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EFFECT OF NONACHLAZINE AND OXYFEDRINE ON CENTRAL REGULATION OF VASOMOTOR TONE

N. V. Darinskii

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The peripheral effects of the new Soviet antianginal drug nonachlazine are largely determined by its effect on adrenergic structures of the myocardium and blood vessels [4, 5, 9]. Nonachlazine increases the noradrenalin concentration in myocardial tissue and blocks the reverse transport mechanism in adrenergic neurons [2, 4]. Its effects are not manifested after preliminary injection of α- and β-blockers [5, 9]. It is well known that drugs affecting peripheral adrenergic processes of regulation of the circulation can induce changes also through central processes of regulation of sympathetic vascular tone [8]. There have been reports that a large dose of nonachlazine has a central inhibitory action [1, 3].

The object of this investigation was to compare the central effects of two modern antianginal drugs [7, 12] with a β-stimulating component of their action on adrenergic structures of the myocardium, namely nonachlazine and oxyfedrine (Ildamen). The central effects of the drugs were judged by their effect on tonic and reflex activity in the sympathetic nerves of the kidney and also on vasomotor reflexes evoked by stimulation of different groups of afferent fibers of a somatic nerve in anesthetized animals with an intact brain.

EXPERIMENTAL METHOD

Experiments were carried out on cats weighing 2.5-4 kg anesthetized with urethane and chloralose (300 and 40 mg/kg respectively, intravenously). The animals were artificially ventilated and immobilized with myorelaxin (succinylcholine, 0.1 mg/kg/min, intravenously). The body temperature (rectal) was maintained at 36-37° by artificial external heating. The systemic arterial pressure (BP) in the femoral artery was measured by means of an electromanometer. Electrical activity in the renal nerve was recorded by buried platinum electrodes with an interelectrode distance of 3-4 mm. Reflex responses in the renal nerve and vasomotor reflexes were evoked by electrical stimulation of n. tibialis (NT) by stimuli of different parameters. In other series of experiments, reflex responses detected by a monopolar technique were averaged by means of the ATAK-350 analyzer (Japan).

Nonachlazine was injected intravenously in doses of 1 and 6 mg/kg and intra-arterially (a. carotis com.) in a dose of 1 mg/kg. Oxyfedrine was injected in a dose of 0.3 and 1 mg/kg intravenously or in a dose of 0.3 mg/kg intra-arterially. To study the role of adrenergic mechanisms in the central effects of nonachlazine and oxyfedrine the β-adrenoblocker propranolol was used in a dose of 3 mg/kg (intravenously) and reserpine (Rausedil – 0.25%) in a dose of 1 mg/kg.

The results were subjected to statistical analysis.

Laboratory of Pharmacology of the Cardiovascular System, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow.

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TABLE 1. Effect of Nonachlazine and Oxyfedrine on Amplitude of Reflex Changes in BP (in mm Hg) Evoked by Stimulation of Afferent Fibers of NT

Drug	Dose, mg/kg	I series		II series			III series		IV series		
		C	D	C	R	D	C	D	C	R	D
Nonachlazine	1,0 (intravenously)	−16±5 (7)	−7±3	−19±4 (6)	−16±5	−15±4	+51±5 (7)	+73±8	+48±8 (6)	+41±7	+45±6
	6,0 (intravenously)	−19±4 (6)	−25±5	−16±5 (8)	−18±6	−24±5	+56±6 (8)	+29±4	+50±6 (7)	+46±5	+30±4
	1,0 (intraarterially)	−17±5	−28±4	18±5 (7)	−14±5	−21±4	+48±6 (6)	+16±4	+45±5 (5)	+39±4	+26±3
Oxyfedrine	1,0 (intravenously	−15±4 (7)	−20±5	−19±5 (6)	−16±5	−22±6	+47±5 (7)	+32±4	+53±4 (6)	+46±6	+35±4
	0,3 (intraarterially)	−17±6 (6)	−19±5	−16±4 (6)	−18±4	−21±5	±52±6 (6)	+30±5	+47±6 (5)	+43±4	+25±3

Legend. C) Control response before administration of drug; R) response 3 h after injection of reserpine, 1 mg/kg intravenously; D) maximal amplitude of reflex change in BP after injection of drug. Number of animals in series shown in parentheses. Sign before mean value: +) pressor reflex, −) depressor reflex of BP. Parameters of stimulation for series: I and II − 1 V, 0.2 msec, 30 Hz, for 15 sec; III and IV − amplitude 15 V, duration of stimuli 1 msec, frequency of stimulation 30 Hz, for 15 sec.

