Changes in Feeding Behavior, Locomotor Activity, and Metabolism in Rats upon Modulation of Opioid Receptors in the Gastrointestinal Tract

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We studied the role of μ-, δ-, and κ-opioid receptors of the stomach in the regulation of natural feeding behavior, metabolism, and locomotor activity of rats. Locomotor activity (number of crossed squares), food and water intake, oxygen consumption, and carbon dioxide release in animals were estimated in the standard home cage using a Phenomaster device (TSE) for 24 h at 40-min intervals. Administration of a μ-opioid receptor agonist DAMGO suppressed feeding behavior of animals in the light phase, but had little effect on locomotor activity and metabolism. Treatment with a δ-opioid receptor agonist DADLE was followed by the increase in metabolism over 24 h. These changes were accompanied by a decrease in locomotor activity during the light phase and activation of feeding behavior in the transition period. Intragastric administration of a κ-opioid receptor agonist ICI-204,448 inhibited feeding behavior, metabolism, and locomotor activity of rats only in the nighttime. These data suggest that opioid peptides produced in the stomach during food digestion play an important role in the regulation of food motivation and metabolism in rats. Various subtypes of opioid receptors probably regulate feeding behavior and metabolism of animals in different phases of vital activity.

Key Words: *opioid receptors; metabolism; feeding behavior; locomotor activity; rats*

Milk is the major nourishment product in mammals, which contains proteins. β-Casomorphins are formed from milk in GIT and possess opioid properties [6]. They are resistant to gastric and intestinal peptidases, but are rapidly degraded by plasma dipeptidyl peptidase [7]. β-Casomorphin-like opioid peptides (*e.g.*, soy morphines from soybean [9] and gluten derivatives from wheat [8]) were also found in food products.

GIT has a large number of opioid receptors. However, their role in the regulation of tonic activity and peristalsis of GIT, as well as in the modulation of CNS functions remains unclear [5]. Opioid peptides formed during digestion of dietary proteins can interact with opioid receptors of the stomach and, therefore, serve as an exogenous regulatory factor for the central and peripheral components of feeding behavior.

Our previous studies showed that activation of GIT μ-opioid receptors by loperamide is followed by the inhibition of feeding behavior in fasting rats [4].

Here we studied the role of μ-, δ-, and κ-opioid receptors of the stomach in the regulation of natural feeding behavior, metabolism, and locomotor activity of rats.

MATERIALS AND METHODS

Experiments were performed on 32 Wistar rats weighing 250 g. The animals were housed in individual ventilated Techneplast cages (4 rats per cage) and had free access to water and standard combined feed. The rats were maintained at 21°C and artificial light/dark cycle (light 08.00-20.00). The research was

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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 Research Institute of Normal Physiology; Protocol No. 1, 03.09.2005).

During the study, all rats were placed in a Phenomaster device (TSE). Locomotor activity (number of crossed squares), amount of consumed food and water, oxygen consumption, and carbon dioxide release were recorded over 24 h at 40-min intervals under standard conditions ("home" cage).

The solutions (0.1 ml per 100 g body weight) were administered intragastrically through a metal probe. The study was performed with opioid receptor agonists (peptides) that are rapidly degraded in GIT. After intragastric administration, these peptides produce no systemic or central effects. Group 1 animals (control) received water. A μ-opioid receptor agonist DAMGO (200 μg/kg), δ-opioid receptor agonist DADLE (200 μg/kg), and κ-opioid receptor agonist ICI-204,448 (200 μg/kg) were administered to rats of groups 2, 3, and 4, respectively. The doses of these substances were selected from the results of our previous experiments [1].

The significance of differences between the treatment and control groups was evaluated by ANOVA and Student's *t* test.

RESULTS

Locomotor activity, feeding behavior, and intensity of metabolism in control animals were shown to decrease during the daytime. It should be emphasized that these rats exhibited a short-term increase in locomotor activity during both the light and dark periods, which was

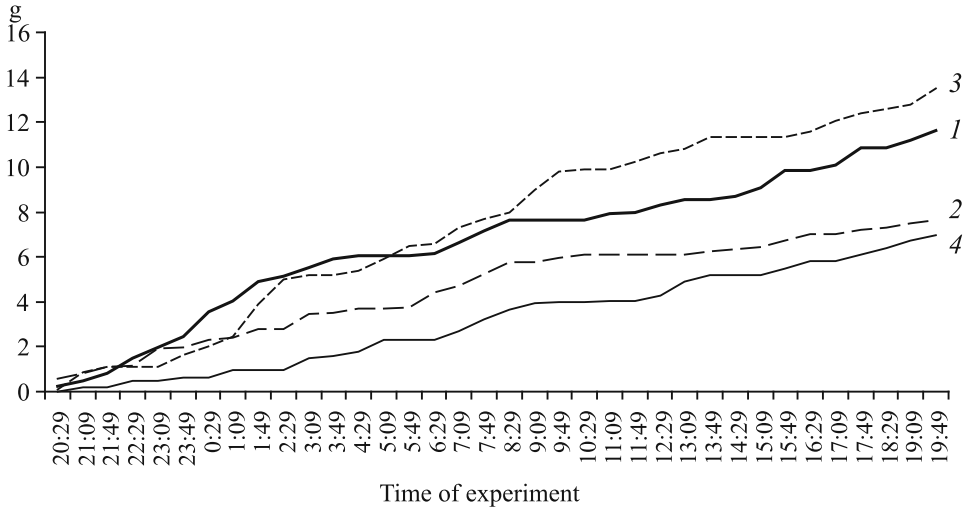

Fig. 1. Feeding behavior of rats after intragastric administration of water (*1*), DAMGO (*2*), DADLE (*3*), or ICI-204,448 (*4*). Ordinate: amount of consumed food. Each subsequent value is summed with the previous value (cumulative curve). Here and in Figs. 2 and 3: nighttime period 20.00-08.00.

