ROLE OF CENTRAL ADRENERGIC PROCESSES IN THE MECHANISM OF ACTION OF GLYCERYL TRINITRATE ON SYMPATHETIC TONE AND VASOMOTOR REFLEXES

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Glyceryl trinitrate (0.5-1 mg/kg) lowers the tonic activity and depresses reflex discharges in the central ends of divided sympathetic nerves to the heart and kidneys and also reduces the intensity of pressor reactions of the arterial pressure. A similar effect is produced by monoamides and their precursors. This action of glyceryl trinitrate does not appear at a time of exhaustion of labile reserves of monoamines in the brain tissue by reserpine. Meanwhile the depressant action of glyceryl trinitrate does not coincide in time with the decrease in total content of catecholamines in the brain tissue and is accompanied by the appearance of free noradrenalin in the cerebrospinal fluid. Division of the brain stem between the superior and inferior colliculi causes an increase, and spinalization a sharp decrease in the action of glyceryl trinitrate. These facts, together with the results of experiments with direct stimulation of bulbar structures of the brain and injection of microdoses of catecholamines and DOPA, suggest that an important role in the depressant action of glyceryl trinitrate on sympathetic tone is played by an increase (caused by free monoamines) in the intensity of descending reticulo-spinal inhibition, which is effected through structures of the ventromedial reticular formation.

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The writers have previously shown that glyceryl trinitrate can depress the constrictor reflex reactions of the coronary vessels and pressor vasomotor reflexes, and that this effect is due to the action of glyceryl trinitrate on centers for regulation of the circulation [2, 3]. After the comparison of these findings with those described by other investigators, showing that glyceryl trinitrate does not increase the blood flow in the vessels of the heart [7, 9], it was postulated that its clinical efficacy is due to its central action.

The object of the present investigation was to study the mechanism of action of glyceryl trinitrate on the central regulation of vascular tone.

EXPERIMENTAL METHOD

Experiments were carried out on cats anesthetized with urethane (200-300 mg/kg) and chloralose (20-50 mg/kg). Altogether 78 experiments were performed. The method of electroneurographic recording of tonic and reflex activity in the central ends of the divided sympathetic nerves to the heart and kidney was used. Reflex discharges generated in response to electrical stimulation of the central end of the divided tibial nerve, with differentiation of the responses between impulses in afferent fibers of the A- and C-groups [6], were recorded. The arterial pressure and ECG were recorded at the same time. To determine whether the action of nitroglycerine is dependent on changes in activity of particular systems of the brain, special series of experiments were carried out on decerebrate and spinal animals. Reflex responses and

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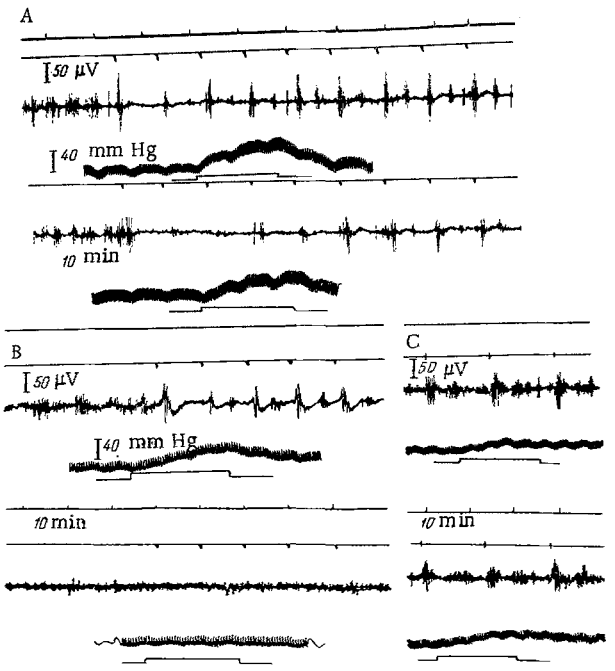

Fig. 1. Effect of glyceryl trinitrate (1 mg/kg) on tonic activity in inferior cardiac and renal nerves, reflex discharges, and vasomotor reflexes arising in response to stimulation of afferent fibers of tibial and greater splanchnic nerves. A) Intact animal; B) decerebrate animal; C) spinal preparation. From top to bottom: time marker 1 sec, marker of stimulation of tibial (A, B) and splanchnic nerves (C), tonic activity and reflex A- and C-discharges in inferior cardiac (A) and renal nerves (B, C), pressor vasomotor reflex, marker of stimulation of tibial and splanchnic nerves; bottom curves recorded 10 min after injection of glyceryl trinitrate.

also changes in sympathetic and vasomotor tone were studied during direct stimulation of structures of the bulbar ventromedial reticular formation (gigantocellular nucleus, inferior olivary complex).

