Effects of Peripheral μ, δ, and κ-Opioid Receptor Agonists on the Levels of Anxiety and Motor Activity of Rats

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The effects of intragastric administration of μ-, δ, and κ-opioid receptor agonists DAMGO, DADLE, and ICI 204,448, respectively, on the anxiety and motor activity of rats in an elevated plus-maze were studied. Peripheral administration of ICI 204,448 produced an anxiolytic effect, but had no effect on motor activity of rats. DAMGO and DADLE reduced motor activity; DADLE also increased anxiety. The data on the opposite effects of ICI 204,448 and DADLE on anxiety confirmed our previous hypothesis on the interactions between the central and peripheral components of the endogenous opioid system.

Key Words: *peripheral μ-, δ, and κ-opioid receptors; central opioid system; anxiolytic effect; motor activity; elevated plus-maze*

The endogenous opioid system plays an important role in organization of emotions and reactions of the organism [3]. The main types of receptors of the endogenous opioid system are μ-, δ, and κ-receptors, their endogenous agonists are endorphins, enkephalins, and dinorphins. Stimulation of the central μ- and δ-receptors induces positive emotions [1,2], while κ-receptors are linked with the central mechanisms of dysphoria and their stimulation as a rule leads to presynaptic suppression of the postsynaptic μ- and δ-opioid receptor activities [8]. Hence, central administration of peptide μ- and δ-opioid agonists leads to anxiety suppression [9], while κ-agonists stimulate anxiety [4].

We previously showed that peripheral administration of opioid receptor agonists or antagonists not penetrating through the blood-brain barrier led to effects opposite to the central activity of the same substances [10-12]. It was therefore interesting from theoretical and practical viewpoints to study the role of the peripheral opioid receptors of different subtypes in the mechanisms regulating the emotional status.

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We studied the effects of the peripheral (intragastric) administration of μ-, δ-, and κ-opioid receptor agonists DAMGO, DADLE, and ICI 204,448, respectively, on the levels of anxiety and motor activity of rats with consideration for the fact that through this route of administration the peptide molecules could modulate only the gastroduodenal opioid receptors.

MATERIALS AND METHODS

The study was carried out on male Wistar rats (n=32; 180-210 g). The animals were kept 5-6 per cage, with individual ventilation and free access to water and standard combined fodder. Seven days before experiment, each rat was individually handled for 15 min daily. The experiments were carried out 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 Institute of Physiology, Protocol No. 1, 03.09.2005).

The rats were divided into 4 groups, 8 animals each. All animals were administered the solutions (0.1 ml/100 g) intragastrically through a metal tube. Group 1 animals (control) received 0.9% NaCl. Group 2 rats received DAMGO in a dose of 200 μg/kg, group 3 re-

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TABLE 1. Effects of DAMGO, DADLE, and ICI 204,448 on the Rat Anxiety and Motor Activity in EPM

Substance, dose	Time spent, sec			Total number of crossings of entries into arms
	in open arms	in closed arms	in the center	
0.9% NaCl solution (control)	14.63±6.60	265.13±11.00	20.25±6.60	2.63±1.10
DAMGO, 200 μg/kg	11.0±5.4	243.38±31.00	45.63±32.00	1.5±0.3*
ICI 204,448, 200 μg/kg	47±28*	239.88±33.00	12.0±6.8	2.75±1.10
DADLE, 200 μg/kg	1.78±0.60*	293.33±1.50	4.89±1.40*	4.67±0.90*

Note. *$p<0.05$ in comparison with the control group.

ceived DADLE in the same dose, group 4 received ICI 204,448 in the same dose (all substances from Tocris).

Anxiety and motor activity were evaluated in an elevated plus-maze (EPM) and by a previously described method for evaluation of animal behavior [6]. The basal EPM modification was used (50-cm arms 15 cm wide, two opposite closed arms of the maze with 15-cm-high walls, and a 15×15 cm central platform). The maze was 75 cm elevated above the floor. The rats were placed into the EPM center 30 min after drug injection and the following parameters were recorded for 5 min by the standard method: total number of ventures into all arms, number of ventures to the open and closed arms, time spent in open arms, vertical activity (number of rearing episodes), and time spent on the central platform.

The differences between the experimental and control groups were evaluated by nonparametric Mann–Whitney *U* test. The results were considered significant at $p<0.05$.

RESULTS

ICI 204,448 prolonged, while DADLE shortened the time spent by the animals in the EPM open arms in comparison with the controls. DAMGO virtually did not change the duration of stay in the open arms (Table 1).

Peripheral ICI 204,448 did not change motor activity of rats evaluated by the total number of crossing the entries to and exits from the maze arms. DAMGO reduced, while DADLE increased this parameter (Table 1).

The results indicate that stimulation of δ-opioid receptors of the stomach and, presumably, of the duodenum led to increase of anxiety in the presence of total motor excitation, while stimulation of κ-opioid receptors led to anxiolytic effect. Presumably, the level of anxiety changed in response to δ-agonist by the following mechanism. Administration of DADLE into the rat stomach stimulated δ-receptors of the gastric wall, which presumably via vagus afferentation (according to our hypothesis [12]) led to inhibition of the central δ-opioid system, reduction of the central receptors affinity and, presumably, to a decrease of enkephalin release from the nerve endings. Some authors showed that inhibition of the δ-opioid system in the brain structures could augment anxiety [5,7]. Intragastric ICI 204,448 activating the gastric (and presumably duodenal) κ-opioid reception, supressed the κ-opioid reception normally inhibiting the brain δ-opioid system. This could lead to an increase of enkephalin release in the segmental and limbic structures, resulting in anxiolytic effect.

The results open new approaches to development of principally novel rather safe peripheral drugs regulating human emotional functions.

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