Electrical Activity in the Dorsal Spinal Cord Horns and the Somatosensory Cortex of Rats with and without a Pain Syndrome Following Sciatic Nerve Transection

G. N. Kryzhanovskii, V. K. Reshetnyak, M. L. Kukushkin, V. S. Smirnova, and V. A. Zinkevich

UDC 616.8-009.7-02:616.833.59-089.85]-092.9-07

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 115, № 5, pp. 461-463, May, 1993
Original article submitted January 5, 1993

Key Words: *pain syndrome; pathological algetic system; dorsal horns; somatosensory cortex*

According to the theory of generator and systemic mechanisms responsible for nervous disorders [1,2], a sine qua non for the emergence of central pain syndromes is the formation and activity of a generator of pathologically enhanced excitation (GPEE) in structures of the nociceptive system. The manifestations of these syndromes depend in large measure on the location of the GPEE and on how it works. However, the formation of a GPEE does not necessarily result in a pain syndrome. The latter will not occur unless that part of the nociceptive system which is hyperactivated by the GPEE involves other parts of that system in the pathological process to give rise to a new pathodynamic entity referred to as a pathological algetic system (PAS).

As found in our previous studies [3,4], rats that had developed a pain syndrome after sciatic nerve transection, unlike those that had not, showed greatly increased amplitudes of, and reduced thresholds for, evoked potentials (EP) in the somatosensory cortex of the contralateral hemisphere. These findings, however, may be a reflection of altered neuronal activity not only in the somatosensory cortex itself, but also in the underlying brain structures. We therefore deemed it necessary to compare bioelectric activity in the dorsal horns, which are the primary nociceptive relay structures of the spinal cord, and in the cerebral hemispheres of animals with and without a pain syndrome after sciatic nerve transection.

Laboratory for Pathophysiology of Pain, Institute of General Pathology and Pathophysiology, Russian Academy of Medical Sciences, Moscow

MATERIALS AND METHODS

Male Wistar rats were used for the experiments. The sciatic nerve of their left hindlimb was transected under hexenal (hexobarbital sodium) anesthesia (30 mg/kg body weight intraperitoneally) at the popliteal fossa level distal to the site of ligation, and the central end of the nerve was then placed in a polyethylene capsule (sealed on one side) and left in the wound, which was closed by a suture. The animals were considered to have developed a pain syndrome if the phenomenon of autotomy was observed (gnawing away of pieces of tissue in the paw with cut nerve) and hyperalgesia was present. Hyperalgesia was assessed by measuring pain sensitivity thresholds in the reaction of paw licking using a hot plate test (the plate surface had a temperature of 55°C). Electrophysiological studies were started 8 to 30 days after sciatic nerve transection depending on the time it took for the pain syndrome to develop. For these studies, rats were fixed in a stereotaxic apparatus under ether anesthesia, made immobile by a muscle relaxant (Myo-Relaxin), and artificially ventilated. EP in the dorsal horns and the cerebral cortex were recorded in response to electrostimulation of a hind- or forelimb with rectangular pulses of 0.1 msec in duration using bipolar needle electrodes. On the hindlimb with cut nerve, electrostimulation was carried

