INVESTIGATION OF A PAIN SYNDROME OF SPINAL ORIGIN (ON THE CONCEPT OF THE GENERATOR MECHANISM OF THE PAIN SYNDROME)

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A pain syndrome was induced in rats by means of a microinjection of purified tetanus toxin into the posterior horns of gray matter of the lumbosacral segments of the spinal cord. The toxin was used as a means of disturbing inhibitory mechanisms. Investigation showed that a pain syndrome can be reproduced if afferent stimulation from the periphery is blocked (by division of the nerves of the hind limbs or division of the dorsal lumbosacral roots on the side of injection of the toxin). Under these conditions the latent period of onset of the syndrome was lengthened and the degree of its development weakened a little in the initial stages by comparison with animals with intact afferentation. In many animals with blocked afferentation from the hind limb general manifestations (restlessness, aggressiveness, crying, etc.) were accompanied by a localized response in the form of increased licking, biting, or even chewing the tissues of the deafferented limb at the site of projection of the pain (the phantom syndrome). In some animals only the general reaction was observed without localization of the pain (protopathic pain). In all cases the attacks of pain arose paroxysmally. In animals with intact limb innervation the zones of licking were trigger zones of facilitated induction of an attack of pain. Injection of glycine into the affected posterior horns of the spinal cord abolished the pain syndrome during the time of action of the glycine. It is concluded that the pain syndrome is based on the formation of a generator of pathologically intensified excitation, as a result of disturbance of inhibitory processes, in the system of neurons connected with pain sensation. These mechanisms are evidently those principally concerned in the pathogenesis of all pain syndromes.

KEY WORDS: spinal cord, disturbance of inhibition; excitation generator; "dispatch station"; phantom syndrome.

Previous investigations [10] aimed at establishing the principal of the "dispatch station" [5, 6, 8, 9, 12] showed that injection of tetanus toxin, disturbing various types of inhibition [6, 13, 15], into the posterior horns of gray matter of the spinal cord can induce a pain syndrome characterized by a severe clinical picture. These observations were interpreted on the basis of ideas concerning the appearance of a powerful excitation generator (a pathologically strengthened "dispatch station") on account of disturbance of inhibitory processes [4-8] in the system of spinal neurons connected with pain sensation.

The object of the present investigation was to obtain additional data on the role of the excitation generator in the production of the pain syndrome.

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EXPERIMENTAL METHOD

Albino rats weighing 270-300 g were used. As in the previous investigation [10] tetanus toxin was used to produce an excitation generator ("dispatch station"). The toxin was injected exactly into the region of the posterior horns of the lumbar segments of the spinal cord, by means of a stereotaxic method and using a microinjector enabling 10^{-4} ml of fluid to be injected. The doses of toxin were 0.1-3.0 MLD for rats. Full details of the method are described previously [10].

To block the sensation of the hind limb a high division of the nerves (sciatic, femoral, obturator) was carried out 4-14 days before the injection of toxin. Before the toxin was injected into the spinal cord, the sensation of the denervated limbs was tested in all the experimental animals. It was completely absent on the toes, foot, and leg and partly in the thigh but remained intact in the upper half of the thigh in the region where the skin adjoins that of the lateral surface of the trunk and the abdomen. A single injection of toxin was given into the posterior horns of segment L6 of these animals and also into animals with an intact limb innervation (corresponding to the zone of blocked sensation).

In a second series of experiments deafferentation of the hind limb was carried out by dividing the dorsal roots over the range LI-S2 and, in some experiments, T2-S4 either immediately or 3-14 days before injection of the toxin. In these experiments the toxin was given either as a single injection into L6 or as three injections into L5-S1. In these deafferentation experiments considerable wastage occurred among the animals because of damage to the spinal cord. Altogether in the preliminary deafferentation experiments 15 rats were usable, compared with 10 rats in the simultaneous deafferentation experiments.

The experiments with glycine were carried out on animals with a pain syndrome and with intact innervation of the hind limb. Glycine (20% solution, 10^{-4} ml per injection) was injected from the same microinjector under general ether anesthesia into the poisoned posterior horns of the lumbar segments as one or three injections. In control experiments 8% NaCl (isotonic with the glycine solution and with the same pH) was injected into the same regions by the same method. Altogether 90 rats were used.

