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EFFECT OF A SPIRAL PAIN SYNDROME ON REFLEX PAIN EVOKED BY NOCICEPTIVE THERMAL STIMULATION

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A difficult and neglected aspect of pain and analgesia is interaction between the nociceptive (NS) and antinociceptive (ANS) systems. It has now been shown that nociceptive impulsation at different levels of transmission is regulated through activation of ANS. Activation of the structures of ANS by electrical stimulation [5], by application of drugs to various zones of ANS [7], and by the creation of a generator of pathologically enhanced excitation (GPEE) in the key structures of this system [1] can depress pain of varied genesis. The mechanism of interaction between ANS and NS is not unidirectional. Although much research is currently in progress, mainly to study one aspect of this phenomenon, namely the regulatory effect of ANS on pain, there are isolated facts which indicate that pain of one type can contribute to manifestation of the antinociceptive effect against pain of another type. Cases when a pain syndrome has been abolished by additional nociceptive stimulation are known in clinical practice [4]. It has been shown that after nociceptive electrical stimulation of an animal's limbs the latent period of response tested by the hotplate method and the tail withdrawal test is increased [8]. These facts suggest that interaction between ANS and NS may lie at the basis of phenomenon such as activation or inactivation of ANS and regulation of its activity.

The aim of this investigation was to study the effect of a pain syndrome of spinal origin on reflex pain arising in rats to nociceptive thermal stimulation, and also to study neuronal activity of a key structure of ANS, the dorsal nucleus raphe, during development of the pain syndrome.

EXPERIMENTAL METHOD

Experiments were carried out on male and female Wister rats weighing 200-250 g. An experimental model of a spinal pain syndrome was created by forming a GPEE in the posterior horns of the lumbosacral segments of the spinal cord with the aid of penicillin [1]. An agar wafer measuring 8 × 3 × 1.5 mm, containing penicillin in a concentration of 25 U/mm^3, was applied to the dorsal surface of the lumbosacral segment of the spinal cord on the right side [2, 3]. The pain response to the thermal stimulation was studied by the hotplate test. The latent period (LP) of the complete pain response of the rat, placed on a hotplate (55 ± 0.5°C) was determined. Spontaneous unit activity in the dorsal nucleus raphe (AP 5.8-6.0 mm, LD 0.2-0.2 mm, H 5.5-6.5 mm according to the atlas [6]) was investigated extracellularly by means of glass microelectrodes filled with 2.5 M NaCl solution, before and during development of the pain syndrome. The results were subjected to statistical analysis by nonparametric tests and by Student's test.

EXPERIMENTAL RESULTS

Determination of LP of the animal's complete pain response to nociceptive thermal stimulation revealed a statistically significant increase in its duration both during development of the spinal pain syndrome induced by creation of the GPEE in the dorsal horns of the spinal

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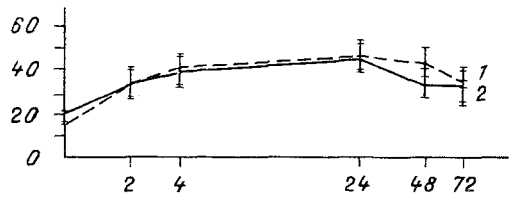

Fig. 1. Latent period of pain response to thermal stimulation at different stages of a spinal pain syndrome evoked by creation of a GPEE in the posterior horns of the lumbrosacral segments of the spinal cord. Abscissa (logarithmic scale), time (in h) after penicillin application; ordinate, value of LP (in sec). Points on ordinate — values of LP before application. 1) LP of pain response of right limb; 2) LP of pain response of left limb.

cord, and after cessation of episodes of the pain syndrome (Fig. 1). Testing began 0.5-2 h after penicillin application, when a clearly defined pain syndrome was present, and all parameters of the syndrome (vocalization, motor activity, local response in accordance with pain projection to the right hind limb, response to provocation, number of episodes and their duration in the course of 1 min) had the highest scores on a 3-point scale. Subsequent testing of LP was carried out in the period of weakening of the syndrome (3-4 h) and also 1, 2, and 3 days after creation of the GPEE in the posterior horns of the spinal cord. As Fig. 1 shows, LP of the pain response to nociceptive thermal stimulation doubled in intensity 2 h after creation of the GPEE and remained higher than initially for a long time. Some rats had no pain response to thermal stimulation whether during development of the pain symdrome or on the 2nd and 3rd days after the operation. Responses to thermal stimulation were depressed equally in the right and left limbs, although the GPEE was created in the posterior horns of the spinal cord on the right side.

