Mechanisms of Pefloxacin-Induced Pain

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In electrophysiological and behavioral experiments on rats we studied the effects of pefloxacin, a member of fluoroquinolone family, on the nociceptive system. Intraperitoneal injection of pefloxacin (80 mg/kg) decreased the thresholds of nociceptive response to noxious stimulation in the hot-plate test. In addition, it decreased the threshold of the late component of nociceptive flexor reflex. Intrathecal application of pefloxacin in a dose of 20 μg provoked allodynia, while the higher dose of 400 μg induced behavioral pattern characteristic of central pain syndrome. It was hypothesized that pain induced by pefloxacin results from disturbances in GABAergic inhibition in the central subdivisions of the nociceptive system.

Key Words: *fluoroquinolone; pefloxacin; hyperalgesia; allodynia; central pain syndrome*

Pefloxacin (PF) is a typical fluoroquinolone containing fluorine atom and methyl-substituted piperazinyl in positions 6 and 7 of the quinolone nucleus, respectively. Fluoroquinolones occupy a leading position among modern antimicrobial agents and are highly efficient medical preparations with a wide spectrum of indications [4,8,13]. However, in some cases these drugs provoke arthralgia, myalgia, visceral pain and headache [4,6,12]. It was also shown that fluoroquinolones stimulate some structures in CNS [4,5,10,14].

The mechanisms of PF-induced pains are unclear and need further investigation. PF can cross the blood-brain barrier, so its effects can be explained by direct action on the central subdivisions of the nociceptive system. For verification of this hypothesis, we studied the effect of PF of the nociceptive system in behavioral and electrophysiological experiments.

MATERIALS AND METHODS

Experiments were performed on 49 male Wistar rats (220-250 g) in strict adherence to the ethic requirements of International Association of Study of Pain during neurophysiologic investigations in animals. The animals were maintained under standard vivarium conditions with natural day/night cycle and food and water *ad libitum*. Pain sensitivity was assessed in the standard hot-plate test, *i.e.* licking of the hind paw in response to nociceptive thermal stimulation (55°C). The latency of the nociceptive reaction was measured before and after intraperitoneal injection of 80 mg/kg PF.

Peculiarities of modulation of nociceptive behavior were examined after unilateral application of agar plate (6×1, 5×2 mm) containing PF (20 or 400 μg) to the dorsal surface of the spinal cord (L4-L6). This method was described in details elsewhere [2,3]. Nociceptive response was assessed by 6 modalities: vocalization, total motor activity during pain attack, local behavioral response (licking and biting of the tissues in pain projection area in the hind paw), allodynia (nociceptive response to a tactile stimulus), and incidence and duration of pain attacks. Solutions and agar plate were prepared immediately before the experiment.

The effect of intrathecal administration of PF on nociceptive flexor reflex (NFR) was studied in electrophysiological experiments. The rats were narcotized with Nembutal (40 mg/kg intraperitoneally). NFR was recorded with two needle electrodes in biceps femoris muscle in response to nociceptive stimulation of *n. suralis* receptive field with 1-msec electrical pulses [11]. The signals were fed to a wide-band amplifier of VC-9 oscillograph (Nihon Kohden) and then to PC via a digitizer. Analysis of electrical activity was performed on a Microlink data acquisition and procession

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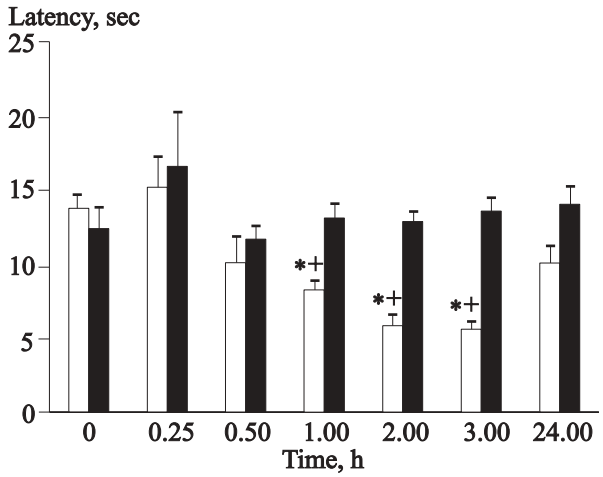

