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BRIEF COMMUNICATION

Dextrofenfluramine, but not 8-OH-DPAT Affects the Decrease in Food Consumed by Rats Submitted to Physical Exercise

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CHAOULOFF, F., J. DANGUIR AND J.-L. ELGHOZI. *Dextrofenfluramine, but not 8-OH-DPAT affects the decrease in food consumed by rats submitted to physical exercise.* PHARMACOL BIOCHEM BEHAV 32(2) 573–576, 1989.—The effects of physical exercise (1 hr of treadmill running) on nocturnal food consumption were investigated in trained rats. On the basis of previous reports which indicated that exercise increases central 5-HT synthesis, we also measured the consequences of 5-HT (indirect or direct) agonist administration. Noncumulative food intake data revealed that exercise diminished food consumption during the late postexercise periods whereas that of the first 4 hr of analysis remained unaltered. Treatment with dextrofenfluramine (d-FEN) at the end of the exercise session promoted hypophagia in both groups of rats; however, the anorexigenic effect of the 5-HT releaser and 5-HT uptake inhibitor d-FEN was found to be more pronounced in the runners. Lastly, an attempt was made to modify the feeding consequences of exercise by administering at the end of running an orexigenic compound, namely the 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT). At the two doses used, 8-OH-DPAT proved to be inactive on the respective amounts of food consumed by the controls and the runners. The data obtained herein suggest that (a) moderate exercise promotes late hypophagia, (b) 8-OH-DPAT is devoid of hyperphagic property when administered at the onset of the dark cycle, i.e., when the rats normally begin their gross daily food intake. The data obtained from the d-FEN study suggest that exercise-induced alterations in central serotonergic system could participate in the consequences of exercise on feeding behavior.

Physical exercise Food intake Serotonin Dextrofenfluramine 8-OH-DPAT

INVESTIGATIONS into the effects of physical exercise have usually ended at the peripheral level, as if brain chemistry was not affected by such a situation. Indeed, previous studies have revealed that brain catecholaminergic metabolism is largely modified by physical activity (2, 7, 19). This is also true for another monoaminergic system, i.e., that of serotonin (5-hydroxytryptamine, 5-HT): thus, we have shown that following a moderate exercise, tryptophan (TRP) and 5-hydroxyindoleacetic acid (5-HIAA), 5-HT precursor and 5-HT metabolite respectively, are increased in the CNS of the running rat (4,6). By modifying blood TRP disposition and then TRP supply to the brain (4,5), exercise-induced lipolysis is responsible for the increase in central 5-HT synthesis.

Brain serotonergic activity is generally believed to exert an inhibitory influence upon feeding behavior (3,14). Thus, numerous pharmacological and behavioral studies indicate that the administration of a 5-HT (direct or indirect) agonist promotes a profound decrease in food consumption (3,14). As an example, the anorexigenic property of the 5-HT indirect agonist dextrofenfluramine (d-FEN) has been shown to depend on its great ability to block 5-HT neuronal reuptake while it increases the amine release (14).

The effects of physical exercise upon food intake are still a matter of debate. Thus, several reports indicate that, depending on the paradigm used, acute and chronic exercise either diminish food consumption or primarily induce a compensatory hyperphagia (1, 10, 16, 21, 22, 25, 29). As far as human studies are concerned, data are even less homogeneous [for a review, (28)].

The aim of the present work was to investigate the consequences of an exercise session of moderate intensity upon

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food consumption. In addition, pharmacological experiments were led to analyze the hypothesis according to which exercise-induced alterations in central serotonergic activity could underly these changes in feeding behavior. For this purpose, trained resting and exercising rats were acutely treated with drugs known to affect central 5-HT synthesis and activity, i.e., d-FEN or 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT). The novel 5-HT agonist 8-OH-DPAT has been shown to have a great affinity for one of the serotonergic site subtypes, namely the 5-HT_{1A} subtype, which largely exceeds its affinity for either the 5-HT_{1B}, 5-HT_{1C} or 5-HT_2 receptor sites (18,27). Biochemical and behavioral studies have indicated that 8-OH-DPAT elicits changes indicative of central postsynaptic 5-HT_{1A} receptor occupancy (17,31). On the other hand, some reports have clearly demonstrated that this tetralin derivative also binds to presynaptic sites; thus, 8-OH-DPAT binds to striatal serotonergic uptake systems (30) and to the 5-HT_{1A} autoreceptors localized on serotonergic cell bodies and/or dendrites (15,32). Hyperphagia elicited by 8-OH-DPAT (12,13) is mediated by such a presynaptic-dependent mechanism since prior 5-HT synthesis inhibition prevents the consumption of food that is triggered by 8-OH-DPAT (13) whereas local injections in the raphe nuclei promote marked hyperphagia (20). Taken together, this data and other demonstrated that 8-OH-DPAT increases feeding by a presynaptic mechanism responsible for inhibition of 5-HT synthesis and release (13,20).