EXPERIMENTAL RESULTS AND DISCUSSION

As was described earlier [10] animals with an intact hind-limb innervation become restless and aggressive a certain time after receiving an injection of toxin (the duration of this period is determined by the dose of the toxin); the animals began to lick a certain part of the limb on the side of injection of the toxin – usually the leg, toe, or foot. The attacks were paroxysmal in character. Meanwhile stimulation (squeezing a fold of skin with anatomical forceps) of the area licked by the animal induced a marked reaction: with a cry the rat turned to the limb and began to lick the same area vigorously. Application even of weak tactile stimuli (touching or running a bristle along the hair) to the zone of licking, which was the trigger zone, induced a sharp and prolonged response: with a cry the animal turned curiously to the limb and started to lick it and chew it. This effect was accompanied by dilation of the pupils, protrusion of the eyeballs, and changes in respiration. The paroxysmal character of the attacks was clearly manifested. Attacks of pain arose without any special provocation. In the final stages, if the process was drawn out the animals frequently chewed the tissues of the limb.

A picture of the pain syndrome similar in principle was observed in most animals with a denervated or deafferented limb. These animals also licked the corresponding areas of the limb vigorously, they turned on it furiously and with a cry whenever attacks of pain occurred (Fig. 1a, b). However, stimulation of these areas itself induced no response. The attacks of pain developed paroxysmally in these animals. Some of the animals in the final stages of development of the syndrome chewed the tissues of the limb (Fig. 1c). A distinguishing feature of the pain syndrome in the animals with blocked sensation of the hind limb was its slow development. For instance, after injection of 1 MLD toxin into the posterior horns of L6 the first signs of the pain syndrome in rats with intact innervation usually appeared after 2 h; in the animals with the denervated limb they appeared 5-6 h after injection of the toxin. A similar delay in the onset of the pain syndrome was observed in the animals with the deafferented limb. In some rats with blocked sensation a general response to pain was observed: the animals were excited and aggressive, they attacked the walls of the cage with a cry, they chewed the bars, but they gave no visible localized response.

Injection of glycine into the region of the posterior horns of the poisoned segments in animals with an intact limb innervation on the side of injection of the toxin completely inhibited the pain syndrome: the animals became quiet, the paroxysmal attacks of pain disappeared, and stimulation of the areas that had previously been licked evoked no pain response (Fig. 2, I). This picture was observed throughout the period of

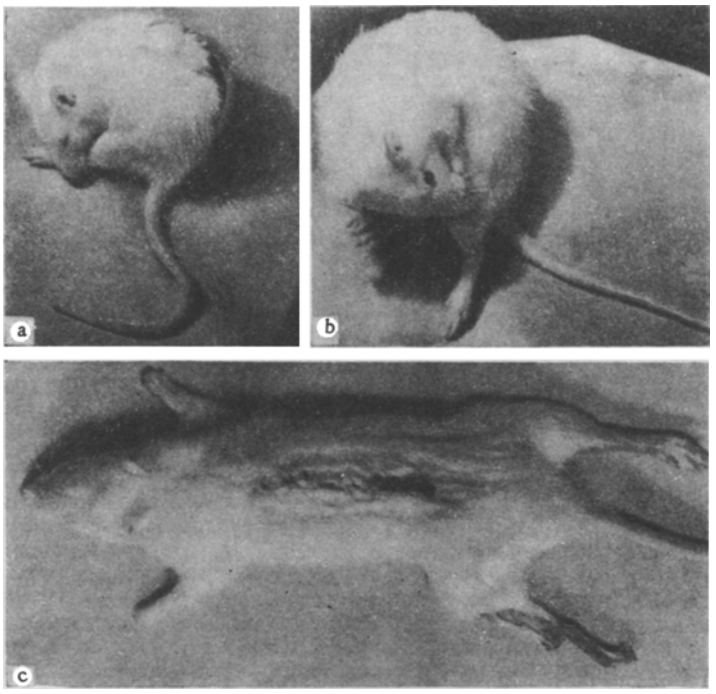

Fig. 1. Spinal pain syndrome after blocking sensation of hind limb on side of injection of toxin in lumbar segments: a) pain syndrome in rat with dorsal roots (L_2-S_2) divided on the left. Toxin (1 MLD $\times 3$) injected into posterior horns L_4-L_6 on the left 3 days after division of roots; b) pain syndrome in rat with divided nerves of left hind limb. Toxin (1 MLD) injected into posterior horn of L_6 on the left 3 days after division of nerves; c) final stage of pain syndrome in one rat with divided nerves on left hind limb. Toxin (1 MLD) injected into posterior horn of L_6 6 days after division of nerves. Photograph taken after death of animal.

