Effect of Stress on the Development of the Deafferentation Pain Syndrome in Rats Following Sciatic Nerve Transection

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Numerous clinical and experimental data suggest that injuries of the peripheral nerves result in the development of deafferentation pain syndromes [3,5,6]. The development of deafferentation pain has been shown to be related to the formation of generators of pathologically enhanced excitation (GPEE) in the brain nociceptive structures, promoting the development of the pathological algetic system (PAS) underlying the pathophysiology of the pathological pain syndrome. This system causes dysfunction of the structures regulating algesthesia [2,12]. Little is known about the conditions which either stimulate or inhibit the formation of the PAS. The few clinical data available suggest that phantom limb pain syndromes occur more often in patients who had experienced pain before the limb amputation [8], and the aggravation of phantom limb pain may be caused by different emotional experiences [13]. However, it is a known fact that various stress factors can cause analgesia in animals [7,10], and an additional pain stimulus inhibits the nociceptive impulses emanating from the other source of pain [9]. These data are not consistent with the above-mentioned clinical observations.

The aim of this study was to evaluate the influence of immobilization and pain stress on the development of the deafferentation syndrome in rats following sciatic nerve transection.

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MATERIALS AND METHODS

The experiments were carried out on male Wistar rats. At the time of exposure to stress the rats used for the experiments had not exhibited either autotomy or the hyperalgesia normally characteristic for pain syndrome development [3,5,14]. The weight of the animals at the beginning of the study was 170 to 180 g. The sciatic nerve was cut at the level of the popliteal fossa under thiopental anesthesia (50 mg/kg intraperitoneally), after which the central end of the nerve was placed in a polyethylene tube with a sealed end and left in the wound to be sutured. Pain stimulation was carried out by using a removable clamp which made it possible to regulate the pressure with a screw. The clamp was applied for 30 min to one of the hind paws and placed above the tarsal joint. The compression force was 240 g/mm^2. For the creation of immobilization stress the rats were fixed in the supine position (semirigid fixation: the head and the left hind paw were left free). All the animals were divided into 3 groups. The first group (9 rats) comprised rats which 45 days after sciatic nerve transection were subjected to pain stress by applying a clamp to the left hind paw. The rats in the second group (7 animals) were subjected to pain stress by applying a clamp to the right hind paw at the same time after the operation. The animals of the third group (9 rats) were immobilized 45 days following the operation. The control group (6 rats) comprised animals which had not been exposed to additional stress after nerve section. At that time they did not show any behavioral signs characteristic for the pain

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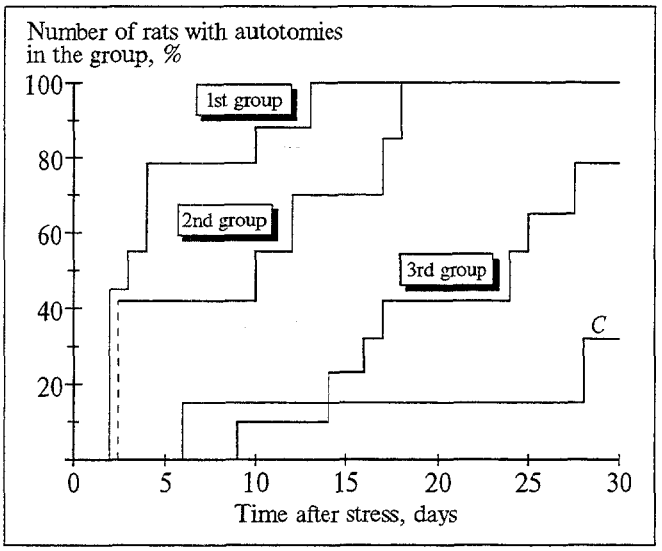

Fig. 1. Development of pain syndrome symptoms in rats after exposure to additional stress. C: animals not exposed to stress. Zero (0) on abscissa corresponds to 45th day after nerve transection.

syndrome either. The development of the pain syndrome in the animals was assessed by the time and severity of the autotomies observed on the operated paw. The severity of the autotomies was evaluated by the number of points assigned arbitrarily to the injuries observed in the animals [11]. Autotomy of one claw was assessed as 1 point, while injuries to 2, 3, 4, and 5 claws were allocated 2, 3, 4, and 5 points, respectively. Autotomy of the phalanx on one toe was assessed as 6 points, and on 2, 3, 4, and 5 toes as 7, 8, 9, and 10 points, respectively. The maximal number of points (11) was assigned to autotomies reaching the metatarsal bones and above the metatarsals. The significance of the results was evaluated according to Student's t test.