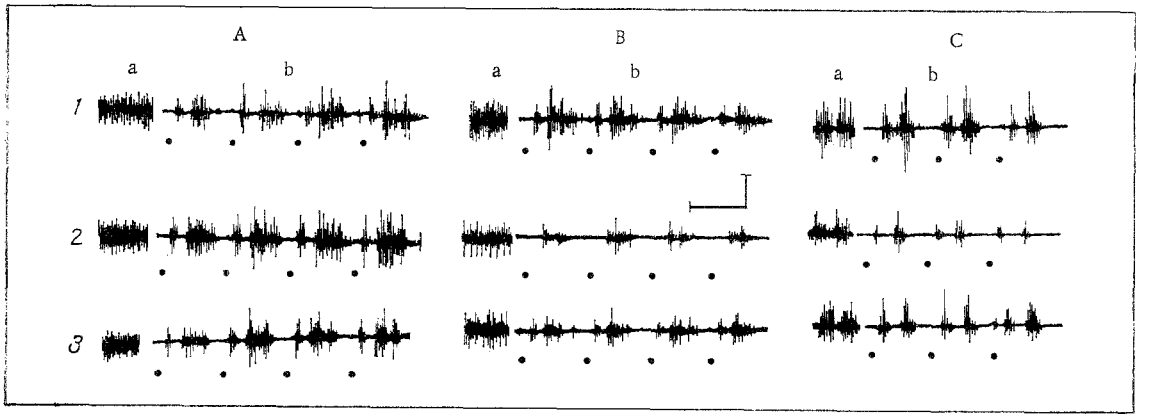

Fig. 1. Effect of nonachlazine in doses of 1 mg/kg (A) and 6 mg/kg (B), and also of oxyfedrine in a dose of 1 mg/kg (C) on tonic (a) and reflex (b) electrical activity in renal nerve evoked by electrical stimulation of NT (1 msec, 15 V, 1 Hz − stimuli represented by points). Calibration: 100 μV, 10 sec (a) and 1 sec (b). 1) Before injection of drug, 2 and 3) 10 and 30 min respectively after injection.

EXPERIMENTAL RESULTS

The effect of nonachlazine and oxyfedrine in different doses on the character of vasomotor reflexes evoked by stimulation of NT was studied in the experiments of series I. Stimulation of only A-groups of afferent fibers of NT, corresponding to stimulation with a strength of 1 V [6], evoked a hypotensive response of BP in the anesthetized animals with an intact brain. Stimulation of the whole spectrum of afferent groups of fibers of NT (A +C-fibers) with a strength of 15 V evoked a hypertensive response of BP. The mean statistical data on the effect of nonachlazine and oxyfedrine on the maximal reflex chain in BP (the amplitude of the vasomotor reflex) are given in Table 1. Nonachlazine in a dose of 1 mg/kg, in which it did not exhibit any marked antianginal effect, reduced by 56% the depressor response of BP to stimulation of A-groups of fibers of NT and potentiated by 43% the pressor reflex of BP to stimulation of the A +C-fibers of NT. The activating effect of nonachlazine in this dose was manifested to the greatest degree 3-5 min after injection and the effect lasted not more than 10 min. Nonachlazine in a dose of 6 mg/kg, which is optimal for manifestation of its antianginal

