Role of Opioid System in Modulation of Pain Sensitivity under Conditons of Low and High Environmental Temperature

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The dependence of pain sensitivity in acetic acid-induced writhing test on environmental temperature was described by a bell-shaped curve. The maximum number of writhings was observed in thermoneutral environment and minimum in hot and cold environment. Under conditions of opioid receptor blockade with naloxone, naltrindole, norbinaltorphimine, analgesia is partially mediated by μ-, δ-, and κ-opioid receptors.

Key Words: *analgesia; temperature; opioid receptor blockers*

Temperature is an important factor modulating pain sensitivity [13]. The mechanisms of analgesic effects of cold and heat are now intensively studied. In mammals, six ionic channels belonging to the TRP family (transient receptor potentials) were identified; they are sensitive to thermal influences and are characterized by different activation temperature thresholds [2] with receptor activity range from 0 to 50°C [12]. It is accepted that TRP channels function as a molecular integrator of nociceptive, chemical, and physical stimuli, including thermal stimuli [10]. However, recent experiments on mice lacking TRPM8 protein responsible for cold sensitivity showed that pain and cold sensitivities are partially preserved [6,8], while TRPV1-knockout mice are not completely insensitive to pain and heat [1,7,14,15]. There are experimental data that the opioid system can be involved in thermal.

Here we studied the effect of environmental temperature on pain sensitivity and the role of the opioid system in analgesic effect of cold and heat. Changes in pain sensitivity at different environmental temperatures and against the background of treatment with μ-, δ-, and κ-opioid receptor (OR) blockers were studied on the model of nonthermal pain (writhing test).

MATERIALS AND METHODS

The study was performed on male outbred mice (n=374) weighing 20-22 g (10-12 animals per group). Blockers of μ-, δ-, and κ-OR naloxone, naltrindole, norbinaltorphimine were purchased from Sigma. The blockers were injected intraperitoneally in doses of 1 and 10 mg/kg (10 ml/kg, in aqueous solution) 20 min before testing. Controls received an equivalent volume of distilled water.

We used the model of nonthermal pain (writhing test). The animals in individual boxes were placed in a thermocontrolled chamber with preset temperature and adapted to experimental conditions for 1 h. Then, 0.6% acetic acid was administered to the mice (10 ml/kg) and the number of writhings was recorded over 30 min [3]. Pain sensitivity was evaluated in 5 temperature regimens: in cold chamber (0-6°C and 13-14°C), at room temperature (21-22°C), and in thermoneutral (26-27°C) and hot (31-33°C) environment, corresponding to different func-

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tional states of the thermoregulation system [5]. The effect of OR blockers was studied in three temperature regimens: in cold (0-6°C), thermoneutral, and hot environment.

The data were processed statistically using nonparametric Wilcoxon test for paired comparison.

RESULTS

In control animals, the number of writhings at room temperature was 31.6±5.0. At 13-14°C this parameter decreased to 8.3±3.6 and at 0-6°C to 3.8±1.0. In thermoneutral environment, the number of writhings increased to 53.8±4.2, but further increase in environmental temperature sharply decreased this parameter to 9.2±3.9 (Fig. 1).

Under thermoneutral conditions, administration of naloxone, naltrindole, and norbinaltorphimine led to a clear-cut decrease in the number of writhings. Naltrindole and norbinaltorphimine were more effective in a dose of 1 mg/kg, while naloxone similarly reduced pain in both administered doses (Table 1).

In cold, naloxone in a dose of 1 mg/kg had no effect on pain sensitivity, while in a dose of 10 mg/kg it significantly increased the number of writhings. Hence, naloxone in the high dose partially abolished the analgesic effect of cold temperature.

The number of writhings after administration of naltrindole was the same in cold and thermoneutral environment (irrespective of naltrindole dose). However, the blocker in a dose of 10 mg/kg significantly increased the number of writhings compared to that observed in the control group kept in cold environment (Table 1).

