GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Effect of Akatinol (Memantine) in Central Spinal Pain Syndrome

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On the model of central spinal pain syndrome in rats induced by application of penicillin to the dorsal surface of the lumbar spinal cord, akatinol injected intraperitoneally at the peak of syndrome or applied locally simultaneously with penicillin produced a dose-dependent analgesic effect. Intraperitoneal injection of akatinol at the peak of pain syndrome inhibited neuronal activity in spinal dorsal horn: the amplitude of total evoked neuronal response significantly decreased and the duration of action potentials returned to normal. It is concluded that activation of NDMA receptors plays a significant role in the development of central spinal pain syndrome, in particular spontaneous pain attacks, hyperalgesia, and tactile allodynia. Akatinol can be an essential component of the complex pathogenetic therapy of central pains.

Key Words: *akatinol; central spinal pain syndrome; penicillin; spinal dorsal horns; evoked potentials*

It was previously reported that penicillin application to the dorsal surface of the spinal cord induces central spinal pain syndrome (CSPS) [1,3]. The development of CSPS is associated with the formation of a generator of pathologically enhanced excitation in the spinal dorsal horns, presented by a cluster of sensitized neurons with self-sustained activity [3,4]. In the mechanisms underlying the neurogenic pain syndromes (in particular, CSPS) an important role is played by the release of excitatory amino acids from central terminals of the primary sensory neurons. The interaction of these amino acids with NDMA receptors leads to persistent sensitization of nociceptive neurons [2,7, 11,15].

Our aim was to study the analgesic properties of akatinol, a preparation used in psychiatric practice, acting via the blockade of NDMA receptors in CNS [5].

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MATERIALS AND METHODS

Experiments were performed on 45 Wistar rats (250-290 g) in accordance with ethic principles for the study of experimental pain and neurophysiological investigations in animals. For modeling of CSPS, left-sided lumbar laminectomy of L_{IV}-L_{VI} was performed under ether narcosis. Benzyl penicillin (BP) sodium salt, a blocker of GABA-ergic inhibition, was used to induce hyperactivation of neurons in L_{IV}-L_{VI} dorsal horns and provoke the pain syndrome. For prolonging the effect, BP was dissolved in 1% liquid agar and then a 4×2×1.5-mm agar plate containing 20,000 U BP was applied to the dorsal spinal cord. Before behavioral experiments the wound was sutured, and the rats were placed in a Perspex chamber. Akatinol (memantine hydrochloride, Merz) was applied with BP to the spinal cord in doses of 2.5 and 5 mg/ml or injected intraperitoneally at the peak of syndrome (30-40 min after application of BP) in the doses of 10, 20, and 30 mg/kg. The incidence and duration of spontaneous

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pain attacks, vocalization intensity, intervals between pain attacks, response to tactile and mechanical nociceptive stimulation of the projection zone, allodynia, and motor activity were scored using a 4-point scale: absence of symptoms (0), mild (1), moderate (2), and severe (3) symptoms.

In electrophysiological experiments, evoked potentials (EP) in response to electrical stimulation of the sciatic nerve (SN) were recorded in L_V dorsal horns before application of BP, at peak of CSPS (determined in the behavioral tests), and after intraperitoneal injection of akatinol (30 mg/kg) at the peak of CSPS. The recording microelectrode was fixed at a constant depth of 800 μ from the dorsal surface corresponding to Rexed's lamina V [14]. Glass electrodes (tip diameter 8-10 μ) were filled with 2.5 mM NaCl. The signals were imputed into an MZ-4 microelectrode amplifier coupled with a VC-9 wide-band amplifier (Nihon Kohden) and averaged by 10-15 presentations using a Microlink data acquisition system (Biodata Limited). Electrical stimulation of SN was performed with 0.1-msec rectangular pulses delivered via bipolar silver electrodes. The results were analyzed statistically using Student's t test at p=0.01 and by nonparametric Wilcoxon's test.

RESULTS

First signs of CSPS were observed 10-20 min after application BP: the rats licked toes and thigh of the left hind limb and ran around the chamber sparing the affected limb. As the pain syndrome developed, spontaneous pain attacks were accompanied by vocalization. Allodynia, a nociceptive reaction provoked by a light touch to the pain projection area, was observed between the pain attacks. CSPS persisted for 4-6 h and then gradually decreased (Fig. 1, *a*).

After application of akatinol (2.5 mg/ml) with BP, the latency of CSPS increased to 40 min, while all 6 symptoms of CSPS decreased to 1.5-2 points. Akatinol in a dose of 5 mg/ml prevented the development of CSPS (Fig. 1, *a*). Minor signs of limb sparing were observed only in 2 rats, and there were no other manifestations of pain behavior during 6 h.

