Effect of Activated Peripheral κ-Opioid Receptors on the Action of Nicotine and Its Withdrawal in Nicotine-Dependent Rats

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 156, No. 11, pp. 549-551, November, 2013
Original article submitted July 15, 2012

We studied the possibilities of modulating the effects of nicotine and its withdrawal in nicotine-dependent rats by peripheral injection of κ-opioid receptor agonist ICI 204,448. Injection of nicotine to rats previously treated with nicotine for 14 days reduced motor activity, suppressed metabolism, and increased food intake. In rats receiving ICI 204,448 after chronic administration of nicotine, food intake did not differ from that in control animals receiving isotonic NaCl solution. ICI 204,448 had virtually no effect on suppression of motor activity and metabolism. The rats receiving the last injection of nicotine 24 h prior to the experiment demonstrated an increase in metabolism, locomotor activity, and food intake. In these animals, ICI 204,448 completely abolished the effects of nicotine withdrawal. It was found that peripheral administration of compound ICI 204,448 did not significantly inhibit the effect of nicotine in nicotine-dependent rats, but abolished symptoms of nicotine withdrawal. It can be hypothesized that nicotine withdrawal syndrome is related to inhibition of dopamine release in the nucleus accumbens probably caused by enhanced κ-opioid activity in presynaptic terminals. Activation of peripheral κ-opioid receptors apparently suppressed (via vagal afferent pathways) central κ-opioid activity and reduced nicotine withdrawal symptoms in nicotine-dependent subjects.

Key Words: *κ-opioid receptors; nicotine; metabolism; feeding behavior; motor activity*

Tobacco smoking is a risk factor for lung cancer, obliterating endarteritis, cardiovascular and other diseases [6]. Well-known quit smoking medications are nicotine replacement therapy products or toxic agents used in aversion therapy [1]; however, neither of them has the desired effect due to the resumption of intensive withdrawal syndrome or lack of the effect on pathogenic mechanisms of addiction.

Agonists of κ-opioid receptors potentiate nicotine withdrawal syndrome due to inhibition of dopamine release from dopamine-containing terminals in the nucleus accumbens and activation of dopamine reuptake [8,11]. Thus, inhibition of κ-opioid system activity in the CNS, particularly in the nucleus accumbens, is necessary for the relief of nicotine withdrawal. However, central κ-opioid receptor antagonists can seriously disturb CNS functions. Our previous studies have demonstrated that peripheral opioid receptor agonists produce an inhibitory effect of the opioid system in CNS [2,3,9,10]. Thus, peripheral administration of κ-opioid receptor agonists not crossing the brain-blood barrier may suppress κ-opioid system in CNS, enhance dopamine release in the nucleus accumbens, and inhibit nicotine withdrawal syndrome. Moreover, nicotine withdrawal in nicotine-dependent subjects increases food intake and weight gain concern can prevent the individual from quitting. We have shown [4] that selective κ-opioid receptor agonist ICI 204,448 administered intragastrically significantly inhibits feeding

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behavior that would greatly simplify smoking cessation. Since ICI 204,448 does not penetrate through the brain-blood barrier, it is used in cases when it is necessary to investigate central and peripheral effects on the κ-opioid system separately [7].

Here we studied the possibility of modulating the effects of nicotine and its withdrawal in nicotine-dependent rats by peripheral injection of κ-opioid receptor agonist ICI 204,448.

MATERIALS AND METHODS

The study was carried out on male Wistar rats (n=40) weighing 230-250 g. Before the experiment, the animals were housed in ventilated Techeplast cages, 5 animals in each cage with free access to water and standard combined chow (light from 08.00 to 20.00 h, 21°C).

The experiments were performed in accordance with the Order No. 267 of the Ministry of Health of the Russian Federation of 19.06.2003 and Regulations on Studies with the Use of Experimental Animals (P. K. Anokhin Research Institute of Physiology, Protocol No. 1, 03.09.2005).

The rats were divided into 5 groups (8 rats per group). Group 1 animals received isotonic NaCl solution subcutaneously twice a day for 14 days; animals of groups 2, 3, 4, and 5 received subcutaneous injections of nicotine (nicotine tartrate, ISN biomedical Inc.) in a dose of 2 mg/kg twice a day for 7 days and then in a dose of 3 mg/kg for the next 7 days.

Group 1 animals were subcutaneously injected with isotonic NaCl solution before the experiment and in 5 min they received isotonic NaCl through a gastric tube. Group 2 animals intragastrically received isotonic NaCl 5 min after nicotine injection (3 mg/kg). Group 3 rats were subcutaneously injected with nicotine (3 mg/kg) and then κ-opioid receptor agonist ICI 204,448 (Tocris Bioscience) was administered intragastrically in a dose of 200 μg/kg. Group 4 animals received the last injection of nicotine 24 h before the experiment and were administered intragastrically with isotonic NaCl solution immediately before the experiment. Group 5 animals also received the last nicotine injection 24 h before the experiment and were administered with ICI 204,448 at a dose of 200 mg/kg immediately before the experiment.

Directly after intragastric administration of substances, the rats were individually placed into the modular phenotyping platform TSE PhenoMaster, where in standard home cage in given environments, locomotor activity (by the number of squares crossed), amount of food and water intake as well as O_2 consumption and CO_2 production were recorded every 60 min over 24 h, and the metabolic rate of the animal (kcal/h/kg) was calculated.

Significance of differences between the control and experimental groups were evaluated using ANOVA and Student's t test.

