ANALGESIA ON ELECTRICAL STIMULATION OF MESENCEPHALIC NUCLEI IN RATS WITH A PAIN SYNDROME OF SPINAL ORIGIN

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Effects of electrical stimulation of the periventricular gray matter and dorsal nucleus raphe in the midbrain on physiological pain induced by nociceptive stimulation (crushing the tail or skin of the limbs with forceps) and on pathological pain (a pain syndrome of spinal origin) were studied in experiments on albino rats. This last pain syndrome was produced by creating a generator of pathologically enhanced excitation in the posterior horns of the spinal cord with the aid of tetanus toxin, which disturbs various types of inhibition. Electrical stimulation of the above structures was shown to depress both physiological and pathological pain. It is concluded that analgesia during electrical stimulation of brain structures is connected not only with the strengthening of descending inhibition in the spinal cord, as in the case of physiological pain caused by peripheral nociceptive stimulation (as several workers have shown), but also with blocking the spread of excitation at the supraspinal level. This mechanism must play the decisive role in the production of analgesia in pain syndromes of central origin, including those arising under natural conditions.

KEY WORDS: *excitation generator; tetanus toxin; antinociceptive system; pain syndrome of spinal origin; periventricular gray matter; dorsal nucleus raphe of the midbrain.*

During electrical stimulation of certain brain structures and, in particular, of the periventricular gray matter and the dorsal nucleus raphe of the midbrain an analgesic effect has been demonstrated [13-16, 18, 20]. In the investigations cited, the analgesic effects of electrical stimulation of brain structures were studied in relation to physiological pain induced by nociceptive stimulation (electrical, mechanical, thermal) of the skin of the limbs and tail. The study of the effect of electrical stimulation of the antinociceptive structures of the brain on pathological pain and, in particular, on various pain syndromes of central origin is of special interest.

The object of this investigation was to study the effect of electrical stimulation of the nuclei raphe and of the periventricular gray matter of the midbrain on an experimental pain syndrome of spinal origin arising in the presence of a generator of pathologically enhanced excitation in the posterior horns of the spinal cord [2, 4, 5]. For comparison, the effect of electrical stimulation of the above brain structures on physiological pain induced by nociceptive stimulation was studied.

EXPERIMENTAL METHOD

Two series of experiments were carried out: In the experiments of series I (15 animals) the effect of electrical stimulation of the above-mentioned zones of the midbrain on pain induced by nociceptive stimulation of the limbs or tail in normal rats (physiological pain) was studied, whereas in the experiments of series II (15 animals) the effects of stimulation of

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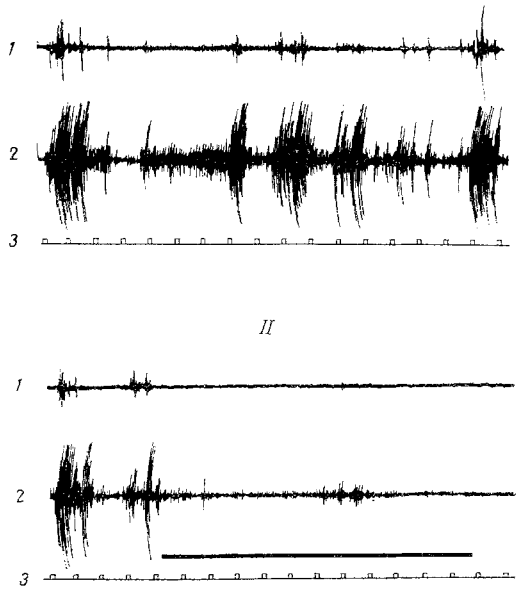

Fig. 1. Depression of vocalization and motor response in rats with pain syndrome of spinal origin during electrical stimulation of dorsal nucleus raphe of midbrain. Phonogram (1) and actogram (2) before (I) and during (II) electrical stimulation of dorsal nucleus raphe. Period of electrical stimulation indicated by continuous line above time marker (3). Time marker 1 sec.

