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Effects of Naltrexone on Food Preference and Concurrent Behavioral Responses in Food-Deprived Rats

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COOPER, S. J. AND S. TURKISH. *Effects of naltrexone on food preference and concurrent behavioral responses in food-deprived rats*. PHARMACOL BIOCHEM BEHAV **33**(1) 17–20, 1989.—Naltrexone (0.05–5.0 mg/kg, SC) was administered to food-deprived rats prior to a 15-min food-preference test. Total food intake and feeding duration was reduced following administration of the opiate antagonist. However, while naltrexone reduced the consumption of the initially-preferred chocolate-coated cookies, the ingestion of the nonpreferred standard laboratory chow pellets was significantly enhanced. These data cannot be explained in terms of a general anorexic effect and nonspecific suppression of feeding responses. Instead, they indicate that naltrexone reduced preference for the highly palatable cookies, so that a feeding response to the chow pellets emerged. Under the conditions of test-familiarity, naltrexone did not reduce grooming, locomotion or rearing duration. An increase in locomotion may have been secondary to the reduction in feeding. The results agree with previous data from animal and human studies in suggesting that endogenous opioid peptide activity is involved in the palatability of preferred foods.

Food preference Grooming Locomotion Naltrexone Palatability Rearing

OPIOID antagonists reduce food consumption in many species, and appear to do so by blocking the effects of endogenous opioid peptides involved in the control of feeding responses (3, 8, 24, 32). Since the release of endogenous opioid peptides could be related to food palatability (10), opioid antagonists should block hedonic aspects of ingestion. In support of this view, opioid antagonists have been shown to reduce the ingestion of palatable liquid diets (5, 7, 20, 28, 33, 34), and to block preferences for saccharin, glucose and sucrose solutions (6, 23, 25, 26, 35). In human subjects, naltrexone attenuated preference for sucrose (11). In sham-feeding studies, opioid antagonists reduce the consumption of sucrose solutions in gastric-fistulated rats (21, 22, 30). Most of these studies, it should be noted, have made use of liquid diets or solutions.

Apfelbaum and Mandenoff (1) carried out a different type of experiment. They administered naltrexone (0.5 and 2.5 mg/kg) to two groups of rats: a control group maintained on ordinary laboratory chow, and an obese group which had been maintained on a high-palatability cafeteria diet. Naltrexone strongly suppressed food intake in the obese group, but had little or no effect on the ingestion of chow in the control animals. Apfelbaum and Mandenoff concluded that endogenous opioid peptides are involved in the hyperphagia associated with access to various highly-palatable foods (1). They did not, however, examine the effects of naltrexone on a choice between a preferred food and laboratory chow carried out in the same test. In the present study, therefore, naltrexone was administered over a wide dose-range (0.05–5.0 mg/kg, SC) to food-deprived rats given a choice between highly-palatable chocolate-coated cookies and standard laboratory chow. We were interested in the effects of naltrexone on the relative preference for the former items.

A number of studies have investigated the effects of opioid antagonists on exploration and general activity measures. When they are effective, opioid antagonists tend to reduce exploratory activity (2, 9, 12, 14, 18, 19, 31, 37). In addition, naloxone has been shown to reduce novelty-induced grooming (14,17). However, there appear to be a few data which deal with locomotion, grooming and other behavioral responses which occur in association with feeding. Hence, in the present study, we investigated the effects of naltrexone not only on feeding responses, but also in relation to a number of other behavioral categories. Such data contribute to establishing the behavioral specificity of naltrexone's effects on feeding responses.