RESULTS

Both the pain and immobilization stress resulted in the development of the deafferentation pain syndrome in the animals which did not exhibit this syndrome following sciatic nerve transection (Fig. 1). In 44% of the rats exposed to pain stimulus to the paw with cut nerve the autotomies occurred on the second day after the exposure to stress, and by the 13th day all the animals of this group had shown clinical signs of pathological pain, manifested in their behavior. The rats became restless, and they often licked and bit the operated paw. Occasional paroxysmal twitching of the paw was observed; the rats squeaked and attacked it, biting off the claws and the soft tissues of the toes. Similar behavior was also observed in the second and third groups. In the second group in 43% of the animals exposed to pain stimulation of the contralateral paw relative to the cut nerve autotomies were also observed on the second day after the pain stress and on the 6th day the incidence of autotomies reached 100%. In the rats of the third group subjected to immobilization stress the development of the pain syndrome was slower in comparison with the animals of the first and second groups (Fig. 1).

The animals of the third group developed the first symptoms of autotomies on the 9th day after stress, and on the 35th day autotomies were observed in 77% of the rats. It should be noted that these animals developed autotomies earlier compared with the control group (Fig. 1).

The dynamics of development of autotomy is shown in Fig. 2. The most severe autotomies were observed in the first and second groups, the autotomies of the former being slightly more severe than in the latter. Thus, the results obtained suggest that both the immobilization and the pain stress result in pathological pain after the injury of the peripheral nerves. It is of interest that the development of the pain syndrome following the sciatic nerve injury for the exposure to additional pain stimulation was not related to the specific area of stimulus application, which suggests the involvement in the process of the central nociceptive structures taking part in the formation of the algetic system.

Acute stress has been shown to result in a marked reduction in the brain benzodiazepin and gamma-aminobutyric acid receptors [1] which produce inhibiting effects. This mechanism might promote the development of generators of pathologically enhanced excitation and the pathological algetic system which could have already been formed after the nerve section. The pathogenic effect of the exposure

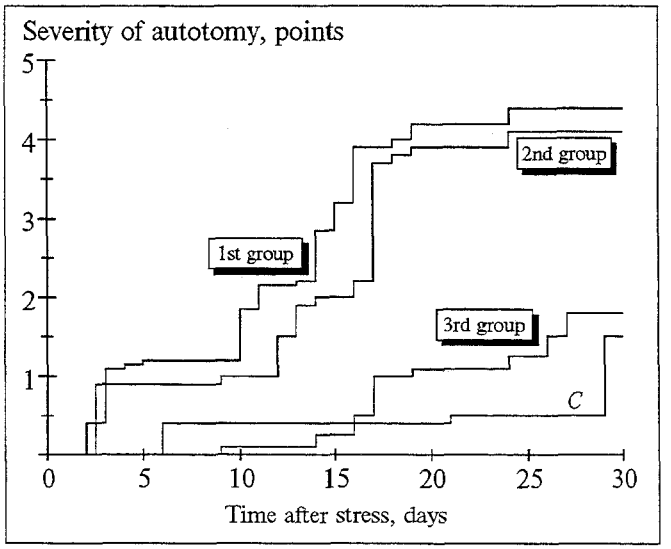

Fig. 2. Dynamics of development of autotomies in rats after additional exposure to stress. Ordinate: severity of autotomy (points). Other symbols as in Fig. 1.

to stress may also manifest itself in the inhibition of the antinociceptive system restricting the development of the PAS [2,12].

The data obtained in the present study are consistent with the clinical observations suggesting that adverse emotional experiences aggravate the course of the deafferentation pain syndrome [13]. The fact that the results of this study do not coincide with the experimental data on stress-induced analgesia can be accounted for by the fact that different mechanisms are involved in physiological and pathological pain [2,4,12].

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Effect of the Somatosensory Cortex on the Development of the Deafferentation Pain Syndrome

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Experimental and clinical data demonstrate that the development of the deafferentation pain syndrome after peripheral nerve injury is caused by morphofunctional changes in the structures of the brain noci- and antinociceptive systems [2,3,7,14]. This is paralleled by increased excitability of peripheral nerve fibers [15], of nociceptive neurons in the spinal cord dorsal horn [13], of the thalamic nuclei [6], and of the cerebral cortex [3,8,10], all this indicating the formation of a pathological algetic system in the structures regulating pain sensitivity [11]. The brain cortex plays an important role in the regulation of pain sensitivity. It participates in the perception and analysis of pain signals [4,5] and has a marked modulating effect on the activity of the antinociceptive structures [4,6].

The study of the role of the somatosensory cortex in the development of the deafferentation pain syndrome appearing in rats after sciatic nerve transection was the aim of this research.

MATERIALS AND METHODS

Experiments were carried out on 48 male Wistar rats weighing 180-200 g. For stimulation of the deafferen-

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