Fig. 1. Effect of pefloxacin on nociceptive sensitivity in rats in the hot-plate test. Open bars: latency before and after peritoneal injection of pefloxacin (80 mg/kg); solid bars: effect of physiological saline. *p<0.01 compared to the control group, ^{+}p<0.01 compared to initial values.

system (Biodata Limited). NFR was recorded before and after intrathecal application of PF (400 μg) via a previously made hole in lumbar vertebra (L4-L6).

The data were analyzed statistically using nonparametrical Wilcoxon test and Student's t tests.

RESULTS

Intraperitoneal administration of PF (80 mg/kg) induced hyperalgesia in the hot-plate test (n=10). Hot-plate latency significantly decreased 60-180 min after PF injection (p<0.01). Significant differences were observed in comparison with both baseline values (before injection) and control rats (n=7) receiving physiological saline (Fig. 1). Direct application of PF to the spinal dorsal horns, the primary central nociceptive "relay", also produced hyperalgesia.

In behavioral experiments, application of PF-containing agar plate to the dorsal horns of lumbar segments of spinal cord induced the development of dose-dependent pain syndrome. PF applied in a dose of 20 μg produced allodynia (n=10), *i.e.* nociceptive reaction (pain attack) in response to tactile stimulation of the sciatic nerve innervation area. Allodynia is a characteristic symptom of severe neurogenic pain syndromes, and its development indicates disturbances in GABAergic inhibition in the central elements of the nociceptive system [1,2,15].

Application of PF in a dose of 400 μg (n=10) apart from allodynia triggered spontaneous pain attacks (Fig. 2). The degree of nociceptive behavior attained maximum by all indices 25 min after intrathecal application of PF. Neither allodynia, nor central nociceptive syndrome were observed after application of agar plate with physiological solution (n=6).

Intrathecal application of PF (L4-L6, 400 μg, n=6) markedly decreased (from 5.05±0.27 to 1.5±0.4) the threshold of the late NFR phase in the biceps femoris muscle, which made it possible to record specific late discharges in this muscle even at a strength equal to the threshold value for the primary response (Fig. 3). Moreover, intrathecal PF triggered spontaneous discharges in the biceps femoris muscle. Dramatic decrease in the threshold of the late NFR phase induced by intrathecal PF and induction of spontaneous discharges suggest that PF enhances excitability of nociceptive neurons in dorsal horns of the spinal cord.

Thus, our experiments demonstrated hyperalgesic effects of PF. PF-induced pain is probably caused by disturbances in central inhibitory processes in the nociceptive system. This hypothesis is corroborated by our findings on PF-induced central nociceptive syndrome and published data on inhibition of GABA-receptors with fluoroquinolones [7,10]. Inhibition of GABA receptors by these agents is potentiated by nonsteroidal antiinflammatory drugs [9], which should be taken into consideration when both fluoroquinolones and analgetics drugs are administered simultaneously.