METHOD

Animals

The subjects were 48 experimentally-naive male rats (General

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TABLE 1

EFFECTS OF NALTREXONE (0.05–5.0 mg/kg SC) ON THE INTAKE (g) OF CHOCOLATE-COATED COOKIES, STANDARD LABORATORY PELLETS, AND TOTAL FOOD, IN A 15-MIN FOOD-PREFERENCE TEST

Food Type	Dose (mg/kg) 0	0.05	0.1	0.5	1.0	5.0
Chocolate cookies	6.6 ±0.7	3.7† ±0.6	3.8† ±0.6	3.4† ±0.7	2.5† ±0.5	1.4† ±0.3
% control	—	56.1%	58.8%	51.5%	37.9%	21.2%
Lab pellets	0.1 ±0.1	0.3 ±0.1	0.2 ±0.1	0.4 ±0.3	0.6† ±0.2	0.5* ±0.2
% control	—	300%	200%	400%	600%	500%
Total food	6.7 ±0.7	3.9† ±0.6	4.0† ±0.6	3.8† ±0.6	3.1† ±0.4	2.0† ±0.3
% control	—	58.2%	59.7%	56.7%	46.3%	29.9%

Results are shown in terms of mean ± S.E.M. N=8 per dose condition levels of significance: *$p<0.05$, †$p<0.01$ (Dunnett's t-test).

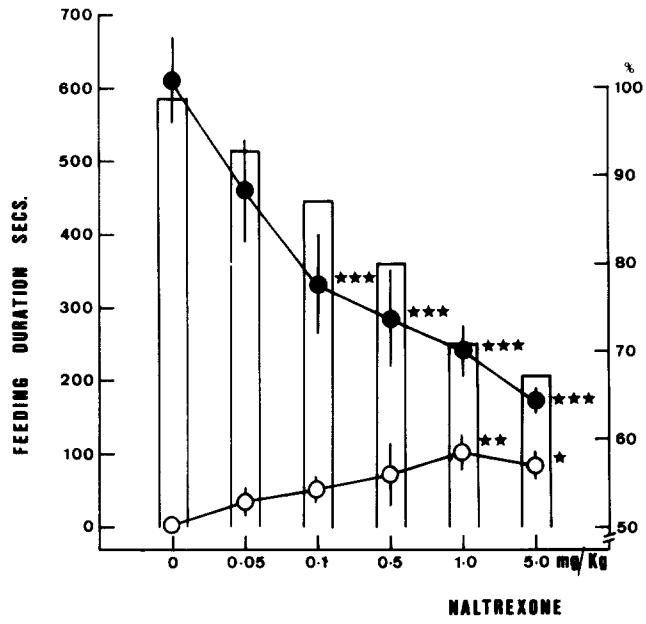

FIG. 1. Naltrexone (0.05–5.0 mg/kg, SC) produced a dose-dependent reduction in the time spent eating palatable chocolate-coated cookies (filled circles) in a 15-min food-preference test. Concurrently, there was an increase in the time spent eating standard food pellets (open circles). Results are shown in terms of mean ± S.E.M. N=8 per group. Significantly different from controls: *$p<0.05$; **$p<0.01$; ***$p<0.005$ (Dunnett's t-test). The histogram bars depict the same data in terms of % preference (right-hand scale) for the palatable cookies; calculated as (time spent eating the cookies/total time spent eating) × 100%.

Strain, bred in our laboratory), housed two per cage. Room temperature was maintained at 21°C, and there was a 12 hr light-12 hr dark cycle (lights on at 7 a.m.). The animals were accustomed to being handled, and weighed 250–400 g at testing.

Drug

Naltrexone hydrochloride (generously supplied by Endo Laboratories) was dissolved in isotonic saline. It was injected subcutaneously 20 min before the food-preference test. The drug was administered in doses of 0.05, 0.1, 0.5, 1.0 and 5.0 mg/kg (in terms of the salt), and was injected in a volume of 1 ml/kg.

Apparatus

The food-preference tests took place in a rectangular clear plastic box (30 × 40 cm, 22.5 cm high). Three round plastic food containers (diameter 6 cm, height 1.2 cm) were placed on the floor of the box at equal distances. Before each test, standard laboratory food pellets (Diet 41B, Heygate and Sons, U.K.), Cadbury's milk chocolate-coated cookies and balsa wood chips were placed in the containers. (There was one type of item per container, and each container always contained the same material.) The test box and containers were cleaned between tests. Data were collected using a Commodore microcomputer, and the software was written by Dr. A. McBeath.

