Electrical Activity in Dorsal Horns of the Spinal Cord and in Sensorimotor Cortex in Rats with the Spinal Pain Syndrome

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 125, No. 3, pp. 269-272, March, 1998
Original article submitted January 16, 1997

In rats with the spinal pain syndrome caused by penicillin application to the dorsal surface of lumbar segments of the spinal cord, the following changes in evoked potentials were observed in the dorsal horn in L_5 segment at the side of penicillin application: a marked increase in primary response and disappearance of the secondary hyperpolarization wave with its replaument by a high-amplitude and long depolarizing wave. In addition to these changes, repetitive spontaneous burst discharges were recorded in the corresponding region of the sensorimotor cortex. Thus, the pathogenic basis of the pain syndrome is a pathological algetic system formed of altered structures that belong to nociceptive apparatus in dorsal horn and higher subdivisions of the pain sensory system.

Key Words: *dorsal horns; sensorimotor cortex, generator of pathologically enhanced excitation; pathological algetic system; spinal pain syndrome; penicillin*

We have shown that application of convulsants (tetanotoxin, penicillin, and strychnine) to various subdivisions of the nociceptive system provokes pain syndromes [1,2,5]. In this work our aim was to study the pathophysiological mechanisms of spinal pain syndrome caused by application of penicillin to the dorsal surface (DS) of the spinal cord lumbar segments and to analyze the characteristic features of electrical activity both in the penicillin-affected primary nociceptive relay (dorsal horn, DH) and in the corresponding area of the sensorimotor cortex.

MATERIALS AND METHODS

The study was carried out on 24 male Wistar rats weighing 270-320 g in accordance to regulations for experimental pain investigations in animals [9] and to the principles of work with animals in neurophysiological studies [10]. In group 1 rats, an agar plate [2] (6×1.5×2 mm) containing 25000 U/ml penicillin sodium chloride salt was applied to the DS of lumbar segments of spinal cord exposed under ether anesthesia. The wound was sutured, and the animals were observed during the development of pain syndrome.

In group 2 rats, electrical activity was recorded in penicillin-affected DH and in the corresponding region of the sensorimotor cortex. Measurements were performed when the pain syndrome reached the maximum in group 1 rats. The rats were anesthetized by intraperitoneal urethane (1400 mg/kg), placed in a stereotaxic apparatus with rigid fixation of the head and spine, trepanized, laminectomized, immobilized with a muscle relaxant (Myo-Relaxin, 50 mg/kg intramuscularly), and artificially ventilated. Muscle tissue, skin, and the vertebral spinous processes in the stereotaxic fixation points were treated with 0.5% procaine. Evoked potentials (EP) in DH of the spinal cord and in the sensorimotor cortex were recorded

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0007-4888/98/0003-0236$20.00

in response to electrostimulation with rectangular 0.1 msec current pulses applied to ipsilateral sciatic nerve (in respect to the side of penicillin application) at the level of popliteal fossa.

To record EPs in spinal cord DH, we used glass microelectrodes (tip diameter of 8-10 μm) filled with 2.5 M sodium chloride. Measurements were made at the depth of 800 μm from DH, which corresponds to lamina V [7] that contains the broad dynamic range neurons [4,8]. EP were studied before and after application of agar plate with penicillin to L_5 segment without changing the position of the microelectrode. Evoked potentials were fed into an MZ-4 direct current microelectrode amplifier and then into a VC-9 broad band amplifier (Nihon Kohden). The data were averaged (n=10-15) in a computer.

In the sensorimotor cortex EPs were recorded with monopolar silver-surface electrodes in the focus of the maximum amplitude before and after penicillin application to the spinal cord. In some experiments, cortical EPs were recorded in response to rhythmic electrostimulation (1 Hz, 5 stimuli) of the forelimb tissue at the side of penicillin application to the lumbar segments. In control rats, penicillin-free agar plate was placed to DS of lumbar segments.

The results were analyzed using Student's t test and Wilcoxon's nonparametric U test (p=0.01).