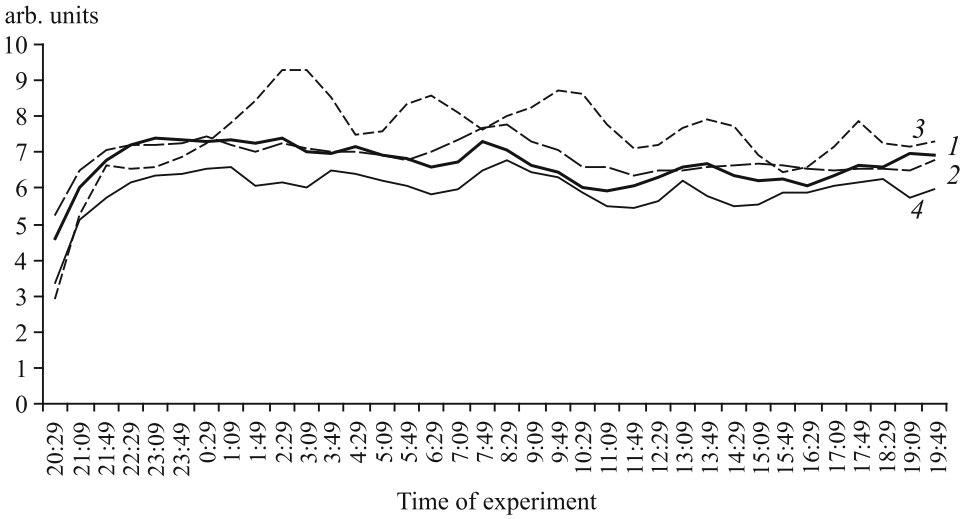

Fig. 2. Horizontal locomotor activity of rats after intragastric administration of water (*1*), DAMGO (*2*), DADLE (*3*), or ICI-204,448 (*4*). Ordinate: locomotor activity.

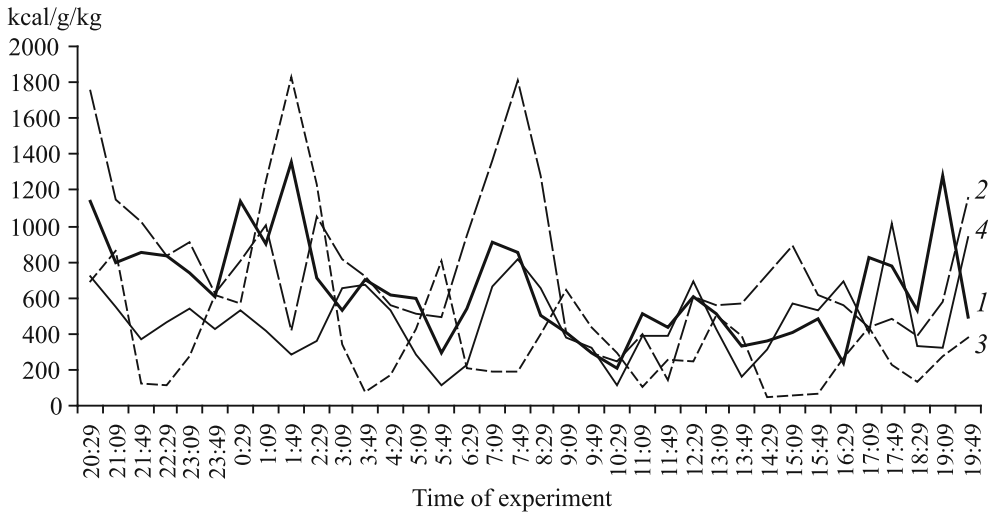

Fig. 3. Metabolism in rats after intragastric administration of water (*1*), DAMGO (*2*), DADLE (*3*), or ICI-204,448 (*4*). Ordinate: energy consumption.

accompanied by food consumption and activation of metabolism (Figs. 1-3).

Intragastric treatment with peptide agonists of opioid receptors was followed by changes in the test parameters. Administration of a μ-opioid receptor agonist DAMGO suppressed the feeding behavior of animals in the light phase, but had little effect on locomotor activity and metabolism. At the same time, locomotor activity of rats increased during the transition from the dark to the light period, which was accompanied by activation of metabolism (Figs. 1-3). Treatment with a δ-opioid receptor agonist DADLE was followed by a significant increase in metabolism over 24 h. These changes were accompanied by a decrease in locomotor activity during the light phase and activation of feeding behavior in the transition period (Figs. 1-3). Intragastric administration of a κ-opioid receptor agonist ICI-204,448 inhibited feeding behavior, metabolism, and locomotor activity of rats only in the nighttime.

These data suggest that opioid peptides produced in the stomach during food digestion play an important role in the regulation of food motivation and metabolism in rats. Our previous studies showed that activation of opioid receptors in the stomach can be transmitted into CNS via vagal afferents [2]. The opioid mechanisms of food motivation in CNS are reciprocally suppressed in the follow-up period [3]. It can be hypothesized that various subtypes of opioid receptors regulate feeding behavior and metabolism of animals in different phases of vital activity.

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