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EFFECT OF NONACHLAZINE ON BRAIN AND MYOCARDIAL NORADRENALIN LEVELS IN NORMAL AND STRESSED RATS

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UDC 616.831+616.127].-008.94:577.175.523]-02:613.863

KEY WORDS: nonachlazine; noradrenalin level; brain stem; myocardium; stress reaction.

Disturbances of neuromediator and, in particular, of catecholamine metabolism during the stress reaction are confirmed by the results of many investigations. Considerable changes in the noradrenalin concentration in the hypothalamus, adrenals, heart, and blood during stress lead to significant disturbances of function of sympathetic regulation of the activity of the cardiovascular system [1, 2, 7, 14]. Changes in catecholamine metabolism also have been observed in patients with ischemic heart disease and myocardial infarction [8, 11, 13].

In connection with the facts described above it was decided to investigate the effect of the new antianginal drug nonachlazine, which acts upon adrenergic processes [5], on the brain and heart noradrenalin levels under normal conditions and during neurogenic stress.

EXPERIMENTAL METHOD

Experiments were carried out on 60 sexually mature rats weighing 200-250 g. The noradrenalin level in the brain stem and myocardium was determined by the modification in [9] of the fluorometric method [12].

There were four series of experiments. In the experiments of series I (control) the noradrenalin level was determined in the brain tissue and myocardium of intact rats. In the experiments of series II the noradrenalin level in the tissues was determined 15 and 30 min after intravenous injection of nonachlazine in a dose of 10 mg/kg. In series III the noradrenalin level was studied 30 min after the beginning of electrical stimulation of the thigh through bipolar subcutaneous electrodes (10 V, 0.5 msec, 20 stimuli/sec, for 10 sec with intervals of 5 min) while the rats were immobilized. In series IV the noradrenalin level was determined in the brain stem and heart 30 min after injection of nonachlazine and electrical stimulation of the animals. During the period of development of the stress reaction changes in the ECG were recorded in standard lead II. The experimental results were subjected to statistical analysis with a $P < 0.05$ level of significance.

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(Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 91, No. 5, pp. 580-582, May, 1981. Original article submitted November 11, 1980.

TABLE 1. Noradrenalin Concentration in Myocardium and Brain Stem of Rats (in $\mu g/g$ wet weight of tissue)

Test object	Control	After injection of 10 mg/kg nonachlazine		Stress	Stress + 10 mg/kg nonachlazine
		15 min	30 min		
Heart	0,66±0,046 (0,71—0,61) $n=6$	1,15±0,19* (1,34—0,96) $n=5$	1,11±0,22* (1,33—0,89) $n=7$	0,30±0,06* (0,36—0,24) $n=6$	0,42±0,06† (0,48—0,36) $n=6$
Brain	0,44±0,11 (0,55—0,33) $n=5$	0,76±0,06* (0,92—0,60) $n=5$	0,59±0,10* (0,69—0,49) $n=6$	0,33±0,03* (0,36—0,30) $n=6$	0,31±0,07* (0,38—0,24) $n=6$

*$P < 0.05$ relative to control.
†$P < 0.05$ relative to stress.

EXPERIMENTAL RESULTS

Nonachlazine has a marked effect on noradrenalin metabolism, causing an appreciable increase in its concentration in the myocardium and brain stem of intact rats. As Table 1 shows, the noradrenalin content in the myocardium of the rats increased by 74% over the control level 15 min and 68% 30 min after intravenous injection of nonachlazine, and the corresponding increases in the brain stem were 72 and 34%. The noradrenalin content in the tissues fell to its initial level 4 h after injection of nonachlazine.

During stress (immobilization of the animals and painful electrical stimulation), accompanied in rats by a vocalization response and by emotional and muscular tension, a considerable fall in the noradrenalin level was observed both in the heart muscle and in the brain stem (by 50 and 25% respectively).

Changes in the noradrenalin level in the rats during stress also were combined with marked disturbances on the ECG, including ischemic changes and extrasystoles.