RESULTS

Application of penicillin-containing agar plate to DS of the spinal cord lumbar segments provoked the pain syndrome. During pain seizure the rats gave shrieks (vocalization response), licked or bit the pain projection area on the corresponding hind limb (local motor reaction) and run from one place to another (general motor reaction). The pain seizure appeared spontaneously or could be provoked by stimulation, including tactile, applied to the pain projection area (the phenomenon of allodynia). The maximum syndrome was observed 30-60 min after application of penicillin. In control rats (penicillin-free agar plate was applied to DS of the cord lumbar segments) the pain syndrome did not develop.

When behavioral manifestation of pain syndrome were maximal in group 1 rats, group 2 rats demonstrated markedly changed EPs in DH of L5 segment provoked by electrostimulation of the sciatic nerve ipsilateral to the side of penicillin application. The EP threshold significantly decreased to 0.08±0.02 mA (0.12±0.02 mA before penicillin application). The secondary hyperpolarization wave observed in control rats (Fig. 1, *b, 1)* disappeared, and was replaced by a long (> than 80 msec) depolarizing wave (Fig. 1, *2*).

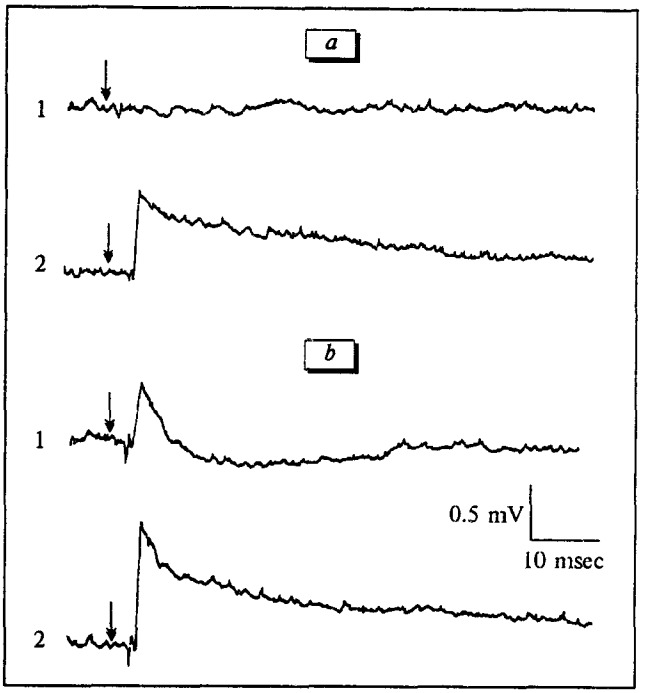

Fig. 1. Potentials in L_5 segment (*1*) before and (*2*) after penicillin application on dorsal area of this horn evoked by stimulation of sciatic nerve (arrows) with electrical current of 0.08 mA (*a*) and 0.12 mA (*b*). Here and in Figs. 2 and 3 stimulation of the sciatic nerve is indicated with arrows.

The amplitude of primary component of EP considerably increased (Fig. 1, *b, 2*): 0.9±0.1 mV *vs.* 0.5±0.1 mV in the control (Fig. 1, *b, 1*).

Profound changes in electrical activity were detected in the contralateral side of the sensorimotor cortex in respect to the penicillin application area. The minimal synchronous response during the pain syndrome development (60 min after application of penicillin to the spinal cord) was recorded when the strength of the sciatic nerve stimulating current was 0.09±0.02 mA, while in the control the threshold current was 0.14±0.02 mA. The structure of cortical EPs was drastically changed: stimulation that was the threshold nociceptive in control conditions [3] elicited now a long primary negative component and late positive waves (Fig. 2, *b, 2*). Spontaneous sharp positive waves appeared during the interstimulus period (Fig. 2, *c, 2*). Electrostimulation of the forelimb tissues with a frequency of 1 Hz evoked responses in the cortical area where the EPs were recorded in response to the sciatic nerve stimulation. During rhythmic stimulation the responses augmented and demonstrated a multicomponent structure characterized by a high-amplitude depolarizing wave and by the late secondary waves (Fig. 3, *2*). These phenomena did not appear in the control rats as in experimental rats prior to the development of pain