these mesencephalic zones on a spinal pain syndrome (pathological pain) was investigated. Electrical stimulation of the midbrain (nuclei raphe and periventricular gray matter) was carried out through bipolar nichrome electrodes, inserted stereotaxically in accordance with the atlas of Pellegrino and Cushman [19]. The electrodes were inserted under hexobarbital anesthesia and the experiments were carried out ten days after the operation. Two types of electrical stimulation were used: with volleys of pulses at different frequencies (10-50 Hz) with 2-10 pulses per volley, and with a volley frequency of 0.3-1 Hz, or continuously (frequency 10-50 Hz), when the duration of stimulation varied. The stimulus duration was 0.1-0.5 msec and its strength 1-15 V.

The pain syndrome of spinal origin was induced in rats by creating a generator of pathologically enhanced excitation in the posterior horns of the spinal cord with the aid of tetanus toxin, as the substance disturbing different types of inhibition [3, 7, 10-12], and consequently converting ensembles of neurons into generators of pathologically enhanced excitation [1, 2, 4-6, 9]. The generator can be triggered by trigger stimulation of insignificant strength, causing it to operate explosively [1, 2, 6, 8, 9]. Such generators of pathologically enhanced excitation lie at the basis of pain syndromes of central origin [2, 4, 5]. A pain syndrome of spinal origin was induced by the agar plate method developed in the writers' laboratory. The essence of this method is that 0.1 ml of purified tetanus toxin (200,000 MLD for mice) was mixed with 0.9 ml liquid 1% agar, and after the agar had solidified, plates measuring 3 × 2 × 1.5 mm were cut from it and applied to the left half of the dorsal surface of the spinal cord in the region of the lumbosacral enlargement. Through slow diffusion of the toxin from the agar into the spinal cord, the syndrome developed gradually. It is important to note that symptoms of the pain syndrome can be observed for a long time in an animal behaving freely. After application of the agar plate the wound was sutured and the anesthesia (ether) stopped. The animals' behavioral responses were observed in a specially equipped chamber and the motor response (actogram) and vocalization (phonogram) were recorded.

EXPERIMENTAL RESULTS

Nociceptive stimulation (crushing the tail or skin of the thigh, leg, or foot) evoked characteristic pain responses in the control animals: The animals turned their heads toward the point of application of the stimulus, bit the forceps, tried to free themselves, shook the limb, and cried.

Electrical stimulation of the periventricular gray matter and dorsal nucleus raphe of the midbrain depressed this response: During stimulation the animals did not respond to crushing of the tail or skin of the limbs. Even very strong nociceptive stimulation, producing injury, if applied during electrical stimulation was unaccompanied by a defensive response: The animals did not respond to such stimulation, just as if it had not been applied.

The use of different regimes of stimulation showed that a definite analgesic effect appeared in response to stimulation of the following parameters: strength 3-4 V, frequency 25 Hz, 5-8 stimuli per volley. The optimal parameters of stimulation for obtaining analgesia were as follows: strength of stimulation 5-10 V, frequency of stimulation 25-40 Hz, duration of stimulus 0.5 msec. The duration of stimulation varied. Stimulation with the strength of over 12 V caused the appearance of hyperactivity: The animals began to move about the cage restlessly. Depression of the pain response was observed throughout the period of electrical stimulation (2-10 min); in some rats the analgesic effect lasted 30-60 sec after the end of stimulation, and in a few cases after-analgesia could persist for 1-2 h. Stimulation of the dorsal nucleus raphe of the midbrain gave a stronger analgesic effect than stimulation of the periventricular gray matter.

