorescent probe method that chlorpromazine [3] and nonachlazine [2] interact with model phospholipid membranes.

The object of this investigation was to use the fluorescent probe method to study permeability of model membranes for these substances.

EXPERIMENTAL METHOD

Phospholipid model membrane bubbles (liposomes) were obtained by two methods: 1) by rapid injection of a solution of total egg phospholipids, containing the fluorescent probe p-terphenyl (molar ratio of probe to lipid 1:40) in ethanol into a buffer solution (0.12 M KCl, 0.01 M Tris-HCl buffer, pH 7.4) [10] — these liposomes were named LPS-1; 2) by slow mixing of the same solutions in the same proportions — these were named LPS-2. The LPS-1 have one bilayer lipid membrane [10, 12], whereas LPS-2 have many such membranes [9].

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