INHIBITION OF THE SPINAL EFFERENT COMPONENT OF PRESSOR REFLEXES BY NORADRENALIN

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Noradrenergic neurons, whose bodies are located in the brain stem and whose axon terminals are found in the dorsal horns of the spinal cord, control the processing of nociceptive signals in the spinal cord [6, 8, 10]. This view is based, in particular, on data showing inhibition by noradrenalin (NA) of responses of dorsal horn neurons to intensive thermal or mechanical stimulation of the skin [3, 4] and the antinociceptive action of NA and its α-agonists when injected beneath the spinal meninges [6, 8, 9]. This type of action has been demonstrated by the lengthening of the latent period or elevation of the threshold of motor responses to nociceptive stimulation of the tail, back, or limbs. It is not known how activation of adrenergic structures of the dorsal horns of the spinal cord affects autonomic and, in particular, circulatory components of nociceptive reactions. A reflex rise of arterial pressure (BP) and tachycardia are considered to be an adequate circulatory component of responses to nociceptive stimulation [2].

The aim of this investigation was to study how changes in pressor reflexes evoked in cats by volleys of impulses in spinal afferents are changed by the action of NA on the inward neuronal systems of the spinal cord.

EXPERIMENTAL METHOD

Cats weighing not less than 2 kg were induced with ether and anesthetized with chloralose (20-30 mg/kg) and urethane (330-500 mg/kg) intravenously. After tracheotomy and connection of the common carotid artery to an electromanometer, the animals were immobilized with succinylcholine (continuous injection of 150 μg/kg/min intravenously), and artificially ventilated, at a rate corresponding to the animal's weight [5]. The rectal temperature was maintained automatically between 36 and 38°C. To record BP, a BMT-503 cardiomonitor (East Germany) and KSP-4 automatic writer were used. NA was applied directly to the dorsal surface of the segments into which the afferent fibers of the nerves chosen for stimulation — the radial (RN) or tibial (TN) — enter the spinal cord. For this purpose, after laminectomy the dura mater was opened in the region of segments C_6-T_1 (18 cats) or L_4-S_1 (4 cats). The exposed brain was covered with a thin layer of cotton, soaked in Ringer's solution, and the whole operative field was covered with a cotton pad soaked with the same solution, covered in turn by polyethylene film. RN was isolated near the wrist joint and TN near the tarsal joint. The nerves were subjected to bipolar stimulation from an ESL-2 stimulator. Stimulation continued until the response had completely developed (usually for 20-40 sec). The interval between successive stimulations was 2-3 min. Recording of reflex changes of BP began not less than 1 h after completion of all the preliminary operations. The presence of pressor responses to infrequent (1-2 Hz) stimulation of A + C-afferents (15 V, 1 msec) or more frequent (4-10 Hz) stimulation of A-afferents (3 V, 0.1 msec) was first established. If the magnitude of these control reflexes was sufficiently stable during repetition of stimulation, the cotton soaked in Ringer's solution was removed from the spinal cord, the surface of which was dried, and a fresh layer of cotton soaked in a solution of NA hydrotartrate was applied. This was arranged so that it covered the region of entry of the dorsal roots and the posterolateral funiculi along the whole length of

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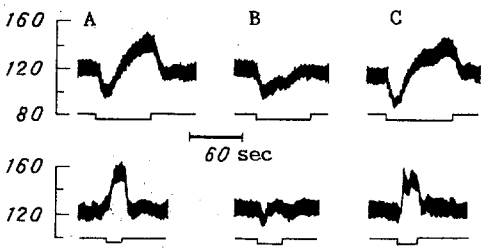

