PHYSIOLOGY

Effect of Peripheral Administration of Peptide Ligands of δ-Opioid Receptors on Anxiety Level and Locomotor Activity of Rats

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We studied the effect of intragastric administration of a peptide δ-opioid receptor agonist DADLE and peptide δ-opioid receptor antagonist ICI 174.864 on anxiety and locomotor activity of rats. Peripheral administration of ICI 174.864 produced an anxiolytic effect, but did not modulate locomotor activity of rats. Agonist DADLE in doses of 50 and 100 μg/kg increased anxiety, but decreased locomotor activity of rats. Our results indicate that ICI 174.864 and DADLE produce opposite effects on anxiety in rats. These data support our hypothesis on the interaction between the central and peripheral compartments of the endogenous opioid system.

Key Words: *peripheral δ-opioid receptors; central opioid system; anxiolytic effect; elevated plus-maze; anxiety*

The endogenous opioid system plays an important role in emotions and reaction of the body to stress factors [1]. The δ-opioid system of the brain is involved in these processes. For example, preproenkephalin gene knockout mice are characterized by considerably elevated anxiety [2,5]. Injection of δ-opioid receptor agonists into the central nucleus of the amygdala [6] or dorsal hippocampus [7] was followed by a decrease in emotional reactivity of rats. Administration of δ-opioid receptor antagonists into the same structures increased anxiety. Therefore, the brain δ-opioid system has a suppressive effect on emotionality and anxiety of animals.

We put forward a hypothesis on the reciprocal interaction between the central and peripheral compartments of the endogenous opioid system [10]. Our previous experiments showed that agonists and antagonists of peripheral μ-opioid receptors have opposite effect on pain sensitivity, feeding behavior, anxiety, and locomotor activity of animals [8,9]. However, the role of the peripheral compartment of the δ-opioid system in emotionality and anxiety remains unclear.

Here we studied the effect of peripheral (intragastric) administration of a peptide δ-opioid receptor agonist DADLE and antagonist ICI 174.864 on the degree of anxiety and locomotor activity of rats. It should be emphasized that under these conditions, the peptide molecules affect only δ-opioid receptors in the stomach and duodenum.

MATERIALS AND METHODS

Experiments were performed on 45 male Wistar rats weighing 180-210 g. The animals were housed in cages (5 specimens per cage) and had free access to

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water and standard combined feed. Over 7 days, each experimental rat was subjected to a handling procedure for 15 min. The experiment was conducted in accordance with the Order No. 267 of the Russian Ministry of Health (19.06.2003) and Rules of Studies on Experimental Animals (P. K. Anokhin Institute of Normal Physiology; protocol No. 1, 03.09.2005).

The rats were divided into 5 groups (9 animals each). The test solutions were administered intragastrically (1 ml/kg) via a special metal probe. Group 1 animals (control) received only physiological saline. Group 2, 3, and 4 rats were treated with [D-Ala^2, D-Leu^5]-enkephalin (DADLE, Tocris) in doses of 10, 50, and 100 μg/kg. N,N-Diallyl-Tyr-Aib-Aib-Phe-Leu-OH: Aib=alpha-aminoisobutyric acid (ICI 174.864, Tocris) in a dose of 50 μg/kg was administered to group 5 rats.

Anxiety of rats was studied in an elevated plus maze (EPM) and using a behavioral test proposed by S. Pellow *et al*. [3]. Standard EPM modification was used. The length and width of each of 4 arms in this maze were 50 and 15 cm, respectively. The height of lightproof boards in the opposite closed arms of the maze was 15 cm. The central area was 15×15 cm. The maze was elevated by 75 cm above the floor. Each rat was placed in the center of EPM 30 min after administration of the test compounds. The behavior of animals was studied by the standard method over 5 min. We recorded the total number of entries into all arms, number of entries into open arms, number of entries into closed arms, times spent in open arms, vertical activity (number of rearing postures), and times spent in the central area.

