Changes in Feeding Behavior After Peripheral Loperamide Administration in Rats

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Changes in the parameters of operant feeding behavior and body weight were studied in rats after intragastric administration of μ-opioid receptor agonist loperamide. Loperamide administration significantly suppressed foraging behavior in rats and reduced their body weight. Our findings suggest that peripheral loperamide administration, according to the hypothesis of reciprocal interactions between the central and peripheral parts of the endogenous opioid system, suppresses activity of central opioid mechanisms of feeding behavior organization. Changes in feeding behavior can appear due to disturbances in the mechanisms of assessment of food reward. We hypothesized that natural activation of μ-opioid receptors of the stomach with food-derived peptides can be associated with "sensory satiation" mechanism limiting excessive food intake.

Key Words: *feeding behavior; positive reinforcement systems of the brain; central and peripheral μ-opioid receptors; loperamide*

Virtually immediately after discovery of endogenous opioid peptides they were shown to be involved in the formation and realization of feeding behavior in mammals [9,10]. There are published data according to which central opioid system is involved in activation of feeding behavior. Thus, administration of μ-, δ- and κ-opioid receptor agonists increased food consumption in animals, whereas opioid receptor antagonists prevented this effect and even reduced food intake and animal body weight [6,12]. The effects of opioids on feeding behavior are now suggested to be associated with activation of the positive reinforcement system of the brain [8], what is probably determined by modulation of opioid receptor activity [7,11,13].

Hypothesis of reciprocal interactions between the central and peripheral compartments of the endogenous opioid system was proposed in Laboratory of Physiology of Reinforcement, P. K. Anokhin Institute of Normal Physiology [4]. Our recent experiments demonstrated that peripheral administration of μ-opioid receptor agonist loperamide and μ-opioid receptor antagonist methylnaloxone not crossing the blood-brain barrier produced opposite effects on the central opioid system [2,5]. In addition, loperamide suppresses and methylnaloxone stimulates β-endorphin release in rat cingulate cortex [3] and its receptor binding in the cortex [1]. Taking into account the fact that activation of the central μ-opioid system enhances foraging behavior, we can hypothesize that, in accordance to our hypothesis, activation of peripheral μ-opioid receptors should result in anorectic effects and body weight loss. The objective of this study was to investigate changes in operant feeding behavior and body weight in rats after intragastric loperamide administration.

MATERIALS AND METHODS

Experiments were carried out on 48 male Wistar rats with mean body weight about 200 g at the beginning of the experiment. Before the experiment, the animals were kept in groups of 8, with free access to standard combined feed and water, under light/dark cycle

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12:12 h. All experiments were carried out in accordance with requirements of the Order No. 267 Ministry of Health of Russian Federation (19.06.2003), as well as with "Rules for operation conduction using experimental animals" (P. K. Anokhin Institute of Normal Physiology, Russian Academy of Medical Sciences, Protocol No. 1, 3.09.2005).

Operant feeding behavior of rats was studied in two series of experiments. In series I, the animals were subjected to 24 h food deprivation. For that purpose, a rat was placed into individual Skinner box where the animal had an opportunity to press the lever placed on the right from the feeder, which was followed by the appearance of a 45-mg pellet of vitaminized feed (BioServ). The animals were placed into the chamber for 1 h every day and then were returned to their home cages, where each rat received 12.5 g standard combined feed. For first 4 days, the rats obtained 1 pellet after each lever pressing during the experiment and then the number of lever pressings increased in geometrical progression, *i.e.* on day 5 rats received the pellet only after two lever pressings, on day 6 after 4 pressings, on day 7 after 8 pressings, on day 8 after 16 pressings, *etc*. On the last day of the experiment, day 11, the pellet was given after 128 lever pressings. Starting from day 2, 30 min before placing to the experimental chamber group 1 animals (controls) received distilled water (0.1 ml of per 100 g of body weight) through a gastric tube and rats of groups 2, 3, and 4 received loperamide in doses of 3, 7, and 10 mg/kg, respectively. Number of pellets eaten per one hour of the experiment was recorded for each animal.

In experimental series II, rats had free access to standard combined food. Loperamide 5 mg/kg was administered intragastrically 2 times a day for 2 weeks. Control rats received water. Changes in body weight were recorded for 14 days of daily loperamide administration and 10 days after the withdrawal.

Statistical processing was performed using ANOVA.

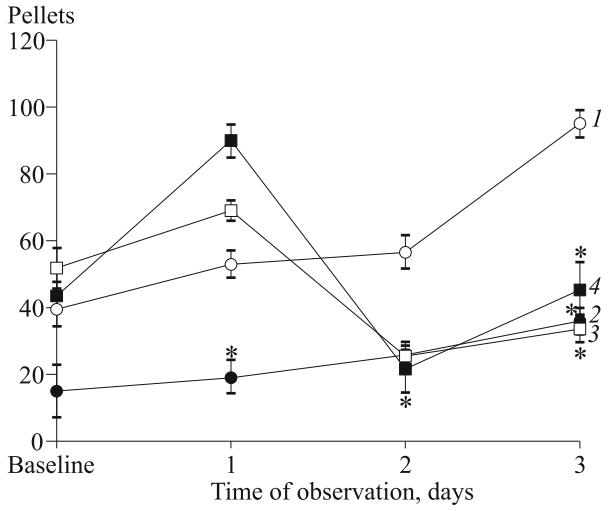

Fig. 1. Number of feed pellets obtained by rats after intragastric administration of distilled water (*1*) and loperamide in doses of 3 (*2*), 7 (*3*), and 10 mg/kg (*4*). Here and at Fig. 2: **p*<0.05 in comparison with control.