Fig. 1

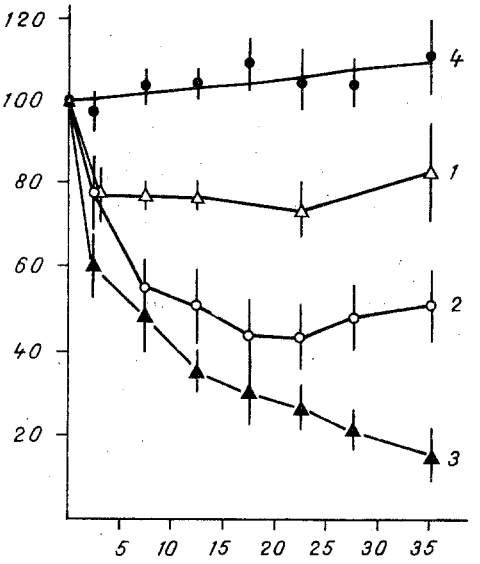

Fig. 2

Fig. 1. Changes in reflex responses of BP to stimulation of radial nerve on application of NA to segments C_6-T_1. Top traces show responses to stimulation of A + C-afferents (15 V, 1 msec, 2 Hz), application of 0.2% Na solution; bottom traces show responses to stimulation of A-afferents (3 V, 0.1 msec, 4 Hz), application of 0.1% solution of NA. A) control, B) 30 min (top trace) and 25 min (bottom trace) after application of NA; C) 2.5 h after removal of NA from surface of spinal cord. On left — BP (in mm Hg). Marker of stimulation shown below each trace.

Fig. 2. Dependence of magnitude of PCR on duration of action of NA. Abscissa, time after application (in min); ordinate, average values of PCR (in percent) for groups of experiments. Stimulation of A + C-afferents of radial nerve (15 V, 1 msec, 1 Hz). Application of NA to segments C_6-T_1: 1) 0.05% solution (4 experiments), 2) 0.1% solution (11 experiments), 3) 0.2% solution (7 experiments), 4) sham application (11 experiments). Average values of PCR for corresponding groups of experiments before application and their mean errors 13.0 ± 2.4, 18.0 ± 1.5, 16.4 ± 1.6, and 18.8 ± 2.7 mm Hg, respectively. Value of PCR before application taken as 100 in each experiment; values of PCR to subsequent stimulations calculated in percentages of this value, and results averaged for groups of experiments.

the exposed part of the spinal cord. In the case of segments C_6-T_1 the layer of cotton usually absorbed 0.4-0.6 ml of the solution, whereas in the case of segments L_4-S_1 it absorbed 0.8-1.6 ml. The operative field was then covered with film again, and the stimulation began to be repeated after 1-2 min, using the same parameters of stimulation as when the control reflexes were recorded. After 20-40 min the cotton soaked in NA was replaced by cotton soaked in Ringer's solution. After restoration of the responses, application of NA was repeated in some animals. Later in this description the series of stimulations after each application will be called an experiment.

EXPERIMENTAL RESULTS

At different stages of the experiment responses of BP to stimulation of RN or TN were pressor, depressor, or mixed — depressor-pressor (Fig. 1). The pressor and depressor components of the reflexes (PCR and DCR, respectively) will be the names given not only to the corresponding components of mixed reflexes, but also to unidirectional reflexes (pressor (PCR) and depressor (DPR).

Application of a 0.05-0.2% solution of NA to the dorsal surface of segments C_6-T_1 of the spinal cord regularly caused either diminution or complete disappearance of PCR evoked both by combined stimulation of A- and C-afferents of RN and by stimulation of A-afferents of this nerve only (Fig. 1).

The action of NA on reflexes evoked by stimulation of A + C-afferents of RN with a frequency of 1 Hz (Fig. 2) was studied in 23 experiments (15 animals). After application of a

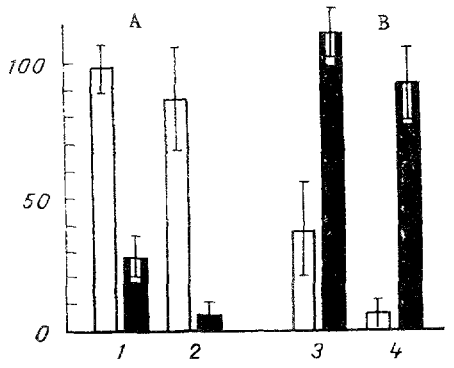

Fig. 3. Action of NA on pressor components of responses of BP to stimulation of TN (unshaded columns) and RN (black columns). Ordinate, mean values of PCR after application of 0.1% solution of NA to segments C_6-T_1 (A) and L_4-S_1 (B) (in percent of initial value). 1, 3) magnitudes of PCR to stimulation of A + C-fibers with frequency of 1-2 Hz (1 — data of 12 experiments, 3 — data of 3 experiments), 2, 4) values of PCR to stimulation of A-fibers with a frequency of 4-10 Hz (2 — data of 4 experiments, 4 — data of 4 experiments).

