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ACTION OF TYRAMINE ON THE SPINAL AFFERENT LINK OF PRESSOR REFLEXES

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Pressor responses of the blood pressure (BP) to electrical stimulation of somatic nerves can be largely suppressed by noradrenalin (NA), applied directly to the region of entry of the stimulated afferents into the spinal cord [2]. Pressor reflexes developing in response to synchronized volleys in somatic Aδ- and C-afferents are the circulatory component of nociceptive responses [3], and this effect of NA can therefore be connected with inhibition both of responses of dorsal horn neurons to nociceptive stimulation when applied iontophoretically close to these neurons [4, 5] and of motor components of nociceptive responses if injected intrathecally [6, 7, 10]. These effects are explained by the action of NA on those adrenergic dorsal horn neurons of the spinal cord on which axons of noradrenergic brainstem neurons, inhibiting transmission of nociceptive impulses at the segmental level, terminate. Thus inhibition of pressor reflexes by NA can be regarded conjecturally as the result of imitation of enhancement of activity of noradrenergic antinociceptive systems. The validity of this hypotheses is increased if it can be shown that this same effect is induced by liberation of NA from axon terminals of noradrenergic neurons. Tyramine has the ability to release NA from these terminals [1].

The aim of this investigation was to determine changes taking place in pressor reflexes to volleys of spinal afferents on application of tyramine to the region of entry of these afferents into the spinal cord, i.e., as a result of release of endogenous NA close to adrenergic neurons composing the sensory systems of the spinal cord. Just as previously [2], the name pressor and depressor components of responses (PCR and DCR respectively) is given not only to the corresponding components of mixed, depressor-pressor responses, but also to responses in one direction, i.e., purely pressor and purely depressor responses.

EXPERIMENTAL METHODS

Experiments were carried out on cats weighing not less than 2 kg, anesthetized (intravenously) with chloralose (20-30 mg/kg) and urethane (330-500 mg/kg). After tracheotomy,

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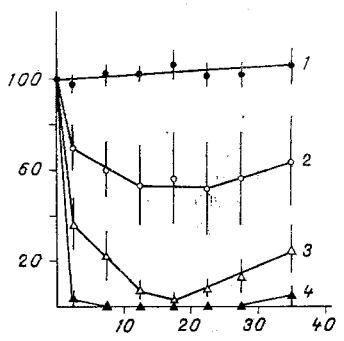

Fig. 1

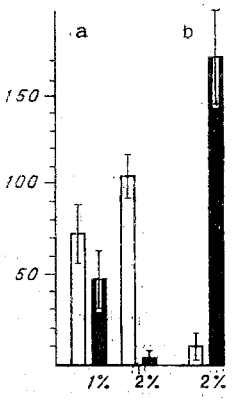

Fig. 2

Fig. 1. Dependence of amplitude of pressor reflexes evoked by stimulation of A + C-afferents of RN (15 V, 1 msec, 1-4 Hz) on concentration and duration of action of tyramine in region of segments C6-T1. Abscissa, time after application of tyramine (in min); ordinate, average values of PCR for groups of experiments (in %). Amplitude of PCR before application of tyramine taken as 100% in each experiment, amplitudes of PCR to subsequent stimulation calculated as percentages of that value, and then averaged for groups of experiments in which tyramine was used in the same concentration. 1) Control (amplitudes of PCR after application of Ringer's solution); 2-4) amplitudes of PCR after application of tyramine in the form of 1, 2, and 4% solutions respectively. Average amplitudes of PCR for corresponding groups before application, their mean errors (in mm Hg), and number of experiments (n) in each groups: 18.0 ± 1.5, n = 11; 15.2 ± 3.2, n = 5; 15.3 ± 2.2, n = 9, 16.7 ± 3.7, n = 13.

Fig. 2. Action of tyramine on pressor components of responses of BP to stimulation of A + C-afferents of TN (unshaded columns) and of RN (black columns). Ordinate, mean amplitudes of PCR after application of tyramine (in % of their values before application); a) effect of application of tyramine to segments C6-T1 (1% tyramine solution – five experiments, 2% solution – seven experiments). Amplitudes of PCR measured in period of maximal depression of reflexes to stimulation of RN. Change in responses to stimulation of TN not statistically significant; b) effect of application of tyramine to segments L4-S1 (2% solution – six experiments). Amplitudes of PCR measured in periods of maximal suppression of reflexes to stimulation TN. Changes in responses are statistically significant.

connection of the common carotid artery to an electromanometer, immobilization of the animals with succinylcholine (150 μg/kg/min, intravenously), and application of artificial respiration, laminectomy was performed in the region of segments C6-T1 (15 cats) or L4-S1 (seven cats) and the dura was opened. The radial or tibial nerve (RN and TN respectively) was stimulated electrically by square pulses. Reflex changes in BP began to be recorded not less than 1 h after completion of the preliminary operations. Once the presence of pressor responses of stable magnitude to infrequent (1-4 Hz) stimulation of A + C-afferents (15 V, 1 msec) or to more frequent (4-10 Hz) stimulation of A afferents (3 V, 0.1 msec) had been established, tyramine was applied to the spinal cord, i.e., the cotton soaked in Ringer's solution covering the exposed part of the spinal cord was replaced by a fresh piece of cotton soaked in tyramine (hydrochloride) solution (1, 2, or 4%), and 1-2 min later the stimulation began again, using the same parameters as when control reflexes were recorded. After 20-40 min the cotton soaked with tyramine was again replaced by cotton soaked in Ringer's solution.

Full details of the technique were described in [2]. In some animals the application of tyramine was repeated after the responses were restored. From now on, the series of stimulations after each application will be called experimental.