0007-4888/93/0005-0495$12.50

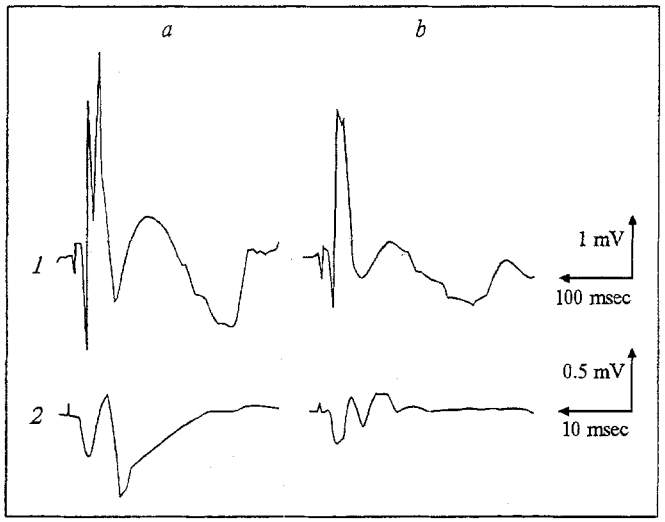

Fig. 1. Evoked potentials (EP) in the somatosensory cortex of the contralateral hemisphere (*1*) and in dorsal horns of the spinal cord on the side of sciatic nerve transection (*2*) in response to electrostimulation of the hindlimb with transected nerve (*a*) and of the intact hindlimb (*b*) in rats with pain syndrome.

out above the transection site. EP in the somatosensory cortex of the brain were recorded with monopolar silver surface electrodes placed at the site where these potentials were highest. The indifferent electrode was fixed at the frontal sinus.

EP in the lumbar segments of the dorsal horns were registered with monopolar glass microelectrodes (10-15 μ in diameter at the tip) filled with a potassium chloride solution (2 mol/liter) and inserted to a depth of 200-300 μ from the dorsal surface of the spinal cord midway between the median dorsal artery and the site of entry of the dorsal roots into the spinal cord. The recorded potentials were delivered to the input of a VC-9 broadband amplifier (Japan) and then averaged for 10 stimulus presentations using a specialized computer.

RESULTS

The development of a pain syndrome in rats with transected sciatic nerve was accompanied, as in our previous studies [3, 4], by alterations in their behavior, signs of anxiety, and progressive hyperalgesia. These manifestations of the pain syndrome were used as criteria for separating the test rats into two groups - those that had developed the syndrome and those that had not by the time that electrophysiological studies were started.

In rats with the pain syndrome, the recording of focal EP from the dorsal horns did not show a significant difference between thresholds for ipsilateral responses to stimulation of the intact limb and the limb with cut sciatic nerve. When the stimulation intensity was doubled or trebled, the EP recorded from the homolateral dorsal horn in response to stimulation of the limb with the cut nerve had amplitudes that exceeded two- to threefold those of the homolateral EP recorded during stimulation of a symmetrical point on the intact contralateral limb (Fig. 1, *2*). In these rats, EP of similarly increased amplitudes were also recorded from the corresponding areas of the contralateral somatosensory cortex (Fig. 1, *1*). On the other hand, the thresholds for EP in the contralateral cortex for stimulation of the limb with the cut nerve were almost two times lower than those for EP in the contralateral cortex in response to stimulation of a symmetrical point on the intact hindlimb (0.67±0.20 mA vs. 1.30±0.28 mA). Moreover, the EP in the contralateral cortex in response to stimulation of the left forelimb (where the sciatic nerve was cut) had significantly higher amplitudes than the contralateral EP produced by stimulating the right forelimb (the intact side). The observation that the amplitudes of homolateral EP in the dorsal horns and the contralateral somatosensory cortex during stimulation of the limb with the cut nerve were higher than those of EP in response to stimulation of the contralateral intact hindlimb can be taken as evidence of the considerably enhanced excitability and reactivity of the structures of interest in rats with a developed pain syndrome.

The increased amplitudes of EP recorded from the somatosensory cortex contralateral to the transected nerve in response to stimulation of the left forelimb do not appear to have been associated with neuronal