After injection of norbinaltorphimine in a dose of 1 mg/kg under conditions of cold environment, the number of writhings increased compared to that observed in control mice placed in cold chamber and in animals in thermoneutral environment. Increasing the dose reduced the efficiency of the blocker.

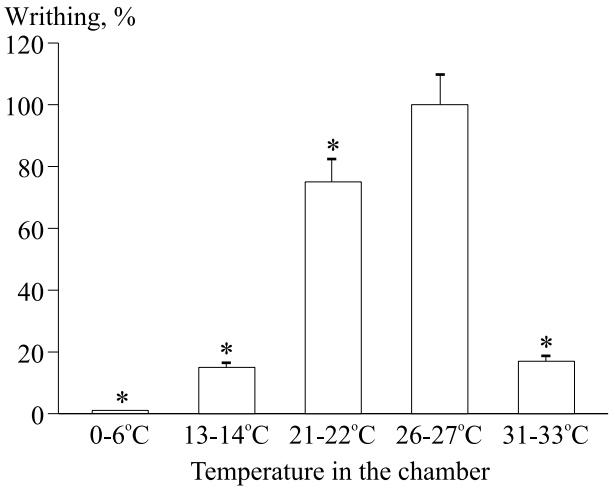

Fig. 1. Effect of environmental temperature on pain sensitivity of mice in the test of acetic acid-induced writhing. *p<0.05 compared to thermoneutral environment (26-27°C).

Thus, μ-, δ-, and κ-OR are probably involved in the analgesic effect of cold.

In hot environment, administration of blockers in a dose of 1 mg/kg increased the number of writhings compared to that observed in the control group placed in hot environment and animals placed in thermoneutral environment. Naloxone in a dose of 10 mg/kg practically did not change the analgesic effect of hot exposure, while naltrindole and norbinaltorphimine increased the number of writhings (Table 1). Hence, naloxone, naltrindole, norbinaltorphimine partially abolished the analgesic effect caused by hot exposure. Thus, analgesia cau-

TABLE 1. Effect of Environmental Temperature on Pain Sensitivity of Mice in the Test of Acetic Acid-Induced Writhing

Blocker		Temperature in the chamber					
		0-6°C		26-27°C		31-33°C	
		abs.	%	abs.	%	abs.	%
Control		1.8±1.8*	5	36.0±11.2	100	4.2±4.1*	12
Naloxone	1 mg/kg	1.9±2.1*	5	6.5±6.1*	18	16.9±10.0*+°	47
	10 mg/kg	11.3±7.1*+	31	6.6±6.3*	18	5.9±5.4*	16
Naltrindole	1 mg/kg	0.3±0.9*+	1	0.3±0.6*	1	8.2±3.6*+°	23
	10 mg/kg	10.2±8.5*+	28	12.3±9.9*	34	9.8±10.1*+	27
Norbinaltorphimine	1 mg/kg	7.7±5.8*+°	21	0.8±1.1*	2	9.8±8.4*+°	27
	10 mg/kg	3.4±3.6*+°	10	17.8±3.5*	49	12.3±10.0*+	34

Note. The number of writhings in thermoneutral environment is taken as 100%. p<0.05 compared to the control: *in thermoneutral environment; +in the same environment; °compared to the effect of blocker in thermoneutral environment.

sed by cold of heat is partially mediated by μ-, δ-, and κ-OR.

The dependence of pain sensitivity in acetic acid-induced writhing test on environmental temperature was described by a bell-shaped curve. The maximum number of writhings was observed in thermoneutral environment and minimum in hot and cold environment. According to definition of The Commission for Thermal Physiology of the International Union of Physiological Sciences, the thermoregulation system does not respond to ambient temperature under thermoneutral conditions [4]. We found that the pain sensitivity of animals and the effect of OR blockers were maximum in this temperature range.

It can be hypothesized that some thermoreceptors (nociceptors), being temperature-insensitive in this temperature range, exhibit maximum pain sensitivity [1,6,8]. In cold and hot environment, the effects of OR blockers differ from those observed under thermoneutral conditions, because the regulation is mediated by receptors, which simultaneously act as thermosensitive and nociceptive receptors.

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