PHYSIOLOGY

Effect of Peripheral D_2 Dopamine Receptor Antagonist Domperidone on Metabolism, Feeding Behavior, and Locomotor Activity of Rats
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We studied the possibility of activation of the central dopaminergic system compartment by modulating activity of D_2 dopamine receptors in the gastrointestinal tract with domperidone, an antagonist not crossing the blood-brain barrier. Intragastric administration of 0.1 mg/kg domperidone to rats was followed by a significant decrease in feeding behavior and stimulation of basal metabolism, but had no effect on locomotor activity of animals in a Phenomaster system. These effects are typical of psychostimulant agents that stimulate dopamine release from nerve endings in the nucleus accumbens and some regions of the brain cortex. Our results indicate that physiological functions associated with activity of the central dopaminergic system can be modulated through peripheral dopamine receptors.

Key Words: dopamine; peripheral D_2 dopamine receptors; domperidone; metabolism; feeding behavior

CNS neurotransmitter dopamine plays an important role in physical and mental activity of humans and animals [11,12]. All pharmacological agents that stimulate dopamine release in the mesocorticolimbic system of the brain have a psychostimulant effect accompanied by an increase in physical activity [7], activation of metabolism [10], and suppression of feeding motivation [8].

We have previously proposed and substantiated the principle of interaction between the central and peripheral compartments of the endogenous opioid system [3]. It was shown that activation of the peripheral compartment is usually accompanied by suppression of the central compartment and vice versa [1,2,4]. We hypothesized that this principle underlies the interaction between other neurochemical systems presented in the brain and peripheral tissues.

Here we studied the possibility of activation of the central dopaminergic system compartment by modulating activity of D_2 dopamine receptors in the gastrointestinal tract with antagonist domperidone not crossing the blood-brain barrier.

MATERIALS AND METHODS
Experiments were performed on 16 Wistar rats weighing 300 g. The animals were housed in ventilated Techneplast cages (4 specimens per cage) at 21°C and 08.00-20.00 daytime and had free access to water and standard combined feed. The research 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).

On the day of experiment, the rats were placed in a Phenomaster system (TSE) allowing evaluation of locomotor activity (number of crossed squares), amount of consumed food and water, oxygen consumption, and carbon dioxide release every 40 min over 24 h under conditions of a standard home cage. Immediately before the experiment, domperidone (0.1 mg/kg; Tocris) in 1 ml/kg water was administered to 8 rats of the treatment group into the stomach through a special catheter; control rats (n = 8) received distilled water.

The significance of differences between the experimental and control groups was evaluated by ANOVA and Student’s t test.

RESULTS

Some authors reported that peripheral administration of domperidone has no effect on feeding behavior of rats [5,6]. However, our experiments showed that administration of domperidone to animals significantly reduced food consumption. Differences between rats of the treatment and control groups were most significant during the daytime period. These differences were practically absent over the first 3 h of the dark phase, but during the second half of the dark phase and light phase, food consumption in the experimental group was much lower than in the control group (Fig. 1).

Fig. 1. Feeding behavior of rats after intragastric administration of distilled water (1) or domperidone (2). Ordinate, amount of consumed food. Each subsequent value is summed with the previous value (cumulative curve). Here and in Fig. 2: abscissa, time of experiment (nighttime from 20.00 to 08.00).

Locomotor activity in both groups was similar during the first 16 h, but during daytime (08.00-16.00) locomotor activity of domperidone-treated