COMPARISON BETWEEN VASOMOTOR RESPONSES TO NERVE STIMULATION AND TO NORADRENALIN

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The causes of differences between responses of the limb vessels in cats to measured nerve stimulation were studied. If stimulation of the sympathetic chain can produce dilator and constrictor effects, noradrenalin also causes dilatation of the vessels in small doses and constriction in large doses. If neurogenic responses were entirely vasoconstrictor, regardless of the dose given, noradrenalin produced vasoconstriction. Infusion of noradrenalin led to the replacement of dual neurogenic responses by constrictor responses only.

During electrical stimulation of sympathetic nerves, vasomotor effects may be produced which differ in direction depending on the quantitative characteristics of the stimulus: vasodilatation appears in response to relatively weak stimulation of low frequency and short duration, while vasoconstriction is observed if the strength, frequency, and duration of stimulation are increased [3]. However, in many experiments it is impossible to obtain two types of responses to nerve stimulation: the response to all parameters of stimulation used is constriction. Animals showing only vasodilator responses are less frequently seen.

Factors modifying vascular responses to intermittent stimulation of the sympathetic system in the same animal include hormonal [4] and pharmacological agents [2], and also the initial level of pressure [1] and temperature [2], and the action of metabolic products [14].

The object of the investigation described below was to study changes in neurogenic vasomotor responses under the influence of noradrenalin.

EXPERIMENTAL

In acute experiments on cats anesthetized with ether and urethane, vascular responses of the hind limbs were studied by resistography. Simultaneous recordings of the arterial pressure in the carotic artery were made with a mercury manometer.

Vasomotor responses were evoked by intra-arterial injection of noradrenalin (in doses of 0.5-50 μg) and electrical stimulation of the sympathetic chain in the lumbar region at the level of segments L2-L6. The frequency of the pulses, the relative number of stimulated nerve fibers, and the duration of the vasomotor spike volley varied within wide limits. After injection of noradrenalin by the drip method into the femoral artery at the rate of 0.005-0.5 μg/kg/min, changes in responses of the peripheral nerves to the same nerve stimuli as were applied before administration of noradrenalin were investigated. Heparin was injected in a dose of 10 mg/kg body weight to prevent the blood from clotting.

EXPERIMENTAL RESULTS AND DISCUSSION

Usually, in animals in which electrical stimulation of the sympathetic chain evoked vasomotor responses of two types (dilatation in response to relatively weak stimulation of short duration and low frequency,

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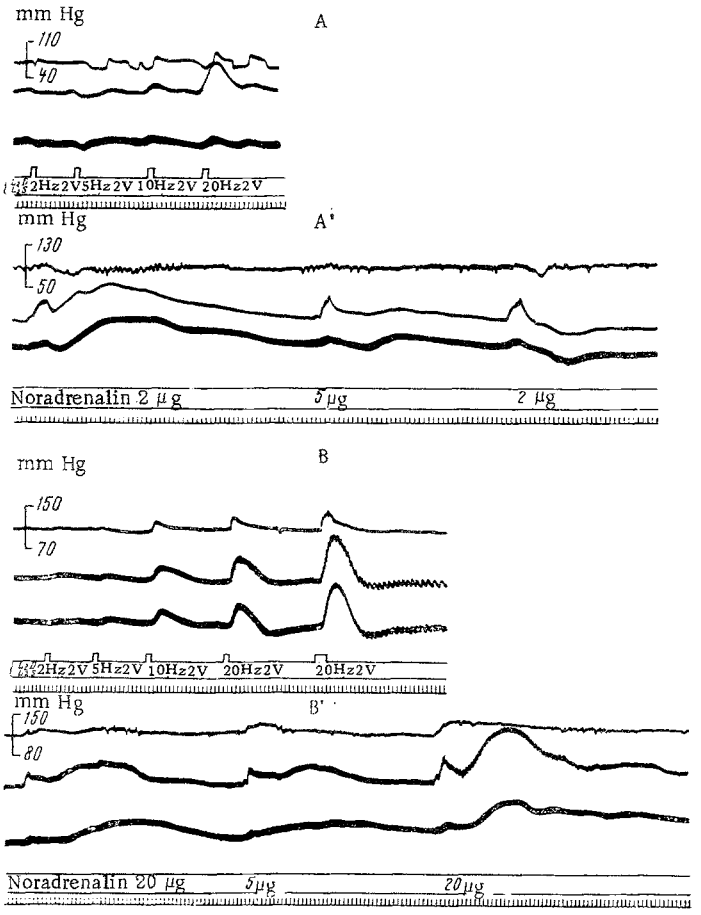