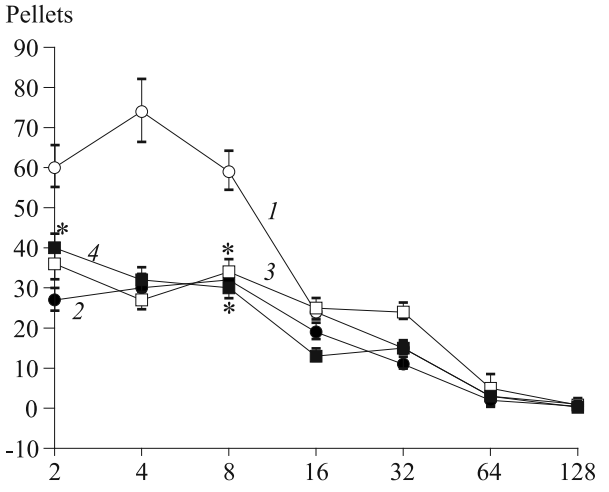

Fig. 2. Number of feed pellets obtained by rats during progressive training after intragastric administration of distilled water (*1*) and loperamide in doses of 3 (*2*), 7 (*3*), and 10 mg/kg (*4*). Abscissa — number of lever pressings for 1 feed pellet.

RESULTS

Rats quickly learned the paradigm of operant foraging behavior. On day 4, one control rat consumed 95±12 g of feed pellets (Fig. 1). Loperamide significantly suppressed foraging behavior in rats: starting from day 2 of treatment, the number of eaten food pellets significantly decreased in all groups receiving loperamide (Fig. 1).

Progressive increase in the ratio of lever pressings for getting one food pellet led to gradual decrease in the quantity of food received in all experimental groups (Fig. 2). In control group, the number of got pellets remained virtually unchanged with increasing this ratio from 1 to 8 and then a dramatic drop in foraging behavior performance was observed (Fig. 2). At the same time, in animals receiving loperamide the number of got pellets decreased gradually (Fig. 3). Significant changes in foraging behavior were observed up to day 7, when the animals had to press the lever 8 times for 1 pellet (Fig. 2).

The results of experimental series I suggest that peripheral loperamide administration inhibits central opioid mechanisms of goal-directed feeding behavior. Loperamide successfully inhibits foraging behavior when it does not require high energy expenditure. If the energy expenditure for obtaining reinforcement outweighs its nutritional value, food-procuring activity dramatically decreased in animals of both the control

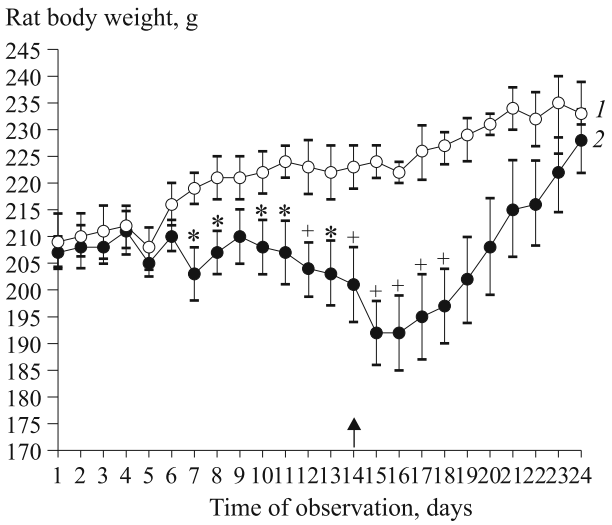

Fig. 3. Changes in rat body weight after intragastric administration of distilled water (*1*) and loperamide 5 mg/kg (*2*). Arrow: compound withdrawal. *$p<0.05$, $^{+}p<0.01$ in comparison with control.

and 3 experimental groups, and between-group differences disappear ($p>0.05$). Such results probably indicate that loperamide to a greater extent suppresses mechanisms of reinforcement assessment, than motivational processes.

In experimental series I, no significant changes in body weight were noted after intragastric loperamide administration. However, all rats were limited in food; therefore even body weight dynamics in control group was not able to reflect natural changes in body weight. Body weight in rats with free access to food was studied in experimental series II to elucidate the effects of loperamide. Chronic administration of 5 mg/kg loperamide significantly reduced animal body weight, probably due to disturbances in the mechanisms of food reward assessment (Fig. 3). Even after loperamide withdrawal, significant differences between control and experimental groups disappeared only on day 20 of observation (day 6 after loperamide withdrawal; Fig. 3).

Thus, our results suggest that loperamide, a μ-opioid receptor agonist not crossing the blood-brain barrier, modulates central mechanisms of feeding behavior regulation. The results suggest that natural activation of μ-opioid receptors of the stomach with food-derived peptide fragments can be associated with the mechanism of "sensory satiation" limiting excessive food intake.

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