Procedure

For a period of two weeks before the tests, the animals were placed individually in the test box for 15 min each day (Monday–Friday) as a familiarization procedure. On each occasion they had access to the food pellets, chocolate-coated cookies, and balsa wood chips. In their home cages, they were maintained on ad lib access to standard food pellets and water. Twenty-four hours before the food-preference test, food was removed from the home-cages.

For the food-preference test, animals were placed individually in the test box for 15 minutes. The test period was limited to 15 min to restrict observation to the first meal following the 24-hr food-deprivation. Throughout the test, the duration of each behavior was recorded by pressing keys on a keypad, according to 7 independent behavioral categories. These categories were: *eating chocolate-coated cookies*, eating, chewing and biting the cookies; *eating food pellets*, eating, chewing and biting the food pellets; *oral contact with balsa wood*, touching, chewing, gnawing or biting the balsa wood chips; *grooming*, washing, licking, scratching any part of the head or body; *rearing*, standing upright on the hindlimbs; *locomotion*, ambulation about the test box; *stationary behavior*, scored wherever the animal remained immobile, and not engaged in any of the preceding behavioral responses. The observational data were analysed in terms of the total time devoted to each response category over the 15-min period of the test. The food items were weighed before and after the test (to the nearest 0.1 g),and intake was calculated by subtraction (taking account of any spillage). All testing took place between 9:30 a.m. and 12:30 p.m. in a quiet room, separate from the animal-holding room.

Statistical analyses were carried out using analyses of variance, followed by Dunnett's t-tests to compare individual dose conditions with the vehicle group (injected with isotonic saline). A portion of the data has been described, in brief, in a recent review (8).

RESULTS

Food Intake

Naltrexone (0.5–5.0 mg/kg) significantly reduced the total

TABLE 2

EFFECTS OF NALTREXONE (0.05–5.0 mg/kg SC) ON THE TOTAL DURATION (SEC) OF FEEDING, GROOMING, LOCOMOTION, REARING AND STATIONARY BEHAVIORAL CATEGORIES IN A 15-MIN FOOD-PREFERENCE TEST

	Dose (mg/kg)					
Behavior	0	0.05	0.1	0.5	1.0	5.0
Feeding	619.9 ±58.0	499.5 ±62.4	382.0† ±59.2	356.1† ±50.7	339.9† ±43.1	254.5† ±31.2
Grooming	32.3 ±9.4	33.1 ±10.8	40.8 ±6.3	78.8 ±24.9	44.3 ±14.9	62.9 ±27.2
Locomotion	146.0 ±28.0	241.9* ±31.1	259.5* ±23.8	263.9* ±27.0	284.7† ±25.1	271.3† ±21.4
Rearing	72.3 ±19.8	87.9 ±23.9	116.9 ±25.5	115.1 ±22.3	129.9 ±22.0	126.8 ±15.4
Stationary	2.1 ±2.0	3.0 ±2.2	43.6 ±19.2	86.6* ±37.0	55.0 ±22.1	105.0† ±28.8

Results are shown in terms of means ± S.E.M. N=8 per dose condition. Levels of significance: *$p<0.05$, †$p<0.01$ (Dunnett's t-test).

food consumption of the food-deprived rats in the 15-min test, $F(5,42)=8.3$, $p<0.001$. Significant reductions were detectable at 0.05 mg/kg and at higher doses (Table 1). Following the vehicle injection, the rats almost exclusively consumed the chocolate-coated cookies, and ignored the laboratory chow. Naltrexone dose-relatedly reduced the consumption of the preferred cookies, $F(5,42)=8.7$, $p<0.001$. Again, the minimum effective dose was 0.05 mg/kg. Interestingly, naltrexone produced a significant *increase* in intake of food pellets, $F(5,42)=2.92$, $p<0.05$ (Table 1). At 1.0 and 5.0 mg/kg, naltrexone had significant effects on food pellet consumption.

