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ANALGESIA CAUSED BY AN EXCITATION GENERATOR FORMED IN THE MESENCEPHALON

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In experiments on albino rats an excitation generator was formed with tetanus toxin in the dorsal nucleus of the midbrain raphe. The formation of an excitation generator in this nucleus was shown to produce general analgesia manifested against physiological (nociceptive stimulation) and central pathological pain (a pain syndrome of spinal origin). It is concluded that prolonged analgesia arising during activation of certain brain structures is due to the appearance of excitation generators in them, which cause prolonged activation of those structures.

KEY WORDS: dorsal nucleus of the midbrain raphe; excitation generator; pain syndrome of spinal origin; analgesia; tetanus toxin.

Recent investigations have shown that electrical stimulation of the gray matter near the aqueduct, the dorsal nucleus of the midbrain raphe, and certain other brain structures produces analgesia against both nociceptive stimulation and pathological pain [1, 2, 13-16, 19]. The analgesic effect is characterized by gradual development [16] and long persistence (sometimes for several hours) after the end of stimulation [13, 15]. This course of the analgesia sugested [2, 3] that it is due to the formation of an excitation generator in these structures during their electrical stimulation. Model experiments have shown that the pain syndromes of central origin are based on the formation of generators of pathologically enhanced excitation (GPEE) in the corresponding regions of the nociceptive system [3, 5-7]. The pain syndrome of spinal origin has been produced by the formation of a GPEE in the posterior horns of the spinal cord [5], a trigeminal syndrome by its formation in the caudal nucleus of the trigeminal nerve [7], and a thalamic syndrome by its formation in the intralaminar nuclei of the thalamus [6]. On the basis of these investigations the theory of the generator mechanisms of central pain syndromes was formulated [3]. In the investigations mentioned above the GPEE was formed by means of tetanus toxin (TT), which disturbs various types of inhibition [4, 8, 10, 11].

In the present investigation TT also was used to produce a GPEE, this time in the mesencephalic nuclei (the dorsal nucleus raphe), in order to obtain prolonged effects of analgesia against physiological and pathological pain.

EXPERIMENTAL METHOD

Experiments were carried out on 45 albino rats weighing 300 g. To form a GPEE in the dorsal nucleus raphe, purified TT was injected stereotaxically by means of a microinjector, in a volume of $1.5 \cdot 10^{-4}$ ml and a

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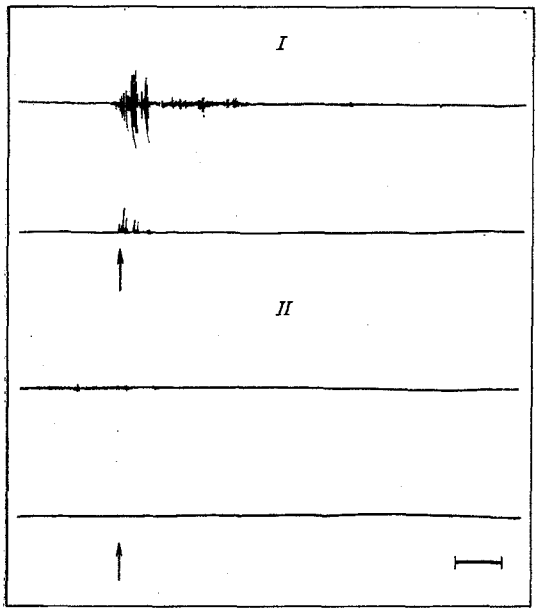

Fig. 1

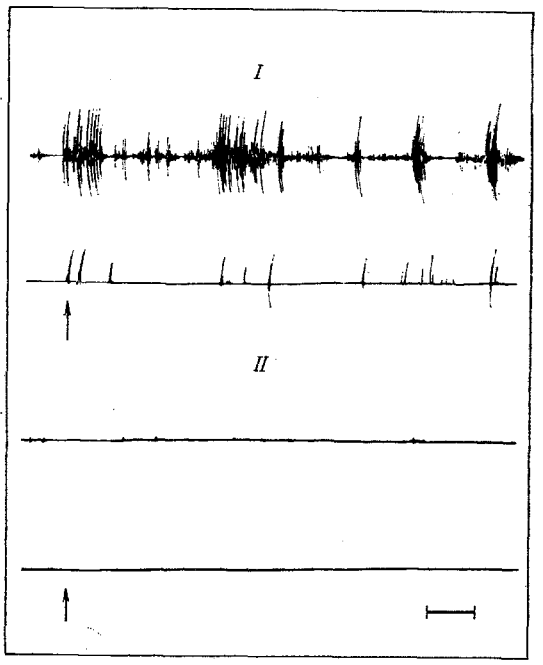

Fig. 2

Fig. 1. Motor and vocal responses to nociceptive stimulation in rats before (I) and after formation of excitation generator (II) in dorsal nucleus of midbrain raphe. Top curves are actograms, bottom curves phonograms. Arrows indicate time of stimulation. Time marker 5 sec.

