ROLE OF THE CENTRAL MONOAMINERGIC MECHANISMS IN THE ACTION OF DRUGS ON THE CARDIAC REFLEXES

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One of us (N. V. K.) has previously shown that the reflexes arising in response to stimulation of the afferent fibers of the somatic nerves and leading to coronary vasoconstriction are effected through the sympathetic innervation of the heart [1].

The object of the present investigation was to study the mechanisms of action of several groups of drugs having the power to influence the conduction of excitation in the central links of reflexes, traveling to the heart and the coronary vessels along the sympathetic nerves.

EXPERIMENTAL

Two methods were used to assess the effect of the pharmacological agents on the reflex changes in the tone of the coronary vessels and on the central processes responsible for the formation of the reflexes: resistography of the coronary vessels [1] and electroneurographic recording of the tonic activity and the reflex responses in the cardiac sympathetic nerves. For this purpose, in experiments on anesthetized cats, after thoracotomy the efferent impulses were recorded in the central end of the divided left inferior cardiac nerve. The central end of the divided tibial nerve was stimulated with rectangular electric pulses. The parameters of the stimuli were chosen so as to produce excitation either of the A group of afferent fibers only (0.5-1 msec, 1-5 V) or of both the A and the C groups of fibers of the tibial nerve (2-3 msec, 20-30 V). The frequency of stimulation was 0.5-1 cps [2, 3, 15, 19].

EXPERIMENTAL RESULTS AND DISCUSSION

The experiments began with administration of analgesics. Besides depressing the reflexes acting on the blood pressure and the coronary vessels, the analgesics (morphine, 0.5-1 mg/kg, trimeperidine, 0.75-1.5 mg/kg) were also found to cause selective depression of the responses to impulses in the afferent C fibers, along which nociceptive impulses are known to travel into the central nervous system (Fig. 1A).

Among the many observations relating to the mechanism of action of analgesics, attention has recently been focused on reports indicating that adrenergic mechanisms are concerned in the development of the analgesic effect. Morphine has been shown to stimulate the liberation of catecholamines from the adrenals, and after adrenalectomy its analgesic action is considerably diminished. The analgesic action of morphine is weakened also, if the catecholamine reserves of the brain are exhausted with the aid of reserpine [8, 9, 14, 16]. These facts are in good agreement with the numerous reports of the analgesic activity of the sympathomimetic amines [6, 11, 12, etc.].

Because of these findings, it was interesting to study the effect of analgesics on the reflex responses in the cardiac sympathetic nerves after administration of reserpine to change the catecholamine and serotonin levels in the brain tissue. However, before resorting to experiments of this type it was necessary to investigate the changes in the character of these reflex reactions caused by reserpine itself in the various phases of its action. In doses of 0.25-0.5 mg/kg (intravenously), reserpine caused complete suppression of the reflex responses starting 100-140 min after injection, i.e., in the phase of liberation of monoamines from the tissue depots, and continuing for 4-6 h. The results were different in experiments in which reserpine in a dose of 2.5 mg/h was injected 24 h before the reflex responses in the cardiac nerves were recorded, i.e., in the phase of exhaustion of the monoamine reserves in the brain tissue. In these

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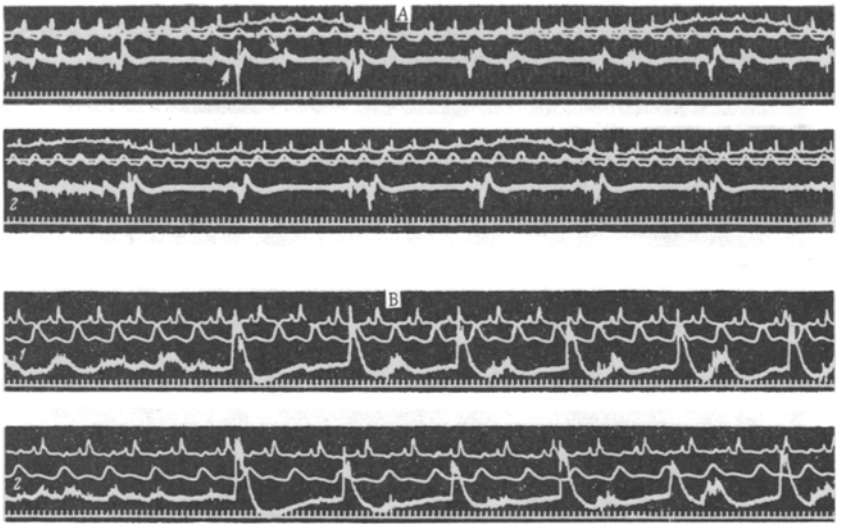

Fig. 1. Effect of morphine (1 mg/kg) on reflex responses in the inferior cardiac nerve in normal conditions (A) and after preliminary (24 h beforehand) injection of reserpine (2.5 mg/kg) (B). From top to bottom: ECG, arterial pulse pressure, electroneurogram, time and stimulation marker (1 sec). 1) Tonic activity and reflex responses in the inferior cardiac nerve during stimulation of the afferent A (↑) and C (↓) fibers of the tibial nerve; 2) 20 min after injection of morphine (reflex responses to impulses in the afferent C fibers absent).

experiments, not only were the reflex discharges not depressed, but the reverse was found: the threshold amplitude of the stimulating pulses was lowered. Morphine, injected in a dose of 1 mg/kg at this time against the background of reserpine, no longer depressed the reflex responses to impulses in the afferent C fibers (Fig. 1B).