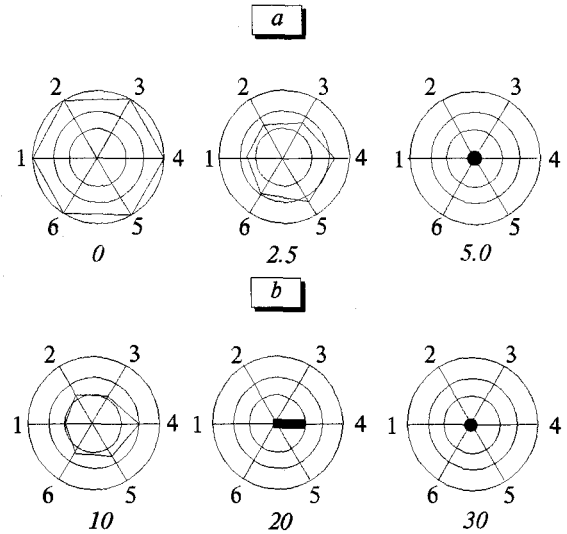

Fig. 1. Effects of akatinol applied simultaneously with penicillin (*a*) and injected intraperitoneally at the peak of the spinal pain syndrome (*b*) on the severity of pain syndrome. Numbers below the plots are the doses of akatinol in mg/ml (*a*) and mg/kg (*b*). The radii are: 1) incidence of pain attacks (1 point — 1 attack per 3 min, 2 points — 1 attack per 1 min, 3 points — 2-3 attacks per 1 min); 2) duration of pain attack (1 point — 5 sec; 2 points — 10 sec; 3 points — 15-20 sec); 3) interval between pain attacks; 4) response to stimulation of pain projection area; 5) vocalization (1 point — weak short squeaks; 3 points — long squeal throughout the attack); 6) motor activity (1 point — 1-2 short runs during pain attack; 3 points — persistent running and jumping throughout the attack). The scores of the pain syndrome are shown by the internal (1), middle (2), and external (3) circles.

Intraperitoneal akatinol (10 mg/kg) against the background of developed CSPS reduced the duration of spontaneous pain attacks and increased the intervals between attacks 20 min postinjection. Pain syndrome score decreased to 1.5 point 40 min postinjection (Fig. 1, *a*). In a dose of 20 mg/kg akatinol decreased CSPS score to 1 point 20 min postinjection, and 30 min postinjection only response to tactile stimulation of the pain projection area persisted in some rats (Fig. 1, *b*). In a dose of 30 mg/kg akatinol completely eliminated CSPS 10-15 min postinjection (Fig. 1, *b*).

Before application of BP, EP recorded in L_V dorsal horns in response to electrical stimulation (0.4 mA) of SN contained a hyperpolarization wave following

TABLE 1. Parameters of Evoked Potentials in Spinal Dorsal Horns L_V Induced by Electrical Stimulation of Sciatic Nerve ($M\pm m$, n=10)

EP parameters	Time		
	before BP application (control)	at the peak of CSPS	after injection of akatinol
Amplitude, mV	1.3±0.1	2.4±0.2	1.7±0.2*+
Duration, msec	9.8±0.2	>100	14.0±3.5*

Note. p<0.01 *compared to the peak of CSPS and +compared to the control.

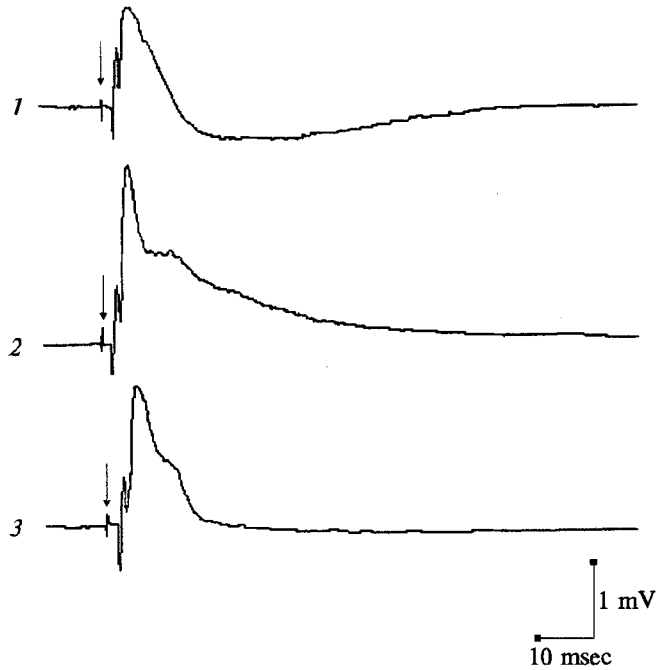

Fig. 2. Evoked potentials in dorsal horn L_V in the spinal cord before application of penicillin (*1*), at the peak of pain syndrome (*2*), and 10 min after intraperitoneal injection of akatinol (30 mg/kg) at the peak of pain syndrome (*3*). Arrows indicate electrical stimulation of the sciatic nerve (0.4 mA).

a primary negative component (Fig. 2, *1*; Table 1). At the peak of CSPS, the hyperpolarization wave was replaced by a long depolarization wave, while the amplitude and duration of EP increased (Fig. 2, *2*; Table 1). Being injected intraperitoneally at the peak of CSPS (Fig. 2, *3*), akatinol decreased the duration of EP to the control values (Table 1). The amplitude of EP also significantly decreased, but still surpassed the control value (Table 1).

The behavioral and electrophysiological data show that akatinol injected intraperitoneally or applied to the spinal dorsal horn produces a pronounced analgesic effect in rats with CSPS. The absence of pain behavior in akatinol-treated rats resulted from inhibition of lamina V neuron in the dorsal horns, which was confirmed by a significant decrease in the amplitude and duration of EP in rats with CSPS. Since akatinol acts primarily via the blockade of NDMA receptors [5], it can be suggested that the formation of the aggregate of sensitized neurons after application of BP to the spinal dorsal cord is mediated via activation of NDMA receptors.

Our data agree with published reports. For instance, in animals with neuropathic pain syndrome, memantine removed thermal hyperalgesia [9] and moderated mechanical allodynia [6]. In animals with formalin-induced trigeminal pain, the drug blocked the second (tonic) phase of grooming, and in high doses inhibited the first (phasic) pain [10]. Memantine moderated carrageenin-induced hyperalgesia for 5-25 h [8,12] and prevented blood pressure rise in animals with acute visceral and somatic pain [13].

Thus, akatinol produces a considerable analgesic effect and can be used as a component in the complex pathogenetic therapy of pain syndromes.

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