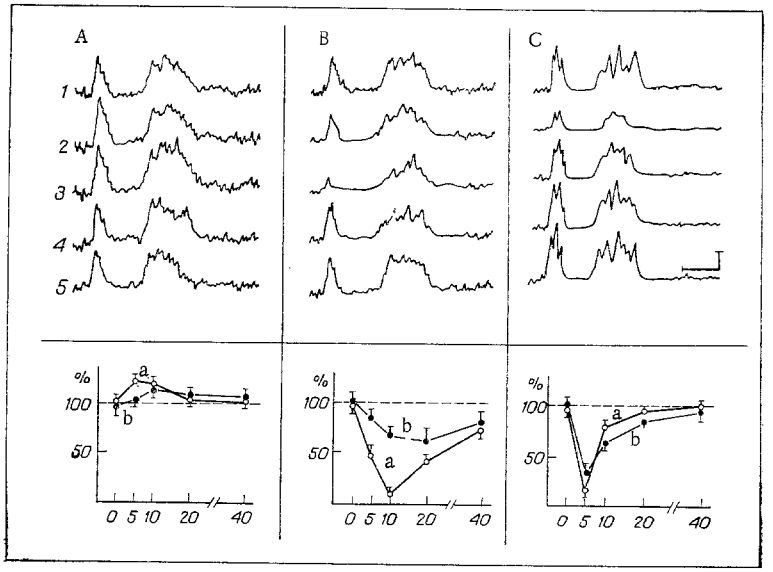

Fig. 2. Effect of nonachlazine in doses of 1 mg/kg (A) and 6 mg/kg (B) and also of oxyfedrine in a dose of 1 mg/kg (C) on characteristics of single responses in renal nerve to stimulation of NT. Averaged responses to 20 stimulations at intervals of 4 sec. Duration of stimuli 1 msec, amplitude 15 V. Beginning of each trace coincides with application of stimulus. Calibration: 50 μV, 200 msec. Top part of figure: 1) before injection of drug, 2, 3, 4, 5) 5, 10, 20, and 40 min respectively after injection. Bottom part of figure: abscissa, dynamics of change in area beneath curve of A-responses (a) and C-responses (b) under influence of drugs (in % of initial level before injection); ordinate, time (in min).

properties [5, 11], strengthened by 32% the depressor response of BP and weakened by 51% the pressor reflex of BP. The inhibitory effect of nonachlazine reached a maximum between the 7th and 10th minutes and it continued for 20-30 min. The central origin of the action of the drug is indicated by the fact that this inhibition of vasomotor reflexes was evoked by a smaller dose of nonachlazine when injected into the carotid artery (Table 1). With its stimulating action on β-adrenergic structures, nonachlazine can interfere in adrenergic processes and produce a significant increase in the noradrenalin concentration in tissues of the myocardium and brain [4]. It can therefore be suggested that the action of the drug on the brain structures is mediated through noradrenalin. In order to shed light on this problem series of experiments were carried out to study the effect of nonachlazine on vasomotor reflexes after exhaustion of catecholamines by reserpine, injected 3 h before the nonachlazine. The results of the experiments of series II and IV (Table 1) showed that the activating action of a small dose of nonachlazine is completely abolished by previous administration of reserpine, whereas the effect of large doses of nonachlazine remained unchanged. These facts may serve as the basis for the conclusion that the activating effect of the drug is evidently mediated through catecholamines, whereas its inhibitory effect, manifested in large doses, is connected with a direct action on adrenergic structures of the brain. This conclusion is supported by the fact that after preliminary blockade of the β-adrenergic structures of the brain by propranolol in a dose of 3 mg/kg, nonachlazine had no inhibitory action on vasomotor reflexes.

By contrast with nonachlazine, oxyfedrine had no activating effect. In a dose of 0.3 mg/kg, the threshold level for manifestation of its antianginal properties [5, 11], oxyfedrine did not affect the character or magnitude of the vasomotor reflexes. With an increase in the dose to 1 mg/kg oxyfedrine, like nonachlazine, but to a much lesser degree, inhibited the reflex change in BP evoked by stimulation of both A- and A+C-fibers of NT. Similar inhibition of BP reflexes was evoked by a smaller dose of oxyfedrine injected intra-arterially (Table 1). Against the background of reserpine, oxyfedrine preserved its inhibitory effect but, on the other hand, propranolol prevented the inhibitory action of oxyfedrine. It can accordingly be concluded that the central effect of oxyfedrine is evidently associated with its influence on adrenergic brain structures.

Changes in BP in response to stimulation of spinal nerves are known to be connected with reflex changes in activity of postganglionic sympathetic neurons [10, 14]. Analysis of the effects of nonachlazine and oxyfedrine

on tonic and reflex responses in the renal nerve, which consists chiefly of vasoconstrictor fibers [10], can therefore shed light on the mechanism of action of these drugs on processes of central regulation of the circulation.

Typical traces of tonic and evoked activity recorded in the renal nerve in response to repetitive stimulation of A+C-afferents of NT with a frequency of 1 Hz are given in Fig. 1. They show that nonachlazine, in a dose of 1 mg/kg, had practically no effect on tonic activity, but at the same time it increased the intensity of the C-reflexes (Fig. 1A). Each of the evoked responses consisted of excitatory and inhibitory components [10, 14]. It can be tentatively suggested that nonachlazine, in small doses, very slightly potentiated the inhibitory component of the A-response and, at the same time, weakened the intensity of the C-response. This is shown more clearly still by the traces of averaged single evoked responses (Fig. 2A). In the diagram of the relative change in intensity of the A- and C-responses given in Fig. 2A (the areas beneath the curve of the responses) potentiation only of the A-response can be seen during the first 5 min after injection of nonachlazine and a small and not significant increase in both components during the next 10 min.

An increase in the dose of nonachlazine to 6 mg/kg led to inhibition of tonic activity in the sympathetic nerves, expressed as a reduction in amplitude and frequency of the discharges (Fig. 1B, a). In addition, the drug considerably inhibited evoked discharges, especially A-discharges, or even caused them to disappear completely. During repetitive stimulation of NT with relatively low frequency (0.5-1 Hz) omission of A-discharges took place. Traces of averaged responses clearly show that nonachlazine inhibited the long-latency part of the A-response, which is due to stimulation of slowly-conducting afferent A_δ-fibers of NT conducting nervous impulses with a velocity of under 15 m/sec (Fig. 2B). The maximal inhibitory effect of the drug was manifested after 10 min and the total duration of its action was not less than 40 min.