EXPERIMENTAL RESULTS

Application of tyramine solution to the dorsal surface of segments C6-T1, i.e., in the region of entry of fibers from RN into the spinal cord, led regularly to inhibition of PCR evoked by stimulation of A + C-afferents of that nerve; both the depth and the rate of development of the effect increased with an increase in the tyramine concentration (Fig. 1). In 12 such experiments reflexes to stimuation of A + C-afferents of RN in the initial state were purely pressor, and in six of them the action of tyramine led not only to depression or total suppression of PCR, but also to the appearance of considerable (by as much as −12 mm Hg) DCR, i.e., a qualitative change in the reflexes.

Pressor responses to stimulation of only the A-fibers of RN developed in five animals. Application of tyramine as 2% solution to segments C6-T1 (three experiments) led to total suppression of these responses, whereas 1% tyramine caused only a significant decrease of the responses (by 70% of the initial value, one experiment), or their total suppression also (two experiments). In four of these animals application of tyramine caused not only suppression of PCR, but also the appearance of DCR, the amplitude of which reached 6-16 mm Hg.

The amplitude of PCR to stimulation of A + C-afferents of TN in the initial state was 20-36 mm Hg. The action of a 1% solution of tyramine through the dorsal surface of segments L4-S1 of the spinal cord reduced these responses by 70-100% of their original value (three experiments), whereas a 2% solution completely suppressed them in five experiments and reduced them in two experiments by 78 and 64% respectively.

This effect of tyramine, namely suppression of the excitatory action of Aδ and C afferents of somatic nerves on sympathetic preganglionic neurons (and, correspondingly, the ability of these volleys to induce pressor responses of BP) with preservation of the inhibitory action of these same volleys, as a result of which DCR also appear, is in full agreement with the effect of NA observed by the writers previously [2]. Consequently, the changes in the reflexes examined above in response to application of tyramine to the region of entry of the stimulated afferents into the spinal cord may be due to the ability of this substance to release NA from axon terminals of noradrenergic neurons, and to the action of the latter on adrenergic neurons of the sensory systems of the spinal cord. In turn, suppression of pressor reflexes both by tyramine and by NA, when applied directly to the region of entry of the stimulated afferents into the spinal cord, can evidently be regarded in fact as the segment of imitation of potentiation of activity of noradrenergic antinociceptive systems.

However, unlike NA, the action of tyramine could not always be reduced to depression of PCR alone, and was not always confined to local effects, i.e., to intervention in processing of afferent stimuli purely in the region of application.

On application of 4% tyramine solution to segments C6-T1, suppression of PCR induced by stimulation of A + C fibers of RN was accompanied by the appearance of DCR, but only during the first minutes of action of the substance, and later the response of BP disappeared completely. After removal of tyramine from the surface of the spinal cord DCR began to appear, the reflexes then became depressor-pressor in type, and not until later did they become purely pressor again. Application of tyramine as a 2% solution to segments C6-T1 led to suppression of DCR to stimulation of A + C fibers of RN in four of nine experiments.

Application of tyramine to segments C6-T1 also led to changes in responses of BP to stimulation of TN. For instance, a 4% solution of tyramine, acting through these segments, completely suppressed the responses of BP to stimulation of TN in one animal, but caused no significant changes in two others. On application of a 2% solution of tyramine to segments C6-T1, in two (of seven) cats PCR to stimulation of A + C afferents of TN, after a brief (for 8-15 min) and small decrase, increased to 143% of their original alue. In one cat, on the other hand, a prolonged decrease of PCR to 50% of their initial value was observed, whereas in the other four cats these responses showed no significant change. Finally, aplication of 1% tyramine solution to these same segments caused an increase in PCR to stimulation of TN in two cats, but a sharp decrease in another three cats. Consquently, the absence of statistically significant changes in average values of reflexes to stimulation of A + C afferents of TN in response to application of tyramine to segments C6-T1 (averaging for experiments in

which tyramine was applied in the same concentration, as a 1% or 2% soltuion; Fig. 2a) was thus due to the opposite character of changes in the reflexes in different animals, and not to their absence. Depression of PCR to stimulation of TN, caused by application of tyramine to segments C6-T1, was accompanied as a rule by an increase in DCR or their appearance de novo.

Application of tyramine to segments L4-S1 led not only to suppression of PCR evoked by stimulation of TN, but also to enhancement of PCR evoked by stimulation of RN. In the period of maximal suppression of PCR to stimulation of TN, caused by the action of a 2% tyramine solution on these segments, the amplitude of PCR to stimulation of the A + C fibers of RN was 171 ± 25.6% of the initial value (Fig. 2b; results of six experiments, the increase iN PCR is statistically significant ($P < 0.01$).

Application of tyramine to the cervical-thoracic and lumbo-sacral segments of the spinal cord was thus accompanied not only by local depression of the ability of impulses traveling along somatic afferents to evoke pressor responses of BP, but also by "distant" effects. In response to application of tyramine to segments L4-S1, distant effects were manifested only as enhancement of pressor responses to stimulation of RN, whereas application of tyramine to segments C6-T1 could lead to both enhancement and suppression of pressor responses to stimulation of TN. Further research is required to shed light on the concrete mechanisms lying at the basis of the "distant" action of tyramine, and also its suppression of transmission, not only of excitatory, but also of inhibitory influences of volleys in spinal afferents to sympathetic preganglionic neurons. It is possible that these features of the action of tyramine, distinguishing it from that of NA, are due to the fact that tyramine liberates not only NA from axons of noradrenergic neurons, but also serotonin [8], which can also modify transmission of nociceptive stimuli along the sensory systems of the spinal cord [9, 11, 12].

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