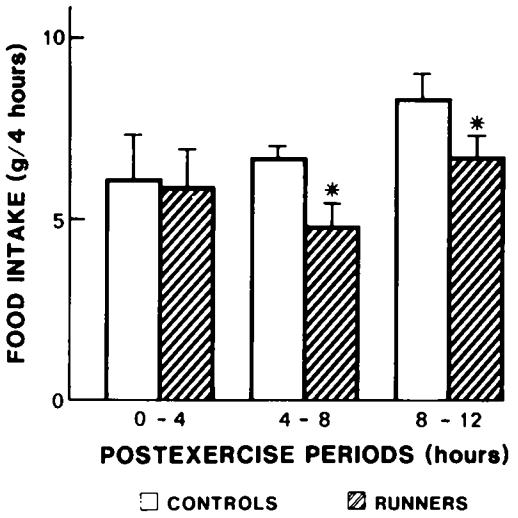

FIG. 1. Noncumulative food consumption during postexercise periods for control and 1 hr running rats. Number of animals=7–8/group. *$p<0.05$ for the effects of exercise.

METHOD

Animals

Forty-four male Wistar rats (IFFA CREDO, Les Oncins, France), weighing 300–350 g, were individually housed in Plexiglas cages. The animal room was illuminated from 06.00 hr to 18.00 hr and the ambient temperature fixed to 24°C. Tap water and food, a standard laboratory powdered diet (Extralabo, M 25: 49% carbohydrates, 23% proteins, 4% fat, 6.5% cellulose and 9% minerals and vitamins) were provided ad lib, except during the running sessions.

Running Protocol

Rats were put on a horizontal treadmill driven by an electrical motor and trained to run daily for 3–4 days. Training duration progressively increased (15 min to 45 min/day) while the running speed was of moderate intensity, i.e., 20 m/min (4). Training sessions always began at 17.00 hr. On the experimental day, trained rats were randomly divided into 2 groups, namely the resting and the exercising rats. Rats were exercised from 17.00 hr to 18.00 hr at a speed of 20 m/min whereas resting rats were deprived of food and water during that period.

Food Intake Analyses

At the end of the final running session, the exercising rats were housed in their respective cages. Fresh food was available in a cup equipped with a strain gauge and connected to a potentiometric recorder. This allowed precise recording of meal pattern (±0.1 g), as previously reported (9). Feeding patterns were recorded from 18.00 hr to 06.00 hr.

Drugs

Drugs and 0.9% saline vehicle were injected SC in a volume of 1 ml/kg of individual body weight: (a) 8-OH-DPAT (60 μg/kg or 600 μg/kg, Research Biochemicals Inc., Wayland, MA) was dissolved by gentle warming in 0.9% saline, (b) d-FEN (1.5 mg/kg, a generous gift from I.R.I. Servier, Neuilly, France) was dissolved in 0.9% saline. Drugs were injected in the flanks at the end of the final running sessions: such a procedure was chosen to avoid the possible side effects of both drugs on running performance.

Statistics

Food intake data, expressed as mean±S.E., were compared by a two way analysis of variance followed by a Mann and Whitney's U-test.

RESULTS

The effects of a 1 hr running session on food consumption are shown in Fig. 1. Exercise affected food intake, $F(1,39)=4.45$, $p<0.05$, but whereas it did not significantly decrease the amount of food consumed during the 4 hr period which immediately followed physical exertion, significant decreases in food intakes during the 4 hr to 8 hr (28%) and 8 hr to 12 hr (21%) postexercise periods were observed in the runners, compared to those of the control rats (Fig. 1).

The behavioral consequences of d-FEN or 8-OH-DPAT administration to control and running rats are displayed in Fig. 2. Treatment with d-FEN induced a significant hypophagia in both groups; in addition, a 28% decrease in the food consumed by the d-FEN-treated rats was observed between the controls and the runners (Fig. 2). On the other hand, 8-OH-DPAT administration was not found to promote hyperphagia in either groups; this was true for the high (600 μg/kg, Fig. 2) and the low (60 μg/kg, data not shown) doses used, as for the first and second hours which followed treatment onset (data not shown). Lastly, analysis of the 12 hr food consumptions in the saline, 8-OH-DPAT and d-FEN-treated groups revealed a significant hypophagic effect of running, $F(1,38)=5.48$, $p<0.05$.