Similar electrical stimulation was carried out during pathological pain — a pain syndrome of spinal origin arising 3-4 h after application of an agar plate with toxin to the spinal cord. The beginning of development of this syndrome was characterized by restlessness and aggressiveness of the animals, which began to lick the hair in that or some other part of the hind limb. The location of this part corresponded to the site of application of the toxin to the spinal cord. Usually it was the lateral surface of the left thigh. With the passage of time the animals licked and bit the skin in this region increasingly often and vigorously, as a result of which it lost some of its hair and became ulcerated, sometimes exposing the dermis. This part became a trigger zone: The least irritation, including weak tactile stimulation such as touching with a bristle, blowing on the limb, and so on, if applied to this region, evoked a sharp response: The animals turned on the limb with a cry and bit it furiously, in some cases even chewing the tissues. This behavioral response was accompanied by dilatation of the pupil, protrusion of the eyeballs, widening of the palpebral fissure, breath-holding, and disturbances of respiration. All these symptoms were similar to those arising during the development of a pain syndrome after microinjection of tetanus toxin into the posterior horns of the spinal cord [4, 5]. The entire picture described above is evidence of a very severe pain syndrome.

Electrical stimulation of the dorsal nucleus raphe of the midbrain during an episode interrupted it: The animals ceased to cry, became quiet, turned their heads away from the site of projection of the pain, which they had previously licked or bitten vigorously (Fig. 1). The optimal parameters of stimulation to obtain analgesia against pathological pain of spinal origin were as follows: strength of stimulation 5-10 V, frequency 25-30 Hz, duration of stimulus 0.5 msec, duration of stimulation 2-5 min. The analgesic effect on increasing the strength of stimulation in rats with a spinal pain syndrome was accompanied by motor hyperactivity more often than in normal rats.

Electrical stimulation of the dorsal nucleus raphe of the midbrain thus depressed both physiological and pathological pain. It has been shown [13, 18] that depression of the pain response may be connected with inhibitory influences of descending pathways of the cells of lamina V of the spinal cord. This conclusion is valid in the case of pain connected with the transmission of nociceptive stimulation of the periphery along thin fibers. In that case the mechanism of inhibition operates on the input into the spinal cord, as postulated by the theory of gate control [17]. It can tentatively be suggested that descending influences regulating the system of the inhibitory afferent input in the spinal cord are connected with activation of the supraspinal regions of the antinociceptive system. In the present case, with a pain syndrome of spinal origin induced by the creation of a generator of pathologically enhanced excitation in the posterior horns of the spinal cord, inhibitory mechanisms are disturbed in the system of the spinal afferent input. The disturbance is due to the action of tetanus toxin, which disturbs various types of inhibition [3, 7, 10-12]. It may accordingly be supposed that the analgesic effect described during electrical stimulation of the nucleus raphe and periventricular gray matter of the midbrain ought to be connected not only (or perhaps, not so much) with the inhibitory mechanisms in the system of the spinal afferent input, but also with blocking of excitation arising from the spinal portions of the nociceptive system at supraspinal levels. Such a blockage is probably one of the essential mechanisms of the analgesia arising during activation of structures belonging to the antinociceptive system. This mechanism must play an essential role also under natural conditions in the production of the analgesic effect in pain syndromes of central origin.

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EFFECT OF HYPERBARIC OXYGENATION ON SOME FUNCTIONAL AND MORPHOLOGICAL PROPERTIES OF THE HEART AND ON CATECHOLAMINE METABOLISM IN COMPENSATORY HYPERTROPHY OF THE MYOCARDIUM

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Less-marked hypertrophy and signs of myocardial degeneration developed in rabbits exposed for one month to hyperbaric oxygenation (HBO) after the formation of stenosis of the ascending aorta, and the contractile power of the left ventricle was increased more than in animals with stenosis of the aorta kept under ordinary conditions. In rabbits with hypertrophy of the heart developing under conditions of HBO increased powers of adaptation of the myocardium to physical exertion were accompanied by an increase in the functional reserve of the sympathetic control apparatus. HBO evidently favors the development of optimal adaptation of the heart to an increased pressure load.

KEY WORDS: *hyperbaric oxygenation; myocardial hypertrophy; catecholamines.*

In recent years hyperbaric oxygen has been used on an increasingly wide scale in the treatment of various heart diseases. The action of hyperbaric oxygenation (HBO) is based not merely on its protective effect against hypoxia, but also on its ability to cause modification to the activity of the energy-forming structures and enzyme systems of the cells and

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