To analyze the analgesic effect thus revealed additional series of experiments were undertaken. In one of them a pain syndrome was induced by creating a GPEE with a different agent, namely tetanus toxin, which disturbs different types of inhibition by blocking release of the inhibitory transmitter and causes the formation of a powerful and long-lasting GPEE [1]. Under these conditions a severe pain syndrome arises. During the development of this syndrome the rats virtually do not respond to nociceptive thermal stimulation. LP of the pain response of the right and left hind limbs was 60 sec — the longest time the animal could remain on the hotplate.

In the control series of experiments the animals underwent a mock operation (exposure of the spinal cord and application of an agar wafer not containing penicillin). Under these conditions no significant increase in LP of the pain response to nociceptive thermal stimulation was observed.

During development of the spinal pain syndrome induced by creation of the GPEE in the posterior horns of the spinal cord, the response to nociceptive thermal stimulation was thus depressed. This analgesic effect was independent of the type of agent used to create the GPEE, for it was observed in experiments in which penicillin and tetanus toxin were used for this purpose. It is an interesting fact that the effect was observed not only during development of the pain syndrome, but for a long time after cessation of the episodes. Incidentally, even though the GPEE was created in the posterior horns of the spinal cord on the right side, and the pain was projected correspondingly to the region of the right hind limb, responses of both limbs to nociceptive thermal stimulation were suppressed, i.e., the effect was bilateral.

It can be tentatively suggested that depression of the pain response to thermal stimulation (physiological pain) during a spinal pain syndrome (pathological pain) arises as a result of activation of ANS due to an increased flow of impulses to ANS from GPEE. To test this hypothesis neuronal activity of the key structure of ANS (the dorsal nucleus raphe) was tested during creation of a GPEE in the posterior horns of the lumbar region of the spinal cord by penicillin application.

Under normal conditions most (40) neurons tested in the dorsal nucleus raphe, mainly in its central part, possessed low-frequency grouped or unitary activity within the 0.2-6 spikes/sec range. Neurons with an average nociceptive discharge frequency of 6 spikes/sec were recorded less frequently and were located mainly in the ventral part of the nucleus.

The character of unit activity in the dorsal nucleus raphe (14 cells) was changed after creation of the GPEE in the spinal cord, 8-10 min after penicillin application. The discharge frequency of the neurons increased on average to 20-80 spikes/sec, and in some cases the in-

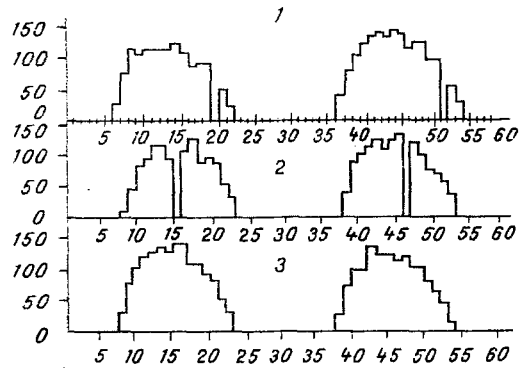

Fig. 2. Mean discharge frequency of dorsal nucleus raphe neurons after penicillin application. 1, 2, 3) 35, 36, and 37 min respectively after creation of GPEE.

crease in the average discharge frequency was 20-fold. The neurons tested continued to discharge at a higher-than-normal frequency throughout the period of observation. A distinguishing feature of unit activity in the dorsal nucleus after creation of the GPEE was the fluctuating character of the discharge frequency; some neurons had a clearly defined period of fluctuation of their discharge frequency, whereas in others the period of fluctuations of the average discharge frequency was inconstant. The average discharge frequency of a neuron 35-37 min after creation of the GPEE is shown graphically in Fig. 2. The distinct period of excitation (17 sec), followed by a period of silence (14 sec) can be noted. This rhythm of unit activity in the dorsal nucleus raphe was observed during 15 min of observation.

Thus, in the period of development of the spinal pain syndrome induced by creation of a unilateral GPEE in the posterior horns of the lumbar enlargement of the spinal cord, responses to nociceptive thermal stimulation of both limbs were suppressed. Meanwhile increased unit activity was observed in the dorsal nucleus raphe — the key structure of ANS. It can be postulated that the cause of suppression of physiological pain in the presence of a pain syndrome (pathological pain) is increased activity in certain structures of ANS. Increased activity of ANS neurons during creation of a GPEE in the spinal cord may be sufficient to suppress physiological pain (short-term nociceptive thermal stimulation), but not pathological pain (spinal pain syndrome).

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