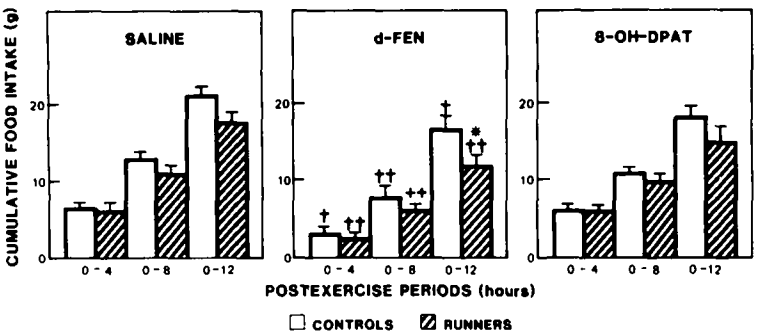

FIG. 2. Cumulative food consumption during postexercise periods for control and 1 hr running rats either treated with saline, d-FEN (1.5 mg/kg) or 8-OH-DPAT (0.6 mg/kg) at the end of running. Number of animals=6 to 9/group. $^{*}p<0.05$ for the difference between controls and runners; $^{-}p<0.05$; $^{++}p<0.01$ for the difference between saline and d-FEN in the control and the exercising groups.

DISCUSSION

The results presented above show that moderate exercise may have some consequences on feeding behavior. Thus, analysis of feeding patterns strongly suggests that following an initial recovery period during which runners ate as much as the controls, food intakes were then depressed in the runners. In addition, the pharmacological study shows that whereas 8-OH-DPAT was devoid of any hyperphagic property, d-FEN administration promoted hypophagia, the intensity of which was more marked in the runners.

It has previously been shown that acute and chronic treadmill exercise may induce satiety regarding food consumption (1, 16, 21, 22). However, some studies clearly indicate that exercise intensity and duration must be taken into account: thus, Katch *et al.* and Mayer *et al.* have respectively shown that increasing exercise intensity reinforces hypohagia (21) while exercise of long duration may trigger hyperphagia (25). In addition, that according to the acute exertion model used, i.e., running or swimming, results are heterogeneous (10,13) reinforces the need for clarity. The latter almost concerns exercise intensity, exercise model or fitness level. In our paradigm, feeding was found to be decreased in the late nocturnal periods. This data does not agree with those previously reported which indicated that running-induced hypophagia concerns the first hours which follow exercise termination (21). Such a discrepancy may find its basis in the difference of training and final exercise intensities.

Numerous hypotheses have been advanced to explain the possible consequences of physical exercise on food intake. Among these hypotheses, the roles of lipolysis (9,23) and glycemia (24) as well as exercise-induced catecholamine (16) or opioid release (10,11) have already been emphasized. Indeed, another candidate could be central 5-HT. This is supported by two main findings: firstly, and as pointed out in the introductory section, central serotonergic activity is believed to act negatively on feeding behavior (3,14). In addition, exercise-induced lipolysis is responsible for the increased brain TRP availability (4,5) and 5-HT synthesis (5,6) which may be measured in trained runner rats. The above cited data led us to treat the animals with compounds respectively known to decrease or increase food consumption (12–14, 20) by directly or indirectly acting on different serotonergic receptors (18, 26, 27) and/or steps in the 5-HT metabolism pathway (14,17). In addition, that one of these two compounds, namely 8-OH-DPAT is able to attenuate stress-induced anorexia (13) was of particular interest. Indeed, this 5-HT_{1A} receptor agonist did not prove to be hyperphagic (at two different doses) in both groups of rats. This lack of hyperphagic effect may find its main origin in the paradigm used: thus, 8-OH-DPAT was injected at the end of the exercise session, which corresponded to the onset of the dark cycle and the beginning of normal gross daily food intake. This strongly suggests that, in addition to the previously reported chewing side effect of 8-OH-DPAT (8), 8-OH-DPAT is not efficient during the normal daily feeding periods. On the other hand, analysis of the individual food consumptions in the saline-treated and the d-FEN-treated rats showed that d-FEN-induced decrease in feeding was more important in the runners (32%) than in the controls (20%), compared to the respective intakes in the saline-injected runner and control rats. Noncumulative food intake data revealed that the latter difference took place during the last 8 hr of analysis (data not shown). The mechanisms underlying the increased anorexigenic effect of d-FEN in the runners are still unknown. It is tempting to speculate that d-FEN, which decreases food intake by specifically acting on the serotonergic system (14), showed a greater effect in the runners since exercise already activates central serotonergic systems. However, the possibility remains that feeding behaviors following d-FEN treatment and exercise were of different origins.

As a conclusion, the present paper shows that treadmill exercise promotes partial hypophagia and that central serotonergic activity may be one of the possible factors responsible for this behavioral imbalance. In addition, the limitative use of 8-OH-DPAT as an orexigenic compound is shown.

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