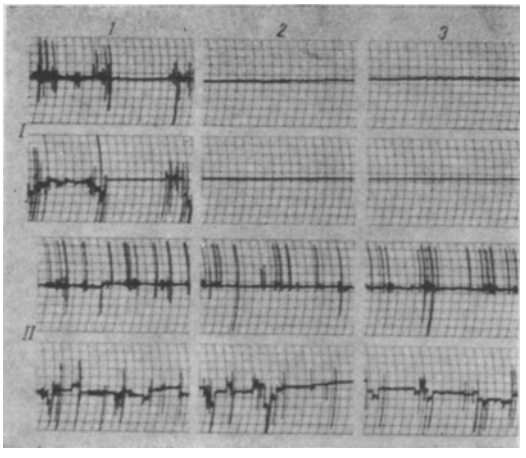

Fig. 2. Effect of glycine injected into posterior horns of lumbar segments in spinal pain syndrome. In both parts (I and II) of the figure, top curves are phonograms, bottom curves are actograms recorded during spinal pain syndrome in a rat before (1) and 20 min (2) and 30 min (3) after injection of 20% glycine solution (I) and 8% NaCl solution (control, II) into posterior horns of lumbar segments (L_4-L_6) in a dose of 1×10^{-4} ml per injection. Tape winding speed (horizontal line) 3 cm in 5 min. Recorded 72 h after injection of toxin (0.1 MLD) in posterior horns of lumbar segments (L_4-L_6) on the left.

action of glycine, after which the manifestations of the pain syndrome recurred. In control experiments a similar injection of hypertonic NaCl solution (isoosmotic with the glycine solution and with the same pH) had no such effect (Fig. 2, II).

Tetanus toxin is known [5, 13, 15] to cause a disturbance of various types of inhibition. As a result of this disturbance, a group of neurons linked together by positive connections becomes an excitation generator if it is acted upon by the toxin, disturbing the inhibitory connections [8-10]. Such generators can be created in various parts of the nervous system [2, 3, 5, 8, 10, 12] and they play the role of dispatch station for the functional volley activating the system in which the dispatch station is created. By virtue of these properties this phenomenon has been called the "dispatch station" phenomenon [5-9].

The pain syndrome described above can be regarded as one form of dispatch station phenomenon based on the creation of an excitation generator in the system of neurons connected with ascending tracts of nociceptive sensation or forming these tracts. It is very likely that neurons of Rexed's lamina 5, responsible for the transmission, wide convergence, and summation of excitation, create such a generator. The activity of these neurons is regulated by special mechanisms [1, 14, 19, 22, 24, 26]. An analogue of this lamina is also found in rats [25]. However, the participation of neurons of other laminae in the formation of such a generator cannot be ruled out. Experiments in which glycine was used to induce effects of postsynaptic inhibition suggest the role of suppression of inhibitory mechanisms in the creation of the generator [16, 17, 27]. If injected into the region of the dispatch station, glycine completely destroys it as a functional structure and suppresses the generator activity. This effect of glycine was observed by the writers if the dispatch station was localized in other systems also [7-9]. It can be concluded from the results of the present experiments that glycinergic inhibitory mechanisms participate in the regulation of the activity of spinal neurons responsible for transmission of the sensory flow manifested at the supraspinal level as pain.

Experiments with blocking of afferent stimulation from the periphery show that this stimulation is of great importance for generator activity only in the first stages of its formation; the blocking of afferentation at this period leads to delay in the development of the syndrome. Later the importance of afferent stimulation is reduced, and in the late stages the generator is no longer required as a constant reinforcing stimulus; at this stage stimulation not only from the trigger zone (the zone of licking) but also from other parts can play the role of trigger stimulus. The paroxysmal attacks of pain were probably due to "triggering" of the generator by some form of converging stimulation not recordable externally. However, the possibility of spontaneous operation of the generator of an increase in its excitation up to a certain critical level cannot be ruled out.

Experiments in which the pain syndrome was reproduced during blocking of afferentation are important also in that they essentially simulate the phantom pain syndrome and give evidence of the role of generator mechanisms in the onset of the syndrome.

It can be concluded from all the facts described above that the genesis of the pain syndrome cannot be explained purely by facilitation of the passage of peripheral impulses along thin unmyelinated fibers through the afferent input in the spinal cord [21, 22]. The formation of a sensory and ascending flow of a certain intensity also plays a significant role, as other workers have already pointed out [18, 20, 22, 23]. To these basic postulates on which the concept of "gate control" of pain [20, 21] rests must be added a very important item: the appearance of an excitation generator in the system of neurons responsible for pain sensation. The formation of the generator is presumably an essential pathogenetic mechanism of any pain syndrome.

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