The facts obtained suggest that the changes in the intensity and character of the reflex reactions brought about by analgesics and reserpine were dependent on the action of these drugs on monoamine metabolism in the brain tissue. From this point of view the study of monoamine oxidase (MAO) inhibitors is of considerable interest. Experiments have shown that MAO inhibitors (iproniazid, nialamide, transamine) depress vascular reflexes and also cause sharp changes in the character of the reflex responses in the inferior cardiac nerve. A particularly interesting finding was that MAO inhibitors, like analgesics, selectively depress reflex responses to impulses in the afferent C fibers in the first phase of their action. The depression of the reflex reactions started 5-15 min after injection of the MAO inhibitors, increased for 1-2 h, and then continued throughout the experiment (4-8 h). Nialamide has this action in doses of 20-40 mg/kg, proniazid in doses of 70-140 mg/kg, and transamine in doses of 2-5 mg/kg.

To determine the duration of the observed effects a series of experiments was carried out in which nialamide was injected in a dose of 40 mg/kg 16, 24, 48, 72, 96, and 120 h before the acute experiment was due to start. These experiments showed that reflex responses to impulses in the afferent fibers were absent 16 and 24 h after injection of nialamide, and the tonic activity in the cardiac nerves was greatly weakened. In the animals receiving nialamide 48 h before the experiment, the excitability of the centers to asphyxia was increased.

The tonic activity increased in these animals 2-3 min after stopping artificial respiration and reflex discharges began to appear. The period of complete recovery of the reflex reactions varied in the individual animals from 72 to 96 h after injection of the preparation.

This similarity between the pattern of depression of the reflex reactions by MAO inhibitors and the pattern of inhibition of the activity of this enzyme is evidence of the connection between these processes and suggests that the influence of MAO inhibitors on autonomic reflexes is exerted via the monoamines of the brain tissue. This suggestion was confirmed by the results of two additional series of experiments.

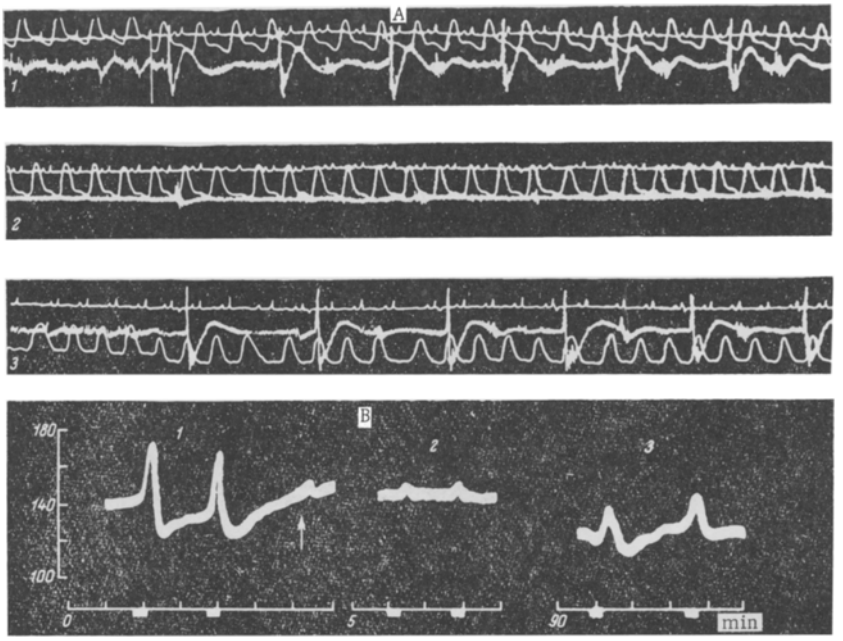

Fig. 2. Effect of DOPA (75 mg/kg) on the reflex responses in the inferior cardiac nerve and the vasomotor reflexes. A: 1) tonic activity and reflex responses to impulses in the afferent A and C fibers; 2) 5 min after injection of the preparation; 3) restoration of reflex discharges 90 min after injection. Legend as in Fig. 1. B: 1) blood pressure reflexes before injection of drug; 2) 5 min after injection; 3) 90 min after injection. Arrow: moment of injection.