It is difficult at present to say whether the inhibitory effect of nonachlazine is connected with stimulation or blockade of β-adrenergic structures. The results of experiments on waking animals [9], which showed that nonachlazine in a dose of 6 mg/kg can inhibit the pulse responses of the heart to isoproterenol, i.e., that besides its ability to stimulate β-adrenergic structures nonachlazine can also weaken their sensitivity to iosproterenol, are interesting in this context. Certain β-adrenoblockers are known to inhibit tonic and reflex activity in sympathetic nerves in the same way [13]. It can therefore be postulated that the inhibitory action of nonachlazine depends on a decrease in the sensitivity of the β-adrenergic structures of the brain to catecholamines.

Oxyfedrine in a dose of 1 mg/kg also had an inhibitory action on tonic discharges and reflex responses in sympathetic nerves (Fig. 1C). However, unlike nonachlazine, it inhibited the excitatory mechanisms of activation of vasoconstrictor neurons by a greater degree than the inhibitory mechanisms and , under these circumstances, it did not exhibit selectivity in relation to A- or C-responses (Fig. 2C). The maximal effect of the drug was manifested at the 5th-7th minute and the total duration of its action did not exceed 20 min.

Nonachlazine thus has a selective effect on reflex responses from high-threshold afferent fibers conducting primary pain signals into the CNS. Oxyfedrine does not possess such selectivity. An attack of angina is known to be accompanied by symptoms of activation of the sympathetic nervous system. It can accordingly be postulated that inhibition of sympathetic tone due to nonachlazine may play an important role in the mechanism of self-limitation of the sympathomimetic properties of the drug. Another possibility is that inhibition of impulses of pain modality facilitates the manifestation of its antianginal effect.

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EFFECT OF NONACHLAZINE ON ATP, ADP, AND LACTIC ACID CONCENTRATIONS IN THE INTACT AND ISCHEMIZED MYOCARDIUM

A. I. Turilova, T. N. Azvolinskaya, and S. A. Kryzhanovskii

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KEY WORDS: heart; ischemia; nonachlazine; adenine nucleotides; lactic acid.

Nonachlazine is a new and original drug synthesized in the Institute of Pharmacology, Academy of Medical Sciences of the USSR. The results of clinical trials have shown that nonachlazine is an antianginal agent distinguished by its high efficacy in the treatment of ischemic heart disease [3, 4, 11, 12]. Experimental studies have shown that an important role in the mechanism of the antianginal effect of nonachlazine is played by its effect on adrenergic processes of regulation of the circulation and cardiac activity [5]. Nonachlazine increases the noradrenalin concentration and activity of phosphorylase "a" in the myocardium [6]. These findings suggest that the beneficial effect of nonachlazine is evidently associated with its ability to activate adrenergic mechanisms in the regulation of glycogenolysis.

In accordance with the facts described above, and taking into account data showing that ischemia leads to a decrease in the ATP concentration in the myocardium [2, 14, 15], it was decided to study the effect of nonachlazine on the concentrations of ATP, ADP, and the end product of glycogenolysis – lactic acid – in the intact and ischemized myocardium.

TABLE 1. Concentration of ATP, ADP, and Lactic Acid (in μmoles/g wet weight of tissue) in Cat Myocardium (M ± m)

Series of experiments	Experimental	ATP	ADP	Lactic acid
I	Control	4,49±0,76 5,25÷3,73	1,05±0,33 1,38÷0,72	3,22±0,08 3,30÷3,14
II	Nonachlazine, 6mg/kg	4,31±0,85 5,16÷3,46	1,07±0,47 1,54÷0,60	3,51±0,44 3,95÷3,07
III	Acute ischemia	3,69±0,13* 3,82÷3,56	1,53±0,24* 1,77÷1,29	7,34±3,01* 10,35÷4,33
IV	Acute ischemia + nonachlazine, 6 mg/kg	4,60±1,08† 5,68÷3,52	1,57±0,54 2,11÷1,03	4,25±0,80† 5,05÷3,45

*Results statistically significant compared with control ($P \leq 0.05$).
†Results statistically significant compared with experiments with acute ischemia ($P \leq 0.05$).

Laboratory of Pharmacology of the Cardiovascular System, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 89, No. 7, pp. 49-51, July, 1980. Original article submitted November 13, 1979.

