ROLE OF DESCENDING INHIBITION IN THE DEPRIMING EFFECT OF CATECHOLAMINES ON SYMPATHETIC TONE AND VASOMOTOR REFLEXES

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UDC 615.357.452.015.45:[612.89+612.18

Tonic activity and reflex discharges in the sympathetic nerves of the heart and kidneys in response to stimulation of afferent A and C fibers of the tibial and splanchnic nerves were recorded by an electroneurographic method. Experiments on anesthetized cats showed that injection of noradrenalin and adrenalin (200-300 μg) into the lateral and fourth ventricles and intravenous injection of DOPA (40 mg/kg) inhibit tonic activity and reflex discharges in the sympathetic nerves of the heart and kidneys, and also inhibit pressor reactions. The depriming effect of the catecholamines is strengthened considerably by decerebration but is not exhibited in spinal preparations. It was also shown that micro-injection of noradrenalin (0.1-5 μg) into the region of the gigantocellular nucleus and inferior olivary complex greatly potentiated the inhibitory influence of these structures on tonic activity and reflex discharges in the sympathetic nerves.

Previous investigations in the writer's laboratory have shown that monoamines (noradrenalin, adrenalin, and serotonin) and their precursors (DOPA, 5-hydroxytryptophan) inhibit tonic and reflex activity in sympathetic nerves and also vasomotor pressor reflexes [2, 3, 5, 7, 9].

Meanwhile, observations made by other workers [1, 6, 13, 16] indicate that catecholamines can activate some central structures responsible for the development of inhibitory processes.

On the basis of these facts it was decided to study the role of descending inhibition in the depriming effect of catecholamines and DOPA on tonic activity, reflex responses in sympathetic nerves, and vasomotor reflexes.

EXPERIMENTAL METHOD

Cats weighing 2.5-4 kg were anesthetized with urethane (600 mg/kg) and chloralose (40 mg/kg). After tracheotomy and vagotomy, the animals received a muscle relaxant (flaxedil) and were maintained on artificial respiration. A constant body temperature was maintained throughout the experiment. Tone of the sympathetic nervous system was assessed by electroneurographic recording of biopotentials in the central ends of the divided sympathetic nerves of the heart and kidneys. Changes in tonic activity and in reflex discharges evoked by electrical stimulation of afferent A and C fibers of the tibial or greater splanchnic nerves were recorded [8]. At the same time, the pressure in the femoral artery was recorded with an electromanometer and the EKG taken in standard lead II. Pressor responses were evoked by stimulation of the tibial and greater splanchnic nerves with square pulses (20-40 V, 1-2 msec, 1-4-40/sec). These various indices were recorded on an 8-channel polygraph ("Mingograf-81," Elema). Special series of experiments were performed on decerebrate (at the intercollicular level) and spinal (transection at the level C_1 and C_2) animals.

Laboratory of Pharmacology of the Cardiovascular System, Institute of Pharmacology and Chemotherapy, 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. 69, No. 3, pp. 65-69, March, 1970. Original article submitted June 2, 1969.