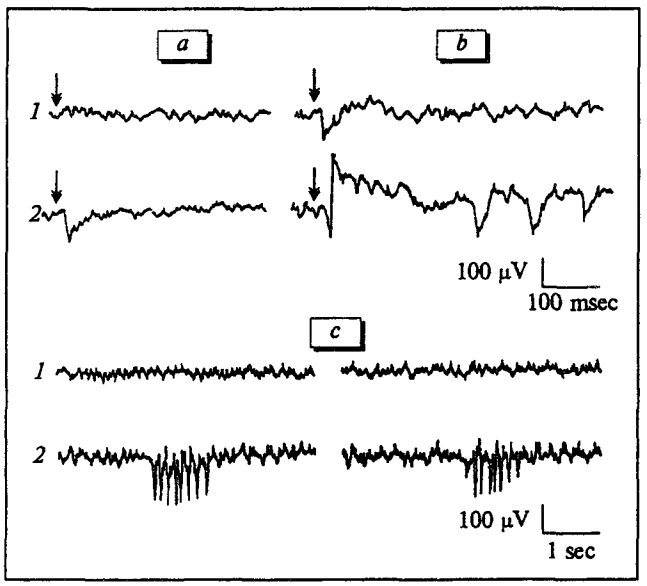

Fig. 2. Evoked potentials (*a, b*) and (*c*) background activity in the sensorimotor cortex (*1*) before and (*2*) after of penicillin appliation on the dorsal surface of L_5 cord segment. *a,b,1*) electrical activity in the sensorimotor cortex during stimulation of sciatic nerve (arrows) with electric current of 0.09 mA; *a,b,2*) electrostimulation with 0.14 mA.

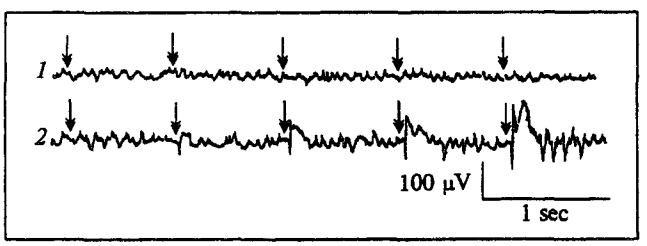

Fig. 3. Electrical activity in the sensorimotor cortex in *1*) control conditions (before penicillin application) and 2) during the development of pain syndrome caused by application of penicillin to the dorsal surface of spinal cord lumbar segment in response to rhythmic electrostimulation (arrows) of the forelimb tissues.

syndrome (Fig. 3, *1*). These data show that the spinal pain syndrome provoked by penicillin application to the DH of spinal cord segments is accompanied by profound changes in various subdivisions of nociceptive system. Changes in EPs observed in the corresponding DHs (decrease in EP threshold, increment of its amplitude, substitution of hyperpolarizing wave by depolarizing one, and marked prolongation of the latter) are indicative of hyperexcitation of a large number of neurons, synchronization of their activity, and ability to fire long excitation after termination of trigger stimulation. These signs are characteristic of the set of hyperactive neurons working as a generator of pathologically enhanced excitation [1,5].

Firing in DH provoked by this generator causes plastic changes in neurons of the higher subdivisions of nociceptive system, thalamus and cortex included. An increase in cortical EPs and the appearance of additional late waves in their structure during rhythmic stimulation from a source unrelated to DH generator (forelimb), i.e., in situation when the ascending stimulation-caused neural traffic is not mediated by a DH generator, indicate changes in cortical neurons which promote rapid development of incrementing responses during rhythmic stimulation. Increased evoked responses in the sensorimotor cortex, increment of their amplitude, and appearance of high-amplitude depolarizing wave and auxiliary secondary waves point to enhanced excitation of modified cortical neurons occurring on after the end of triggering stimulation.

Thus, the spinal pain syndrome provoked by the action of penicillin on the nociceptive apparatus in the spinal cord DH is accompanied by profound plastic changes both in this apparatus and in the higher subdivisions of the nociceptive system. The interaction of these modified structures produces a new pathodynamic system involving primary nociceptive relay and the higher nociceptive subdivisions: the pathological algetic system, which is a pathogenic basis of the pain syndrome [6].

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