Since nonachlazine can increase the noradrenalin concentration in the brain and heart of intact rats, it was interesting to study its concentration during the stress reaction. Nonachlazine gave a considerable protective effect against exhaustion of the noradrenalin reserves in the heart muscle. The myocardial noradrenalin level during exposure to stress factors after preliminary administration of nonachlazine was 40% higher than in the control group of stressed animals (Table 1). In this series of experiments nonachlazine also prevented the development of electrocardiographic disturbances due to stress. Meanwhile nonachlazine did not prevent the fall in the noradrenalin level in the brain stem caused by painful electrical stimulation of the rats (Table 1).

These results are in agreement with those of investigations which showed that nonachlazine can influence adrenergic processes: It increases phosphorylase a activity in the heart, stimulates β-adrenergic structures of the myocardium [6], and affects the process of noradrenalin uptake by the heart [4]. The increase in the noradrenalin reserves in the brain stem under the influence of nonachlazine can play an important role in its action on the adrenergic components of central regulation of the cardiovascular system. However, it is not yet clear which processes are responsible for the high rate of accumulation of noradrenalin in the tissues of intact rats under the influence of nonachlazine or what are the mechanism of tissue differences in noradrenalin storage in the brain stem and the myocardium under the influence of nonachlazine during stress.

In this respect the results of a study of the effect of nonachlazine on the activity of mitochondrial monoamine oxidase and of enzymes participating in catechloamine synthesis deserve attention. In experiments in vitro nonachlazine inhibited MAO activity in the mitochondria of the rabbit and rat heart only in relatively high concentrations [10]. According to preliminary results obtained by Mineeva and Darinskii in the Institute of Pharmacology, Academy of Medical Sciences of the USSR, nonachlazine can increase the specific activity of myocardial tyrosine hydroxylase. The protective effect of nonachlazine against exhaustion of the noradrenalin reserves in the myocardium and the development of ischemic changes in the ECG during stress may be connected with the mechanism of tyrosine hydroxylase activation in the heart.

However, nonachlazine does not prevent the fall in the noradrenalin level in the brain stem of rats during pain-induced stress. This may be due to the relatively weaker effect of nonachlazine on the process of noradrenalin storage in the brain tissue compared with the heart. The noradrenalin level in the brain stem increased by only 34%, compared with 68% in the heart, 30 min after injection of the drug into intact rats. At the same time, this effect may be attributable to the high sensitivity of the brain adrenergic systems to the

absence of a depriming effect of nonachlazine on the pain syndrome formed by impulses in C-group afferents [3]. Pain of both central and peripheral origin is known to lead to exhaustion of the noradrenalin reserves in the brain tissue as a result of its increased liberation, a deficiency of its precursors, and disturbance of processes of catecholamine synthesis [2, 7].

The results thus evidently demonstrate the relative affinity of nonachlazine for the heart with particular reference to its intervention in the adrenergic processes of the heart during the response to stress.

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ACTION OF IONOPHORE A 23187 ON THE FORCE OF CONTRACTION AND SLOW ACTION POTENTIAL OF GUINEA PIG PAPILLARY MUSCLE

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UDC 612.172.014.462.4

KEY WORDS: calcium ionophore A 23187; force of contraction; slow action potential; calcium ions.

The principal property of ionophores, including the calcium ionophore A 23187 discovered in 1972 [12], is their ability to form complexes with cations and to catalyze their passage from a polar medium into a nonpolar medium [10, 13]. Meanwhile, according to a recently expressed hypothesis [5, 6], Ca ions which participate in the formation of the slow inward calcium current must bind beforehand with the sarcolemma, i.e., they must move from the aqueous phase into the lipid phase. It can thus be postulated that if the quantity of Ca^{++} bound to the cell membrane of the myocytes is increased by the action of an ionophore, the potential-dependent inflow of Ca^{++} through the sarcolemma must increase. The investigation described below was carried out to test this hypothesis.

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(Presented by Academician of the Academy of Medical Sciences of the USSR E. I. Chazov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 91, No. 5, pp. 582-584, May, 1981. Original article submitted November 11, 1980.

0007-4888/81/9105-0644$07.50