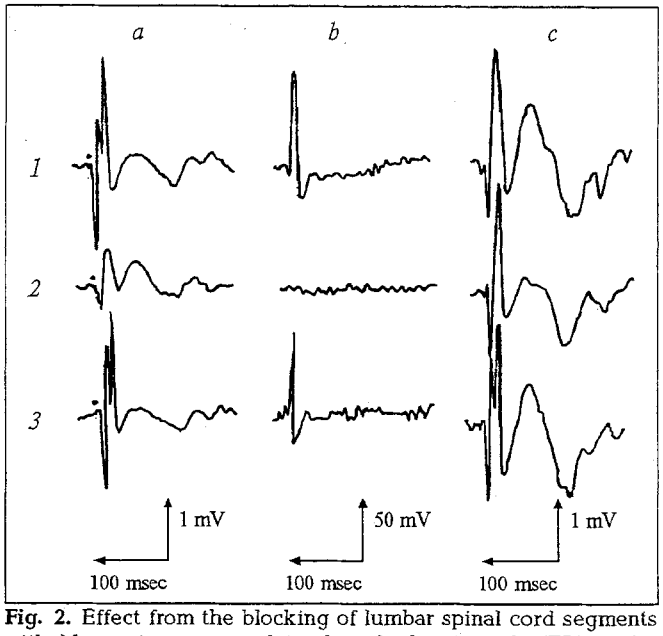

Fig. 2. Effect from the blocking of lumbar spinal cord segments with Novocain on contralateral evoked potentials (EP) in the somatosensory cortex in response to electrostimulation of the hindlimb with transected sciatic nerve (*a*) and of the ipsilateral forelimb (*c*) in rats with pain syndrome. 1) Before Novocain application to dorsal surface of lumbar segments; 2) 10 min after application; 3) after washing off of Novocain; *b*) EP in the dorsal horn of segment L_3.

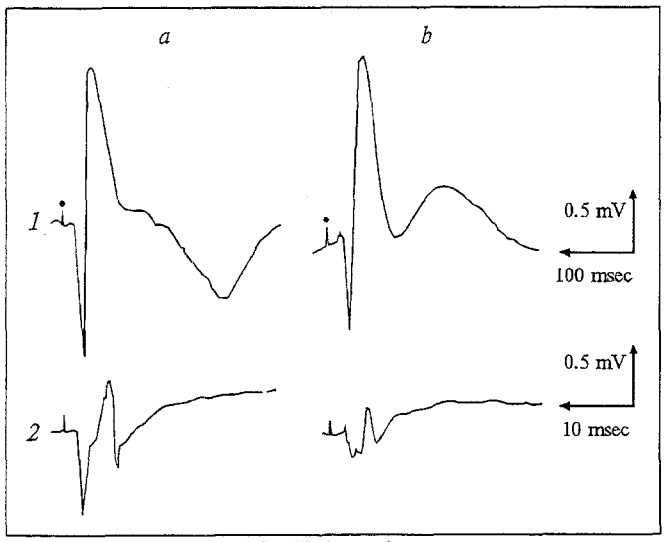

Fig. 3. Evoked potentials (EP) in the somatosensory cortex contralateral to the transected sciatic nerve (*1*) and in the ipsilateral dorsal spinal cord horns (*2*) in rats that did not develop a pain syndrome after sciatic nerve transection. *a*) EP in response to electrostimulation of the hindlimb with transected nerve; *b*) EP in response to electrostimulation of the intact hindlimb.

hyperactivation in the deafferentated dorsal horns of the lumbar segments. To confirm this, a strip of filter paper moistened with a 0.5% Novocain solution was applied to the dorsal surface of the spinal cord in the area of segments L_1-L_5. After the resultant functional blocking of dorsal horn neurons (which occurred 10 min postapplication), EP were no longer recorded either from the dorsal horn of segment L_3 (Fig. 2, *b*, *2*) or from the somatosensory cortex (Fig. 2, *a*, *2*) when the left hindlimb was stimulated. In contrast, the amplitudes of EP in the somatosensory cortex contralateral to the transected nerve remained the same when the left forelimb was stimulated (Fig. 2, *c*, *2*).

In the rats that did not develop a pain syndrome, the EP recorded from the contralateral somatosensory cortex in response to stimulation of either the hindlimb with the cut sciatic nerve or of the ipsilateral forelimb did not differ in amplitude from those in response to stimulation of the contralateral intact hind- or forelimb (Fig. 3, *b*, *1*). However, the EP in the dorsal horns on the nerve transection side had significantly greater amplitudes when the hindlimb with the cut nerve was stimulated (Fig. 3, *a*, *2*). Such a pattern of electrical responses in the dorsal horns and the somatosensory cortex was observed in all rats without a pain syndrome irrespective of the day (8th or 30th) on which these responses were recorded after sciatic nerve transection.