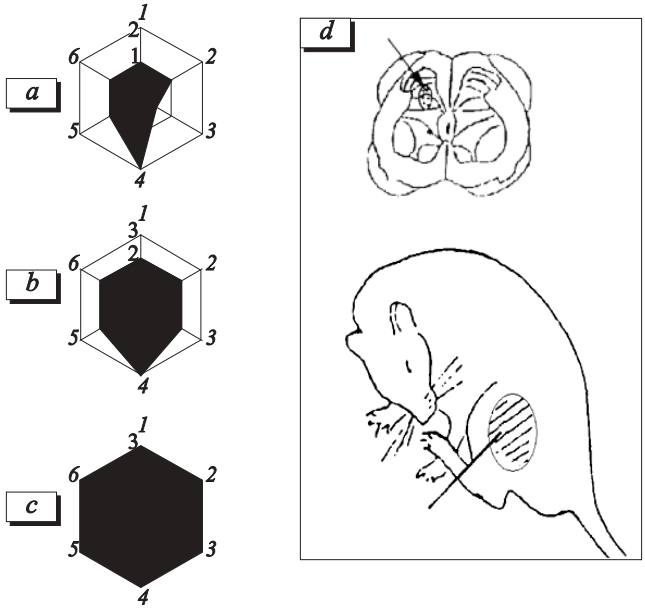

Fig. 2. Development of central pain syndrome in rats after intrathecal application of agar plate containing pefloxacin (400 μg) to lumbar segments of the spinal cord. Radial diagrams (%) show parameters of pain syndrome: *1*) vocalization, *2*) total motor activity during the attack, *3*) local behavioral response (licking and biting of the tissues in pain projection area in the hind leg), *4*) allodynia (nociceptive response to a tactile stimulus), *5*) incidence of pain attacks (min), and *6*) duration of pain attacks (sec). The diagrams correspond to 10 (*a*), 15 (*b*), and 25 min (*c*) after application of pefloxacin. *d*) The arrow in the top fragment marks the area of application of pefloxacin to the dorsal horn L6 of the spinal cord, and hatched area at the bottom fragment shows area of induced allodynia.

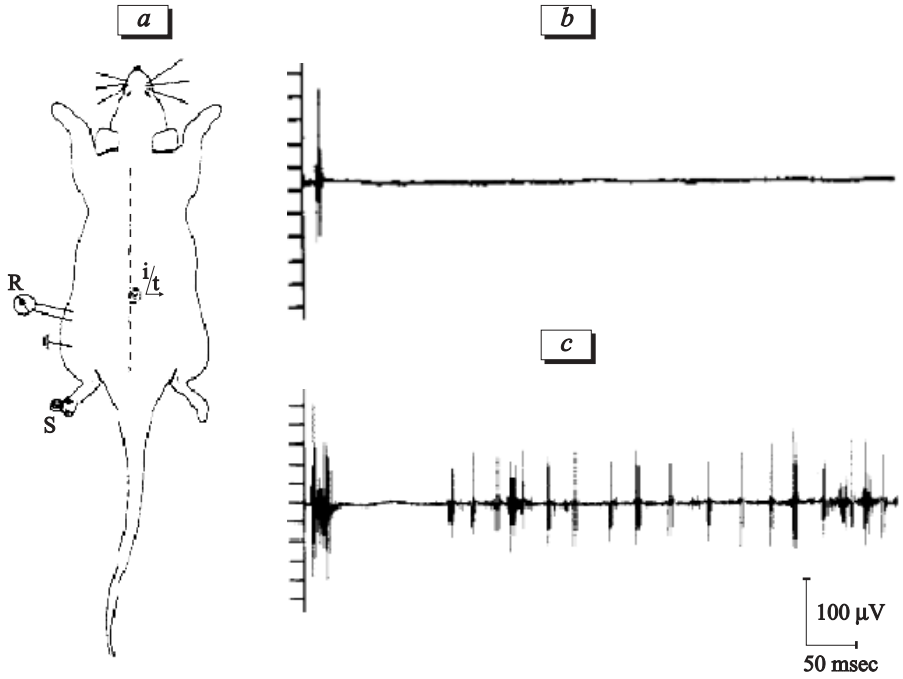

Fig. 3. Effect of pefloxacin on nociceptive flexor reflex (NFR): *a*) position of stimulating (*S*) and recording (*R*) electrodes according to Le Bars; i/t: area of intrathecal application of pefloxacin. Fragments *b* and *c* show NFR before and after application of pefloxacin (400 μg), respectively (electrical stimulation at 2 mA).

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