Fig. 1. Parallel between character of vasomotor responses of hind limbs in cats to electrical stimulation of sympathetic chain and injection of noradrenalin. A, B) Response to stimulation of sympathetic chain; A',B') response to intraarterial injection of noradrenalin. Significance of curves from top to bottom: arterial pressure, resistograms of right and left femoral arteries; marker of stimulation (or injection of noradrenalin), time marker (5 sec).

and vasoconstriction in response to an increase in the frequency, strength, and duration of stimulation) (Fig. 1A), the vascular responses to intra-arterial injection of noradrenalin also were of two types: dilatation in response to a relatively small dose (2 μg) and constriction in response to a higher dose (5 and 20 μg; Fig. 1A').

In animals in which stimulation of the sympathetic chain gave only vasoconstrictor effects (Fig. 1B), irrespective of the dose injected, noradrenalin also produced vasoconstriction (Fig. 1B').

These results indicate that in these two groups of animals, with observed differences in their responses to nervous and humoral influences, the vasomotor responses to nervous and humoral influences with identical qualitative characteristics also take place in different directions. Clearly, if these influences are known to be of the same type, the difference between the responses may depend on the state of smooth-muscle structures responsible for vasomotor reactions. This hypothesis is supported by the findings of Bulbring and coworkers [7], who found that the response of uterine muscles of cats to stimulation of the hypogastric nerve and to noradrenalin is similar in direction. Both stimuli caused relaxation of the virgin uterus and contraction of the pregnant uterus. Differences between the effects produced by the two stimuli can be assumed to be due to differences in the functional state and reactivity of the uterus; other workers have found, for example, that during pregnancy changes in the tissue nonradrenalin reserves take place in the uterus [16].

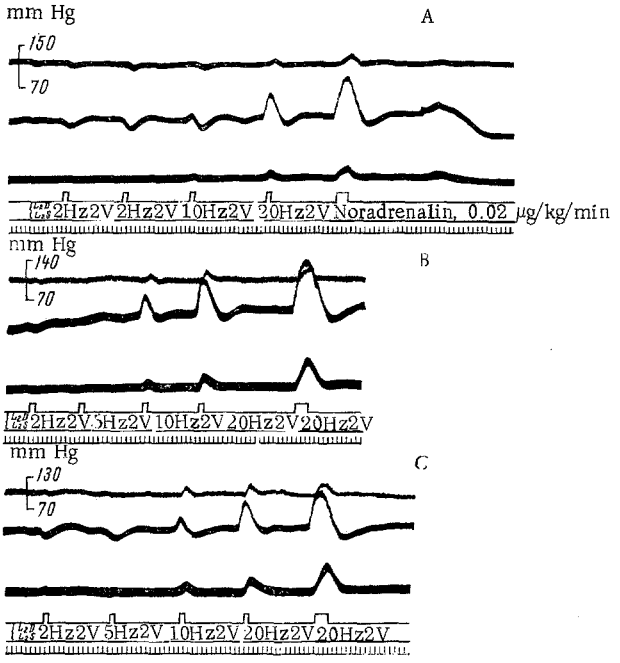

Fig. 2. Changes in neurogenic vasomotor responses of hind limbs in cats during prolonged intra-arterial injection of noradrenalin. A, B, C) before, during, and after injection of noradrenalin, respectively. Significance of curves as in Fig. 1.