0.2% solution of NA considerable depression of PCR took place during the first 5 min, and the maximal effect was usually observed between the 10th and 40th minutes of application. In 5 of 7 experiments the depression was complete, and only in 2 experiments was PCR reduced by 60 and 64% of their initial value, respectively. After the end of NA application in this concentration PCR were restored usually extremely slowly — in the course of 2-4 h. NA, in the form of a 0.1 solution, depressed PCR more slowly; total suppression was observed, moreover, in only 3 of the 12 experiments, and in the rest the maximal decrease of PCR was 30-83% of its initial magnitude. NA, in the form of a 0.05% solution, depressed PCR by only 20-50% of its initial magnitude, and in 3 of 4 experiments they recovered to 80-100% during the application. The effect of sham applications — replacement of the cotton with Ringer's solution covering the spinal cord by similar cotton soaked in the same solution — led to a small and irregular reduction of the reflexes during the first 5 min. The course of the corresponding averaged curve reflects the tendency for PCR to increase with time, possibly due both to gradual weakening of the anesthesia [2] and to the facilitatory action of repeated stimulations, inducing pressor reflexes [1, 7].

After laminectomy at the level of segments C_6-T_1, pressor responses of BP to stimulation of the A-afferents of RN were observed in only 5 animals: in the remaining 13 cats reflexes of BP to stimulation of this kind either were absent or were depressor. During the first 10-20 min after application of the 0.1% solution of NA to segments C_6-T_1, the PCR were completely suppressed.

Besides depression of PCR, application of NA to segments C_6-T_1 frequently induced qualitative changes in the responses of BP to stimulation of RN: If initially the responses were depressor-pressor, during depression and suppression of PCR the magnitude of DCR as a rule was not reduced (15 experiments), but if initially the responses were purely pressor, the DCR could appear after application of NA (16 experiments) and as a result, in 10 experiments responses were converted from depressor-pressor or pressor only into depressor (Fig. 1). Consequently, depression of PCR which was found in these experiments was connected with changes in the processing of afferent signals in the neuronal system of the dorsal horns of the spinal cord, as a result of which the transmission of excitatory influences of these signals to sympathetic preganglionic neurons was weakened, but the transmission of their inhibitory influences was preserved.

However, was depression of PCR due purely to the local action of NA, i.e., to inhibition of transmission of excitatory afferent impulses only along systems of neurons located in the region of application, or was it connected with the more general effect of NA, as a result of which sympathetic preganglionic neurons ceased to respond by excitation to impulses in all spinal afferents?

To answer these questions, RN and TN were stimulated alternately in 20 animals, and NA was applied either as before to segments C_6-T_1 or to segments L_4-S_1. It must be pointed out

at once that on application of NA to segments L_4-S_1 its action on reflexes evoked by stimulation of TN did not differ in principle from its action on reflexes from RN, examined in detail above, on application to segments C_6-T_1. Comparison of the mean values of PCR for these experiments to identical stimulation of the same nerve (RN or TN) before the action of NA and at the time of maximal development of its effect (Fig. 3) shows that on application of NA to segments C_6-T_1 the magnitude of PCR evoked by stimulation of TN did not change statistically significantly, whereas on application of NA to segments L_4-S_1 PCR to stimulation of RN did not change statistically significantly. Consequently, under these experimental conditions depression of PCR to volleys of spinal afferents is in fact due to a local change in the processing of afferent signals.

We do not know how the NA concentration falls as it penetrates into the spinal cord, or what concentration of NA really acts under these experimental conditions. However, it may be noted that release of endogenous NA in the region of the dorsal horns of the spinal cord also leads to depression of PCR induced by volleys of impulses in spinal afferents, as the writers have shown.

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EFFECT OF DELTA-SLEEP PEPTIDE ON PARASYMPATHETIC REGULATION OF THE HEART RATE

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To restore normal sleep in patients with various sleep disturbances, delta-sleep peptide (DSP) has begun to be used in recent years [7, 8]. Meanwhile, as experimental studies of this peptide have shown, it has a marked prophylactic action in negative emotional states [1, 4]. DSP can therefore be used in clinical practice for the prevention and treatment of stress. However, its effect on various functional systems and, in particular, on the cardiovascular system is not yet clear, although there is information to show that DSP can slow the heart and respiration rates and reduce oxygen consumption in unrestrained animals [2].

The aim of this investigation was to study the effect of DSP on parasympathetic regulation of cardiac activity.

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