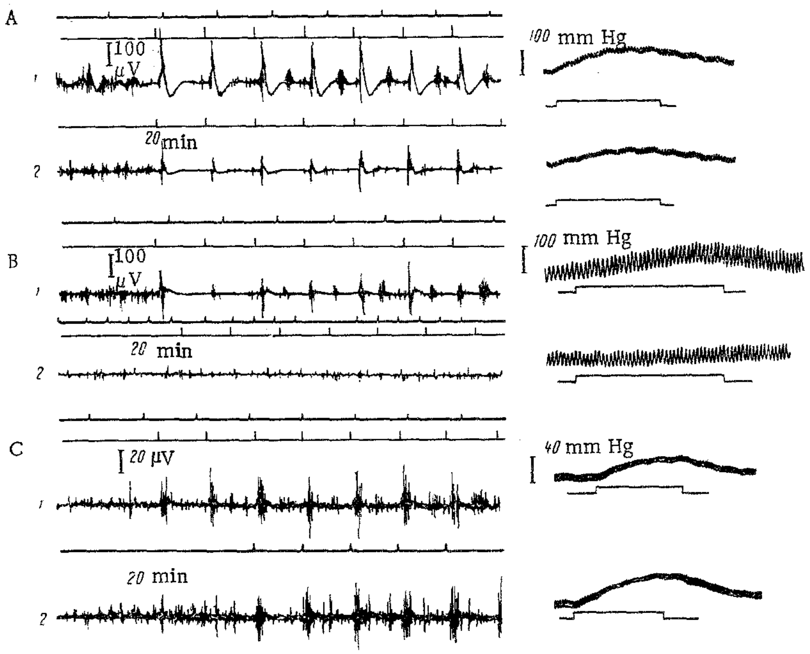

Fig. 1. Effect of noradrenalin (200 μg) on tonic and reflex activity in renal nerve and arterial pressure in intact (A), decerebrate (B), and spinal (C) animals. A: 1) on the left, tonic and reflex activity in renal nerve in response to stimulation of tibial nerve before injection of noradrenalin, on the right, pressor response of arterial pressure; 2) the same 20 min after injection of noradrenalin into lateral ventricle; B: 1) The same after decerebration and before injection of noradrenalin; 2) the same 20 min after injection of noradrenalin into fourth ventricle; C: 1) the same in spinal animal in response to stimulation of tibial nerve; 2) the same 20 min after injection of noradrenalin into spinal epidural space. From top to bottom: on the left, time marker 1 sec, marker of stimulation of tibial nerve (A and B) and greater splanchnic nerve (C), tonic and reflex activity in renal nerve; on the right, pressor responses of arterial pressure.

Noradrenalin and adrenalin were injected in doses of 200-300 μg into the fourth and lateral ventricles and also into the epidural space of the spinal cord. DOPA was injected intravenously in a dose of 40 mg/kg.

EXPERIMENTAL RESULTS AND DISCUSSION

To determine the relationship between the depriming effect of catecholamines on sympathetic tone and vasomotor reflexes and their action on structures of various parts of the nervous system a series of experiments was performed on intact animals, in which noradrenalin and adrenalin were injected into the fourth and lateral ventricles and also into the epidural space of the spinal cord.

After injection of noradrenalin in a dose of 300 μg into the fourth and lateral ventricles, inhibition of tonic activity and reflex discharges in the sympathetic nerves of the heart and kidneys in response to stimulation of afferent A and C fibers of somatic nerves was found to occur. In this case, the catecholamines showed no selective inhibitory effect on reflex discharges in sympathetic nerves evoked by stimulation of afferent C fibers, as is observed if these substances are given in doses of 50-100 μg [4]. Simultaneously with inhibition of tonic and reflex activity in the sympathetic nerves (Fig. 1A), the vasomotor reflexes were diminished (on the average by 66±2.2%).

After injection of noradrenalin into the epidural space of the spinal cord, on the other hand, an increase in tonic activity and reflex discharges was observed in the sympathetic nerves of the heart and kidneys. The intensity of the pressor vasomotor reflexes was increased. Comparison of the results of these series of experiments suggests that the depriming effect of catecholamines on sympathetic and vasomotor tone is associated with their action on supraspinal structures participating in the central regulation of the circulation.