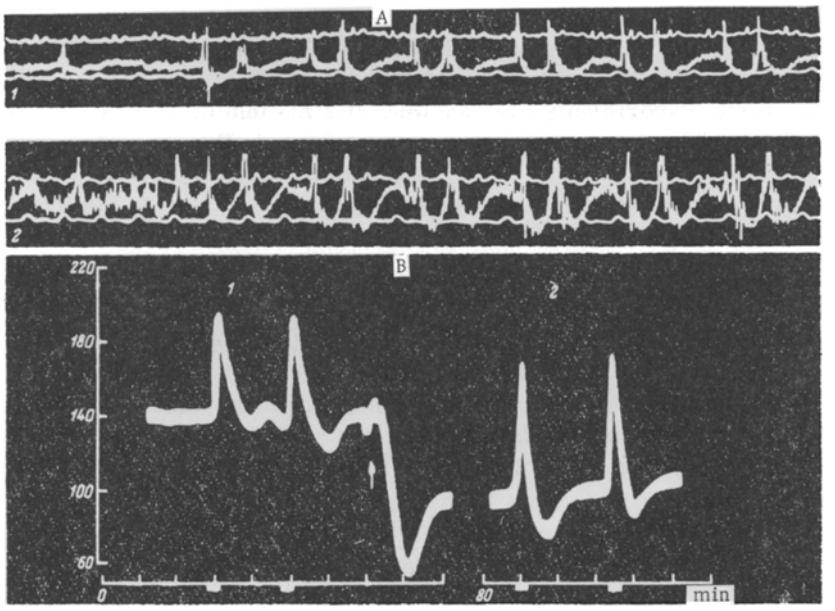

Fig. 3. Increase in tonic activity, reflex responses in the inferior cardiac nerve, and vasomotor reflexes under the influence of dichloroisoproterenol (5 mg/kg). A: 1) tonic activity and reflex responses in the inferior cardiac nerve before injection of the preparation; 2) 80 min after injection. B: 1) blood pressure reflexes before injection of the preparation; 2) 80 min after injection. Arrow: moment of injection.

The first series showed that reflexes affecting the coronary vessels and blood pressure and also reflex responses in the cardiac nerves are depressed if noradrenalin (40-80 μg/kg) or serotonin (1 mg/kg) is injected into the cerebral ventricles. A similar action was produced by intravenous injection of the precursors of these monoamines, DOPA (3, 4-dihydroxyphenylalanine) in doses of 50-100 mg/kg (Fig. 2) and 5-hydroxytryptophan in a dose of 50 mg/kg. In the experiments of series II,the effect of MAO inhibitors was studied on the reflex responses in the cardiac nerves during exhaustion of the monoamine reserves of the brain by reserpine. In these conditions it was found that the effect of the MAO inhibitors, like that of the analgesics, was considerably weakened.

It may be concluded from these findings that the following substances may depress the reflexes evoked by stimulation of the spinal afferent fibers and effected via the sympathetic nerves: analgesics (morphine, trimeperidine), MAO inhibitors (nialamide, iproniazid, transamine), reserpine (in the phase of liberation of monoamines from the tissue depots), noradrenalin and serotonin (injected into the cerebral ventricles), and the precursors of these monoamines (DOPA and 5-hydroxytryptophan).

Analgesics (morphine, methadone, etc.) have been shown to liberate monoamines from brain tissue [10, 18]. Histochemical investigations have demonstrated that MAO inhibitors may also increase the concentration of free forms of monoamines [7]. By comparing these findings with out own observations it may be concluded that the increase in the concentration of free forms of monoamines in brain tissue, caused by various pharmacological agents, leads to depression of the reflex reactions now being studied.

In recent investigations of the cellular localization of monoamines in the central nervous system, Carlsson and co-workers [5] found considerable quantities of noradrenalin and serotonin in a special system of neurons descending from the supraspinal centers in the dorsal fasciculi of the lateral columns of the spinal cord. Since massive accumulations of monoamines were found in the therminal nerve fibers, these workers concluded that they may be mediators of nervous excitation in this particular system of neurons. Other investigators [4, 13, 17] have shown that the dorsal fasciculi of the lateral columns of the spinal cord in fact contain descending fibers of inhibitory neurons, the cell bodies of which are located in the vaso-depressor region of the medulla. This observation led Carlsson and his collaborators to conclude that the system of monoaminergic neurons discovered by them fulfills an inhibitory role. Taking all these factors into consideration, we now claim that the effects of depression of the reflex reactions observed in the present experiments were due to activation of the inhibitory system of neurons by monoamines. This claim is supported by the results of experiments with dichloroisoproterenol, a preparation blocking the β-receptors, the structures with which the adrenergic mediators react in order to cause inhibitory reactions to develop. Intravenous injection of dichloroisoproterenol (5 mg/kg) led to a sharp increase in the tonic activity and in the intensity of the reflexes (Fig. 3). In other words, it produced effects opposite to those observed after injection of monoamines or substances increasing the concentration of their free forms.

The results of this investigation thus suggest that a practicable method of influencing the central regulation of the circulation by pharmacological means is by the use of drugs capable of interfering with monoamine metabolism in the central nervous system.

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