To determine the role of adrenergic processes in the observed effects of glyceryl trinitrate, the dynamics of its effect on sympathetic tone was compared with changes in the content of catecholamines in the brain tissue and cerebrospinal fluid (CSF). The noradrenalin content was determined spectrofluorometrically. Glyceryl trinitrate was injected intravenously in doses of 0.5-1 mg/kg.

EXPERIMENTAL RESULTS

The experiments (15) showed that glyceryl trinitrate depresses spontaneous bioelectrical activity and reflex discharges in the inferior cardiac and renal nerves. In most experiments it had a selective action on reflex discharges arising in response to stimulation of afferent C-fibers, along which pain impulses are transmitted to the central nervous system. Simultaneously with reflex responses in the sympathetic nerves, pressor vasomotor reflexes were inhibited. The duration of this effect was 15-20 min (Fig. 1A).

As the previous investigations showed, changes of a similar character in reflex discharges also arose under the influence of monoamines and their precursors (DOPA and 5-hydroxytryptophan) and also of substances capable of liberating monoamines from their tissue depots: reserpine, analgesics, monoamine oxidase inhibitors [1, 4, 5, 8].

On the basis of these results it was postulated that adrenergic mechanisms may also participate in the mechanism of action of glyceryl trinitrate on centers for regulation of the circulation. To test this hypothesis, in a special series of experiments the action of glyceryl trinitrate on vasomotor reflexes was studied 4 h after injection of reserpine. Judging from the findings of Haggendal and Lindqvist [10], it is at this period that reserpine causes complete exhaustion of the reserves of the labile fraction of monoamines.

It was previously shown that repeated injections of reserpine or other substances affecting sympathetic tone and vasomotor reflexes through liberation of monoamines are ineffective at this time [8]. The experiments showed that glyceryl trinitrate, if injected 4 h after reserpine (1 mg/kg), likewise did not change the intensity of the vasomotor reflexes. Different results were obtained 24 h after injection of reserpine, i.e., at a time when, despite the fact that the total level of monoamines was at its minimum, their labile reserves had been restored. At this period glyceryl trinitrate, like other substances whose action is due to an increase in the content of functionally active forms of monoamines, once again caused depression of the vasomotor reflexes (Fig. 2). The results of these experiments suggested that the effects of glyceryl trinitrate are indirect and are mediated through free, functionally active forms of monoamines. This was confirmed by special experiments to determine noradrenalin in the brain tissue and CSF. It was found that 5-10 min after injection of glyceryl trinitrate, simultaneously with depression of sympathetic tone and vasomotor reflexes, noradrenalin (0.015-0.19 μg/ml) appeared in the CSF, although virtually absent from it under normal conditions. At this time, i.e., 5-10 min after injection of glyceryl trinitrate, no significant changes could