Feeding Duration

This pattern was reflected in the feeding duration data. Naltrexone significantly reduced the total feeding duration, $F(5,42)=5.50$, $p<0.001$ (Table 2), and the duration of eating the chocolate-coated cookies, $F(5,42)=7.93$, $p<0.001$ (Fig. 1). In contrast, naltrexone significantly increased the time spent eating the laboratory chow pellets, $F(5,42)=2.56$, $p<0.05$ (Fig. 1).

Concurrent Behavior

Naltrexone had no effect on the duration of grooming, or rearing (Table 2), or an oral contact with the balsa wood ($F<1.0$ in each case). However, naltrexone did significantly increase the time spent in locomotion, $F(5,42)=3.22$, $p<0.05$ (Table 2). Significant increases were observed at 0.05 mg/kg and at higher doses. There was also a tendency for naltrexone-treated animals to remain stationary for longer periods, $F(5,42)=3.05$, $p<0.05$ (Table 2). Significant increases occurred at 0.5 and 5.0 mg/kg.

DISCUSSION

The most interesting result to emerge from the experiment is that naltrexone not only decreased the consumption of the preferred food item (the chocolate-coated cookies), but also appeared to induce a feeding response to the nonpreferred item (the laboratory chow pellets). This latter finding is an unusual result, which runs counter to the general effect of opioid antagonists to reduce feeding responses (3, 8, 24, 32). It was not a gnawing effect since naltrexone had no effect to induce gnawing of balsa wood chips. Under the present experimental conditions, it is inaccurate to describe naltrexone's effects simply in terms of a generalized anorectic effect.

An alternative interpretation, which is consistent with much of the recent data on opioid antagonists, is that naltrexone selectively attenuated the preference for the initially more-preferred chocolate-coated cookies. In this case, naltrexone may have dose-dependently reduced the preference for the cookies to such a degree that feeding responses directed to the food pellets emerged. At higher doses of naltrexone, therefore, the animals were selecting food from both available food containers, instead of choosing to eat the cookies exclusively (Fig. 1). The results are consistent with the earlier data of Apfelbaum and Mandenoff (1), and support their view that naltrexone acts selectively to suppress hyperphagia related to highly palatable foods. The present results go further in showing that naltrexone not only suppressed intake of a highly palatable food, but also allowed the emergence of a feeding response to a previously nonpreferred food.

Fantino *et al.* (11) recently administered naltrexone to human subjects, and found that hedonic ratings of sweet taste were selectively reduced by the opioid antagonist. Hunger ratings were unaffected, and the authors concluded that naltrexone does not act as an anorectic drug. In animal experiments, opioid antagonists consistently reduce the preference for sweet solutions (6, 23, 25, 26, 35). Our present results support the possibility that opioid antagonists have effects which are more selective than simply to reduce ingestional responses indiscriminantly. The fact that a feeding response to a nonpreferred food item emerged following naltrexone treatments provides unambiguous evidence that a general suppressant effect on feeding is untenable. Endogenous opioid peptide activity may therefore be involved in mediating food preferences determined by palatability factors.

Opioid antagonists generally reduce exploratory responses and locomotor activity when animals are tested in novel environments [e.g., (12, 14, 18, 31)]. They also reduce novelty-induced grooming (15,17). Under the familiar test conditions employed here, naltrexone did not affect grooming, and significantly increased locomotion (Table 2). Rearing duration was not significantly affected. The results indicate that exploratory responses, or the stress associated with exposure to a novel environment, are not factors to be taken into account in the interpretation of the present data. A more likely explanation is that increases in locomotor activity, and stationary behavior, occurred secondary to the reduction in feeding duration. There was certainly no indication that the reduction in feeding produced by naltrexone was due to a nonspecific suppression of behavior, cf. (4).

Naltrexone and naloxone reduce food intake in obese human subjects (36,38). In addition, opioid antagonists have been reported to reduce binge-eating episodes in bulimic patients (13, 16, 27). The present results indicate an important mechanism by which opioid antagonists affect feeding behavior, suggesting that a suppression of food palatability may have the greatest effect in terms of reductions in food ingestion.

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