RESULTS

Nicotine administered to rats previously treated with nicotine for 14 days reduced locomotor activity (Fig. 1), suppressed metabolism (Fig. 2), and increased food consumption (Fig. 3) in comparison with controls receiving saline. In rats receiving ICI 204,448 after nicotine, food intake did not differ from the control during daytime and was significantly lower during dark time (Fig. 3). Administration of ICI 204,448 had virtually no

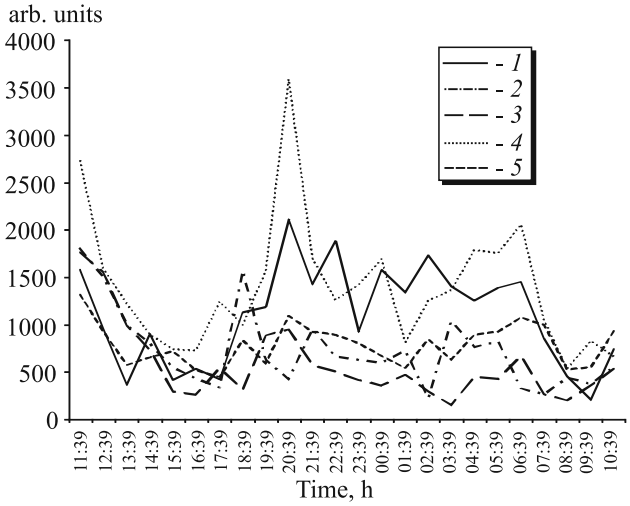

Fig. 1. Horizontal locomotor activity in rats of the studied groups. Here and in Figs. 2 and 3: *1*) control (isotonic NaCl solution for 14 days); *2*) nicotine for 14 days+nicotine and isotonic NaCl solution before the experiment; *3*) nicotine for 14 days+nicotine and ICI 204,448 before the experiment; *4*) nicotine for 14 days+nicotine and isotonic NaCl solution subcutaneously and intragastrically before the experiment; *5*) nicotine for 14 days+nicotine and isotonic NaCl solution+ICI 204,448 before the experiment. Dark time from

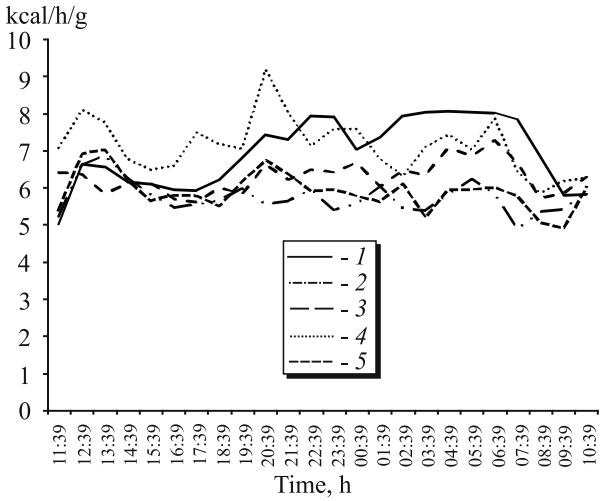

Fig. 2. Metabolism rate in rats of the studied groups.

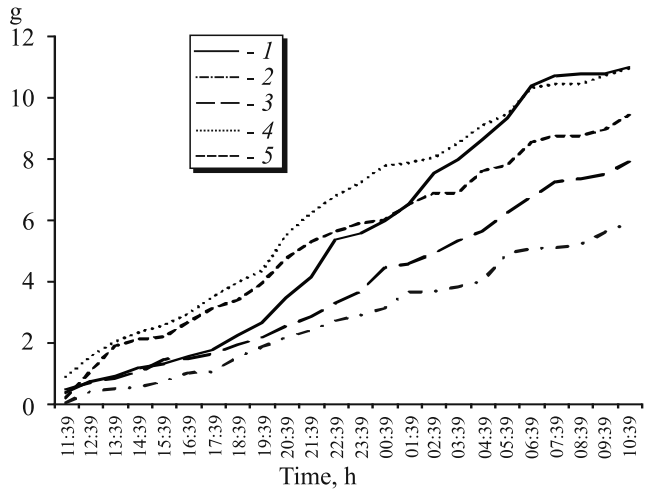

Fig. 3. Food consumption in the studied groups.

effect on suppression of locomotor activity and metabolism caused by nicotine injection (Figs. 1, 2).

Increased In rats receiving the last injection of nicotine 24 h prior to the experiment, metabolism, locomotor activity, and food intake were increased in comparison with the control. Administration of ICI 204,448 to these animals completely abolished the effects of nicotine withdrawal during daytime; during dark time, metabolism, locomotor activity, and feeding behavior in these animals were significantly suppressed in comparison with both nicotine-dependent and control rats (Figs. 1-3).

Thus, peripheral administration of compound ICI 204,448 partially inhibits the action of nicotine in nicotine-dependent rats, and especially its effect on feeding behavior. However, if we consider that peripheral administration of compound ICI 204,448 significantly suppresses feeding behavior [4] and has practically no impact on the effects associated with metabolism and motor activity, we can assume that the influence of ICI 204,448 on the effect of nicotine is negligible. On the other hand, peripheral administration of ICI 204,448 suppressed all recorded parameters of nicotine withdrawal. It can be hypothesized that nicotine withdrawal syndrome is related to inhibition of dopamine release in the nucleus accumbens probably caused by enhanced κ-opioid activity in presynaptic terminals [5]. Activation of peripheral κ-opioid receptors apparently results in inhibition of central κ-opioid activity via vagal afferent pathway and alleviation of nicotine withdrawal symptoms in nicotine-dependent subjects.

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