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

RESULTS

Intragastric administration of δ-opioid receptor antagonist ICI 174.864 in a dose of 50 μg/kg increased the time spent in EPM open arms in comparison with the control (Fig. 1). However, intragastric administration of δ-opioid receptor agonist DADLE in doses of 100 and 50 μg/kg decreased the time spent in the open arms. DADLE in a dose of 10 μg/kg had no effect on the time spent in open arms of EPM (Fig. 1).

Peripheral administration of ICI 174.864 in a dose of 50 μg/kg did not modulate locomotor activity of rats (Fig. 2). Intragastric administration of the peptide DADLE in doses of 100 and 50 μg/kg decreased locomotor activity of animals in EPM arms. The agonist in a dose of 10 μg/kg had no effect on this parameter.

Our findings suggest that activation of δ-opioid receptors in the stomach and, probably, in the duodenum produces an anxiolytic effect. By contrast, inhibition of receptor activity is followed by reduction of animal anxiety.

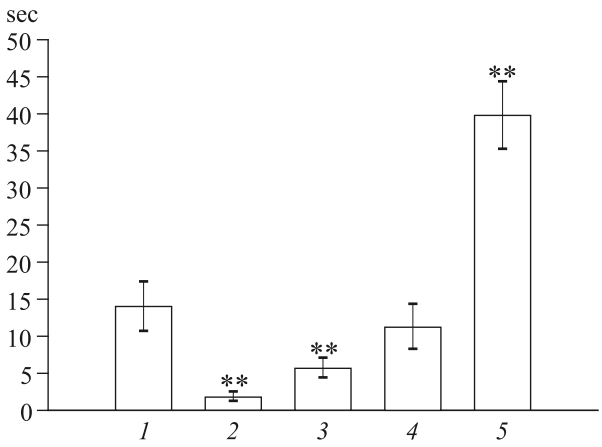

Fig. 1. Effect of δ-opioid receptor ligands DADLE and ICI 174.864 on anxiety of rats in EPM. Ordinate: time spent in open arms. Here and in Fig. 2: control (*1*); DADLE, 100 μg/kg (*2*); DADLE, 50 μg/kg (*3*); DADLE, 10 μg/kg (*4*); ICI 174.864, 50 μg/kg (*5*). ***p*<0.01 compared to the control.

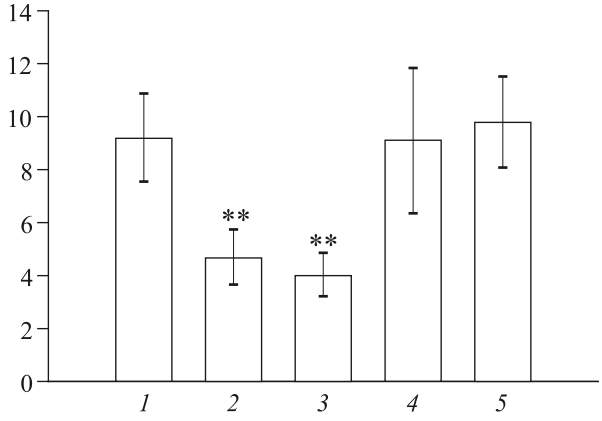

Fig. 2. Effect of DADLE and ICI 174.864 on locomotor activity of rats in EPM. Ordinate: total number of crossings.

Our previous studies showed that peripheral administration of μ-opioid receptor antagonist methylnaloxone reduces anxiety in experimental rats [8]. The observed effect was probably related to an increase in the density of μ-opioid receptors in the brain cortex and midbrain [4] and stimulation of δ-endorphin release under these conditions [9]. It can be hypothesized that the anxiolytic effect of δ-opioid receptor antagonist ICI 174.864 is associated with activation of the central compartment of the δ-opioid system. The anxiogenic effect of DADLE is probably associated with inhibition of central δ-opioid mechanisms.

We conclude that ICI 174.864 and DADLE have opposite effects on anxiety of rats. These data support our hypothesis on the interaction between the central and peripheral compartments of the endogenous opioid system.

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