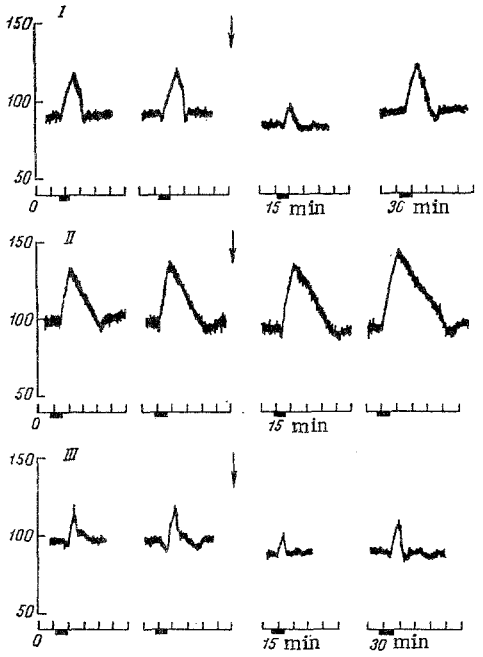

Fig. 2. Effect of glyceryl trinitrate (1 mg/kg) on pressor response of arterial pressure to stimulation of tibial nerve against background of reserpine (1 mg/kg). I) Effect of glyceryl trinitrate on pressor response of arterial pressure (control); II) absence of effect of glyceryl trinitrate 4 h after injection of reserpine; III) effect of glyceryl trinitrate on pressor response of arterial pressure 24 h after injection of reserpine. From top to bottom (in I, II, III): arterial pressure, time marker 15 sec; marker of stimulation of tibial nerve. From left to right: first two curves—before injection of glyceryl trinitrate; arrow indicates time of injection of glyceryl trinitrate; 3rd and 4th curves—15 and 30 min after injection (1 mg/kg).

be found in the noradrenalin content in the tissues of various parts of the brain (hypothalamus, medulla) or in the thoracic portions of the spinal cord. However, 20 min after injection, a marked decrease in the noradrenalin content was observed in the brain tissue. The lowest content of noradrenalin in the brain stem was found 30 min after injection of glyceryl trinitrate (0.24 ± 0.04 μg/g); control 0.55 ± 0.077 μg/g. After 2 h a tendency toward recovery was observed; after 4 h the noradrenalin content was about the same as initially. Differences between the degree of decrease in noradrenalin in the different parts of the brain are not statistically significant.

The experiments described above thus revealed a number of important facts, namely; 1) correlation in time between the depressant effect of glyceryl trinitrate on sympathetic tone and the appearance of free noradrenalin in the CSF; 2) absence of connection between this effect and the decrease in total content of monoamines in the brain tissue and, finally, 3) absence of effect of glyceryl trinitrate when reserves of monoamines of the labile fraction are exhausted by reserpine. These facts convincingly prove that the depressant action of glyceryl trinitrate on electrical activity in the sympathetic nerves and on vasomotor reflexes is due to changes produced by this compound in adrenergic processes in the central nervous system, and is effected evidently through an increase in the content of free, functionally active forms of monoamines liberated from the labile reserve of granules.

To investigate the participation of different systems of the brain in the mechanism of the depressant effect of glyceryl trinitrate on sympathetic tone several series of experiments were carried out. These showed that after division of the brain stem between the superior and inferior colliculi, the depression of sympathetic tone and vasomotor reflexes by glyceryl trinitrate is greatly increased (Fig. 1B) compared with that observed in experiments on intact animals. In experiments on spinal preparations (division at the level of the upper cervical segments), on the other hand, this effect is practically absent (Fig. 1C). The effects of glyceryl trinitrate described above (like those in experiments on intact animals) are similar to effects produced by catecholamines and DOPA.

In a special series of experiments with direct stimulation of deep bulbar structures in the region of the obex (gigantocellular nucleus, inferior olivary complex) the effect of catecholamines and DOPA on the intensity of inhibition of tonic activity and reflex discharges in sympathetic nerves was studied in response to simultaneous stimulation of afferent A- and C-fibers of the tibial nerve (30-40 V, 1-4-20-30 cm/sec, 1 msec) and of the above-mentioned structures of the ventromedial reticular formation (3-7 V, 20-30 cm/sec, 0.1-0.7 msec).

To begin with it was found that microinjections (0.25-5 μg in a volume of 0.5-5 μliters) of catecholamines and DOPA directly into these brain structures led to inhibition of sympathetic activity and of reflex discharges. It was also discovered that these substances strongly increase the inhibition of spontaneous and reflex activity in the sympathetic nerves occurring during stimulation of structures of the ventromedial reticular formation.

The results described above suggest that an important role in the mechanism of the depressant effect of glyceryl trinitrate on vasomotor reflexes is played by stimulation by free monoamines of processes of descending reticulospinal inhibition, which are effected through structures of the ventromedial reticular formation [11-13].

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