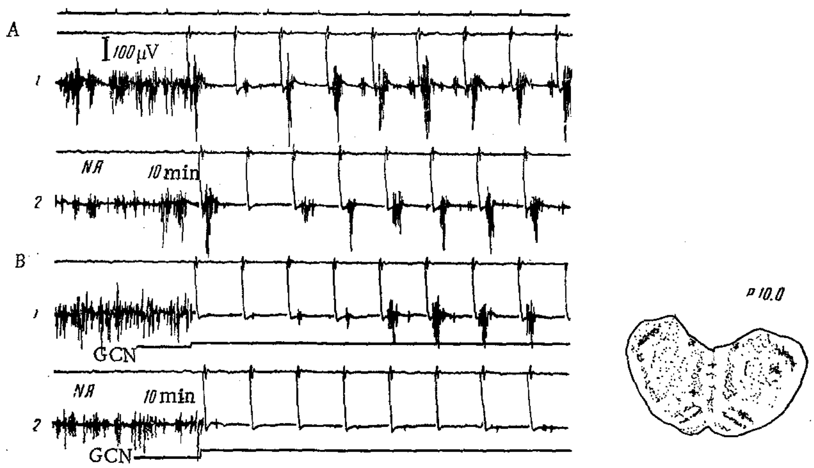

Fig. 2. Effect of noradrenalin (2.5 μg) on tonic and reflex activity in renal nerve during stimulation of tibial nerve and of gigantocellular nucleus. A: 1) Tonic and reflex activity in renal nerve in response to stimulation of tibial nerve before injection of noradrenalin; 2) the same 10 min after microinjection of noradrenalin into gigantocellular nucleus; B: 1) tonic and reflex activity in renal nerve in response to combined stimulation of tibial nerve and gigantocellular nucleus before injection of noradrenalin; 2) the same 10 min after microinjection of noradrenalin into gigantocellular nucleus. From top to bottom: time marker 1 sec, marker of stimulation of tibial nerve, tonic and reflex activity in renal nerve; GCN, marker of stimulation of gigantocellular nucleus; + indicates position of electrical stimulation and microinjection of noradrenalin on diagram.

To study the mechanisms responsible for the inhibitory effects of catecholamines and DOPA on sympathetic tone, experiments were carried out on decerebrate animals. These showed that the depriming effect of noradrenalin, adrenalin, and DOPA is substantially increased after decerebration. This effect was manifested as a stronger and more prolonged inhibition of tonic activity and reflex discharges in the sympathetic nerves compared with intact animals (Fig. 1B). Conversely, the results of experiments on spinal preparations demonstrated absence of inhibitory effects of catecholamines on vasomotor reflexes (Fig. 1C), in agreement with results obtained in the series of experiments in which catecholamines were injected into the epidural space of the spinal cord in intact animals.

The following conclusion can be drawn from analysis of these results. The development of the depriming effect of catecholamines and DOPA on sympathetic tone and vasomotor reflexes in experiments on intact animals and the absence of this effect after division of the spinal cord suggest that catecholamines cause activation of descending inhibition. This view is also supported by experimental results indicating potentiation of the depriming effect of catecholamines and DOPA in experiments on decerebrate animals. In the modern view, one of the brain systems responsible for descending reticulospinal inhibition is the bulbar ventromedial reticular formation [17], the functional activity of which is considerably increased after decerebration. It is possible, therefore, that the increase in the inhibitory effect of catecholamines on sympathetic and vasomotor tone after decerebration is due to activation of central structures of the bulbar ventromedial reticular formation. This view is supported by observations made by other workers [15, 16], who showed that by activating the ventromedial reticular formation, catecholamines promote the development of descending inhibition.

Particularly interesting observations were made by Coote and co-workers [11, 12] and Wang [18], who showed that electrical stimulation of the bulbar reticular formation inhibits reflexes effected through the sympathetic nervous system (vasomotor and psychogalvanic reflexes). In face of the histochemical data indicating that this part of the brain contains adrenergic neurons [14], it may be postulated that catecholamines have a functional role in the mechanism of descending inhibitory control over the segmental apparatus of the spinal cord. This applies, in particular, to vasomotor reflexes, whose arcs in the modern view are closed at the segmental level [10, 12].

This hypothesis was confirmed by the results of experiments in which structures of the ventromedial reticular formation were stimulated or in which catecholamines were injected directly into those structures. The aim of this series of experiments was to study the effect of noradrenalin on inhibition of reflex discharges from afferent A and C fibers in the sympathetic nerves of the kidney in response to stimulation of the gigantocellular nucleus. For this purpose, by means of a stereotaxic apparatus, a hollow electrode was inserted into the gigantocellular nucleus. Unipolar stimulation with square pulses (3-10 V, 0.1-1 msec, 20-40/sec) was used. In response to combined stimulation of the gigantocellular nucleus and of one of the somatic nerves, inhibition of tonic activity and reflex discharge in the sympathetic nerves of the kidney was observed. The duration and intensity of this inhibition depended on the parameters of stimulation of the structures of the ventromedial reticular formation. Under these conditions, microinjection of noradrenalin into these structures in doses of 0.5-5 μg led after 2-5 min to some decrease in activity and to a marked increase in the duration and intensity of inhibition of reflex discharges in the sympathetic nerves of the kidney (Fig 2).

It can be concluded from these results that catecholamines play a role in the descending control of the segmental apparatus of the spinal cord, and especially in the control of vasomotor reflexes. Exogenous catecholamines activate these processes, thereby exerting an inhibitory effect on tonic and reflex activity in the sympathetic nerves and also on vasomotor reactions.

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