Fig. 2. Motor and vocal responses of rats with pain syndrome of spinal origin before (I) and after (II) formation of generator of enhanced excitation in dorsal nucleus of midbrain raphe. Legend as in Fig. 1.

dose of 1.5-3 MLD, the coordinates being taken from the atlas of Pellegrino and Cushman [18]. The operation was performed under hexobarbital anesthesia (100 mg/kg body weight). To produce the GPEE in the posterior horns of the lumbar segments in order to obtain a pain syndrome of spinal origin, the "agar plate" method developed in the laboratory was used: 0.1 ml TT ($2 \cdot 10^5$ MLD/ml) was mixed with 0.9 ml of 1% liquid agar; after the agar had solidified, a plate measuring 3 × 2 × 1.5 mm was made from it and placed on the left half of the dorsal surface of the lumbar segments. The operation was performed under ether anesthesia. As a result of diffusion of the TT from the agar plate into the posterior horns of the spinal cord, a spinal pain syndrome developed, the first signs of it appearing 3-4 h after application. The motor response of the animals (actogram) and their vocal response (phonogram) were recorded in a specially built chamber.

EXPERIMENTAL RESULTS AND DISCUSSION

In the experiment of series I (20 rats) the effect of a GPEE in the dorsal nucleus raphe on physiological pain produced by squeezing a fold of skin, or the fingers or toes, or the tail was investigated. The application of these stimuli caused the animal to cry and give a motor response: The rats turned their head toward the site of application of the stimulus, they bit the forceps, tried to release themselves from them, ran to another place, and so on, and these responses were recorded on the phonogram and actogram (Fig. 1, I). After injection of TT into the dorsal nucleus raphe, nociceptive stimulation, even if very strong, evoked neither a cry nor a motor response (Fig. 1, II). This analgesic effect developed 3.5-6 h after injection of the TT and continued throughout the period of observation of the animals. It was observed in all animals receiving an injection of TT into the dorsal nucleus raphe. In those rats (5 animals) in whom TT was injected into neighboring structures, no analgesic effect was obtained.

It should be noted that the formation of the GPEE in the dorsal nucleus raphe of the midbrain gave not only an analgesic effect, but also led to motor hyperactivity and psychomotor excitation, which resembled spontaneous paroxysms in character. However, the analgesia was unconnected with psychomotor excitation, for it also took place when the animals were in a tranquil state.

In the next series of experiments (on 25 rats) the possibility of development of analgesia after the creation of an excitation generator in the dorsal nucleus raphe was studied under conditions of pathological pain – a pain syndrome of spinal origin. This syndrome was produced by forming a GPEE in the posterior horns of the lumbar segments by means of TT by the "agar plate" method (see Experimental Method). The pain syndrome developed 3-4 h after application of an agar plate containing TT to the dorsal surface of the lumbar segments on the left side. The development of the syndrome was characterized by restlessness and aggressiveness of the animals, which began to lick the hair on a certain area of the hind limb. The location of this area corresponded to the site of application of the toxin to the spinal cord. It was usually the lateral surface of the left thigh. With the course of time the animals licked the skin of this area more frequently and vigorously, as a result of which they lost some of its hair cover and became ulcerated, often exposing the dermis. This area became a trigger zone. The slightest stimulation, including weak tactile (touching with a bristle, blowing on the limb, and so on), applied to this area evoked a sharp response: The animals attacked the limb with a cry, bit it angrily, and even chewed the tissues. This response was accompanied by dilatation of the pupil, protrusion of the eyeball, widening of the palpebral fissure, and breath holding and other disturbances of respiration. Besides these evoked attacks, spontaneous attacks with an acute onset also developed. With time the frequency, intensity, and duration of the spontaneous paroxysms increased. The syndrome as a whole was characterized by its very severe course.