There is considerable experimental evidence to indicate that vascular responses to stimulation of sympathetic nerves are dependent on the noradrenalin reserves; exhaustion of noradrenalin reserves by injection of sympatholytics (ornid, reserpine) leads to the abolition of vasomotor responses to stimulation of sympathetic nerves, while subsequent injection of noradrenalin restores the effects of sympathetic stimulation [15].

In the present experiments, injection of noradrenalin into the femoral artery at the rate of 0.005-0.5 μg/kg/min definitely potentiated the degree of vasoconstriction in response to stimulation of the sympathetic chain. Simultaneously with potentiation of the vasoconstrictor effects, vasodilator responses were weakened during prolonged infusion of noradrenalin, or were replaced by vasoconstrictor (while the parameters of nerve stimulation remained unchanged).

It is clear from Fig. 2A that in the initial state, electrical stimulation of the sympathetic chains at the level of the second lumbar segment with a constant strength of 2 V caused vasodilatation at relatively low frequencies (2 and 5 Hz) and constriction at frequencies of 10 and 20 Hz. Against the background of intra-arterial injection of noradrenalin at the rate of 0.02 μg/kg/min, stimulation of the sympathetic chains at frequencies of 10 and 20 Hz was accompanied by more marked vasoconstriction than before injection of noradrenalin. Under these conditions, stimulation at 5 Hz no longer produced vasodilatation, as it did in the initial state, but slight constriction. Vasodilatation was definitely weakened in response to stimulation at 2 Hz. The dilator effect of stimulation at 10 Hz also was weakened (Fig. 2B).

After the infusion of noradrenalin had stopped, restoration of the original character of the neurogenic vasomotor effects was gradually observed: stimulation at 2 and 5 Hz once more evoked dilatation, and the constriction in response to stimulation at 10 and 20 Hz was weakened (Fig. 2C).

It follows from these results that the quantity of circulating noradrenalin and, probably, the tissue reserves and metabolism of the adrenergic mediator are important conditions influencing vasomotor reactivity.

Burn [8] considers that the synthesis and liberation of acetylcholine and noradrenalin are closely connected and are consecutive reactions, and at low frequencies of stimulation the liberated acetylcholine has a

direct action and produces vasodilatation, while at high frequencies it is almost entirely utilized for the liberation of noradrenalin [9]. On the basis of this hypothesis, changes in the character of neurogenic vasomotor responses (replacement of dilatation by constriction) during administration of noradrenalin can be regarded as the result of changes in the ratio between the amounts of mediators: acetylcholine and noradrenalin. This can also be linked with the vasoconstrictor effect of the mediator itself [11] or with changes in tone of the smooth muscles of the vessels [10].

These results showing the effect of prolonged administration of noradrenalin on the character of neurogenic vasomotor effects may shed light on the cause of differences between responses of different animals to the same nervous and humoral agents. The tissue reserves and content of circulating noradrenalin may play a role in determining the character of the response to nerve stimulation by influencing the functional state and reactivity of the vessels. This hypothesis is supported by evidence showing that noradrenalin can be absorbed and accumulated by the smooth-muscle tissue of arteries and other tissues innervated by the sympathetic nervous system [12], and also by results obtained in the first series of experiments in which different responses to injection of noradrenalin were obtained, depending on the character of response of the vessels to neurogenic influences. After administration of noradrenalin both vasodilatation and vasoconstriction [10], or only vasoconstriction [11], or only vasodilatation [6] were observed. These conflicting results can be attributed to differences in the functional state and reactivity of the vessels in the experimental animals.

These results suggest that one of the conditions modifying responses to neurogenic stimulation may be the metabolism and reserves of noradrenalin. Indirect confirmation of this hypothesis is given by data showing changes in noradrenalin metabolism under the influence of various hormones [13], or of fluctuations in the level of the blood pressure [5] or temperature [12], i.e., under conditions when changes in reactivity of the vessels to uniform neurogenic stimulation are found.

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