The above experiments indicate that the mere formation of a GPEE at the primary relay level (dorsal horns of the spinal cord) is not sufficient for the occurrence of a clinically manifest pain syndrome: if the latter is to develop, systemic pathological changes involving overlying parts of the nociceptive system, in particular the somatosensory cortex, must be present, i.e., a pathological algetic system (PAS) must form.

That such changes were present in the rats with a pain syndrome is evidenced by the observed increased amplitudes of EP both in the deafferentated dorsal horns and in the corresponding contralateral zone of the cerebral cortex when the affected limb was stimulated.

The finding that EP of increased amplitude were recorded from the zone of representation of the affected hindlimb when the ipsilateral forelimb was stimulated (an effect not observed in intact animals) attests to enhanced neuronal excitability in this zone. Such enhanced excitability may also persist for some time even when the primary GPEE in the dorsal horns is suppressed, indicating that plastic reorganization has begun in the cortex. The altered evoked responses recorded from the dorsal horns but not from the somatosensory cortex of rats that did not exhibit a clinically manifest pain syndrome are indicative of the important contribution which the involvement of higher parts of the nociceptive system makes to PAS formation. Without such involvement, no PAS as a pathophysiological basis for the pain syndrome can form, and segmental, autonomic, or other manifestations of the activity of nociceptive structures will probably occur instead.

REFERENCES

1. G. N. Kryzhanovskii, *Determinant Structures in Nervous System Pathology*, Plenum Press, New York (1986).
2. G. N. Kryzhanovskii, *Zh. Nevropatol. Psikhiat.*, **90**, № 10, 3-10 (1990).
3. G. N. Kryzhanovskii, V. K. Reshetnyak, M. L. Kukushkin, *et al.*, *Pat. Fiziol.*, № 6, 8-10 (1991).
4. G. N. Kryzhanovskii, V. K. Reshetnyak, M. L. Kukushkin, *et al.*, *Byull. Eksp. Biol.*, **114**, № 8, 229-231 (1992).
5. D. Bowsher, *Brit. Med. Bull.*, **47**, № 3, 644-666 (1991).
6. M. B. Calford and R. Tweedale, *J. Neurophysiol.*, **65**, № 2, 178-187 (1991).
7. T. J. Coderre, R. W. Crimes, and R. Melzack, *Pain*, **26**, № 1, 61-84 (1986).
8. R. W. Dykes and Y. Lamour, *Brain Res.*, **449**, № 1/2, 1-17 (1988).
9. G. Goulbaud, A. Levante, and J. M. Benoist, *Pain*, Suppl. 5, S 277 (1990).
10. T. Hirayma, J. O. Dostrovsky, J. Gorecki, *et al.*, *Stereotac. Funct. Neurosurg.*, **52**, № 2, 120-126 (1989).
11. W. Janig, *Pflugers Arch.*, **408**, Suppl. 1, S 10 (1987).
12. J. D. Loeser and A. A. Ward, *Arch Neurol. (Chic.)*, **17**, 629-636 (1967).
13. M. C. Lombard and J. M. Besson, *Pain*, **37**, № 3, 335-345 (1989).
14. M. M. Merzenich, R. J. Nelson, M. P. Stryker, *et al.*, *J. Comp. Neurol.*, **224**, № 4, 591-605 (1984).
15. J. Palecek, V. Paleckova, P. Dougherty, *et al.*, *Soc. Neurosci. Abstr.*, **17**, 437 (1991).
16. Z. Seltzer, B. Beilin, R. Ginzburg, *et al.*, *Pain*, **46**, № 3, 327-336 (1991).
17. J. T. Wall and C. G. Cusick, *J. Neurosci.*, **4**, № 6, 1499-1515 (1984).
18. P. D. Wall and M. Gutnick, *Exp. Neurol.*, **43**, 580-593 (1974).