The excitation generator in the dorsal nucleus raphe was formed at different times (2, 4, 6, 8, and 16 h) before the formation of the GPEE in the posterior horns of the spinal cord, and also at the same time. In the case of the simultaneous formation of the two generators, or if the generator in the nucleus raphe was formed 2 h before that in the posterior horns, no analgesia developed: The pain syndrome developed just as in the control animals. If the time between the two operations was 4-6 h or more, the spinal pain syndrome did not develop: The animals showed none of the features described above but remained perfectly quiet, and neither spontaneous nor evoked paroxysms developed (Fig. 2). Stimulation of the areas of the left hind limb that had become trigger zones in the control animals gave no response. No spinal pain syndrome likewise developed later (in the course of 2 days of observation).

In five rats the dorsal nucleus raphe was coagulated in order to destroy the GPEE formed in it. In one animal this coagulation proved to be relatively extensive. In this rat, eradication of the GPEE led to disappearance of the analgesia and to the appearance of a spinal pain syndrome. In two other animals the coagulation was partial and the effect temporary: after initial disappearance the analgesia reappeared. In two rats coagulation was ineffective and the analgesia persisted.

The formation of a GPEE in the dorsal nucleus raphe thus gives a lasting and prolonged effect of analgesia not only against physiological pain (nociceptive stimulation), but also against pathological pain: a central pain syndrome of spinal origin, characterized by a very severe course. The fact that the preliminary formation of a GPEE in the dorsal nucleus raphe was necessary for analgesia to develop in this last case can be explained on the grounds that in order to suppress such a severe syndrome, caused by a very powerful GPEE in the posterior horns of the spinal cord, the GPEE in the dorsal nucleus raphe had to be already formed at the time of formation of GPEE in the posterior horns.

Results of this investigation agree with those of a previous study [2] which showed that electrical stimulation of the dorsal nucleus raphe gives an analgesic effect against both physiological and pathological pain. This fact confirms the role of the excitation generator in the dorsal nucleus raphe of the midbrain in the origin and maintenance of analgesia.

The general conclusion can be drawn from these findings that the analgesia which develops after activation of certain brain structures is based on generator mechanisms. These mechanisms can create the prolonged and intensive activation of antinociceptive structures that gives rise to deep and prolonged analgesia.

Activation of the antinociceptive structures causes descending inhibition of lamina V neurons in the spinal cord and "blocks" the afferent input [14], in agreement with the "gate control" theory [17]. This mechanism, however, is not the only one. In the present case, in the pathological syndrome, segmental inhibitory mechanisms were disturbed by tetanus toxin, and GPEE formation was connected with this fact. This syndrome likewise does not depend on the presence of an inflow of efferent stimulation from the periphery, for it developed after total deafferentation of the lumbosacral segments on the side of the GPEE [3]. It can accordingly be suggested that the analgesia evoked by the excitation generator in the antinociceptive system, in the present case in the dorsal nucleus raphe, is due not only to "blocking" of the afferent input in the spinal cord, but also to blocking of the conduction of excitation or inhibition of neurons of the nociceptive system at supraspinal levels.

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DETERMINATION OF THE LOCAL MUSCULAR BLOOD FLOW IN THE HIND LIMBS OF DOGS DURING ELECTROLYSIS OF ELECTRICALLY CONDUCTING VASCULAR PROSTHESES PREIMPLANTED INTO THE ABDOMINAL AORTA

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The peripheral blood flow in the hind limbs was studied in experiments on 25 mongrel dogs during electrolysis of electrically conducting vascular prostheses preimplanted into the abdominal aorta. After restoration of the trunk blood flow, a positive electrical potential of 3-4 V was applied to the prosthesis by means of a current conductor. The tissue blood flow was determined by a radiographic method using xenon-133. The results showed that during application of the positive potential to the electrically conducting prosthesis the tissue blood flow in the hind limbs of the dogs increased, but after application of the current stopped it fell to its initial level. It is concluded that to obtain a prolonged and stable increase in the tissue blood flow in the limbs of animals, a positive potential from a dc source must be applied continuously to the electrically conducting prosthesis.

KEY WORDS: local muscular blood flow; ^{133}Xe clearance; implantation of prosthesis into aorta.

The limited possibilities for restoring the trunk blood flow by operative means after occlusion of the small arteries of the limb necessitate the constant search for new methods of improving the collateral circulation, and, in particular, methods of overcoming spasm of the peripheral vessels and opening up a powerful collateral network.

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