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BRIEF COMMUNICATION

Failure of Naltrexone to Affect the Pleasantness or Intake of Food[1]

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HETHERINGTON, M. M., N. VERVAET, E. BLASS AND B. J. ROLLS. *Failure of naltrexone to affect the pleasantness or intake of food.* PHARMACOL BIOCHEM BEHAV **40**(1) 185–190, 1991.—Two separate studies were conducted to investigate the effects of oral naltrexone on the pleasantness ratings of foods and food intake. In both studies, normal-weight, nondieting males rated hunger, fullness, mood and the pleasantness of the taste of a variety of foods before and after double-blind administration of 50 mg of naltrexone or placebo. All subjects received a test meal, in a counterbalanced, repeated measures design. In the first study, 12 subjects were given a self-selection test meal after overnight deprivation. In the second study 14 subjects were given an ice cream test meal with no deprivation. In both experiments the pleasantness of the taste of the foods, sensory-specific satiety, hunger ratings and overall energy intake were not differentially influenced by naltrexone administration. In Experiment 2, intake of the ice cream was greater after active drug administration because subjects who received active drug on the first session ate less ice cream in the placebo session. In conclusion, in the short term, naltrexone had no impact on hunger, sensory-specific satiety or food intake.

Hunger Naltrexone Sensory-specific satiety Food intake Fullness Opioid antagonists Hedonics Eating behavior

EATING is pleasurable and the palatability of foods is important in the maintenance of intake (23). A number of studies have suggested that the opioid system is involved in mediating the rewarding aspects of food intake (22,29).

An increase in food intake has been observed (21) following administration of the kappa-sigma opiate agonist, butorphanol tartrate. Preference ratings for sugar and fat mixtures have also been found to be elevated following butorphanol and decreased following the opioid antagonist naloxone (6). Overall, studies using opioid antagonists have not provided a consensus on their effects on hunger, food intake or body weight (Table 1). However, studies on pleasantness ratings have indicated that opioid antagonists influence the hedonic appraisal of glucose solutions (7) and foods (30).

The aim of the present experiments was to follow-up on the findings of Fantino et al. (7) that the oral administration of 60 mg of naltrexone decreased the rated pleasantness of a glucose solution and of food-related odors. Since it is not clear that findings with solutions and odors can be extrapolated to real foods, we examined the effects of a similar dose of naltrexone [50 mg; the recommended starting dose for opioid addicts (10)] on the palatability of foods and drinks, ratings of hunger and fullness, and food intake. We (23,24) have found previously that the pleasantness of the taste of a food declines as it is ingested (sensory-specific satiety). Since the opioid system is thought to be involved in rewarding aspects of food intake, it seemed possible that sensory-specific satiety would be affected by blocking the opioid system.

The results of these experiments were reported at a meeting of FASEB (11).

METHOD

Subjects

Male volunteers aged between 18 and 32 years were recruited for these experiments. Twelve subjects were assigned to Experiment 1 and 14 subjects to Experiment 2. All subjects were normal-weight for height (body mass index between 20 and 25) (4), and were screened using questionnaires (8, 9, 26) to ensure that they were unrestrained, noneating disordered and generally in good health.

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TABLE 1

EFFECTS OF THREE OPIOID ANTAGONISTS ON NORMAL WEIGHT OR OBESE HUMANS

Study	Subjects	Daily Dose*	Effects: Food Intake	Hunger	Palatability	Body Weight	Side Effects
Naloxone: Intravenous Administration							
Atkinson (1)	Obese n=6	2 mg	no effect on meal 30 min later	—	—	—	—
	Obese n=7	15 mg	29% decrease	—	—	—	—
	Lean n=5	15 mg	no effect	—	—	—	—
Trenchard and Silverstone (27)	Normal Wt. n=12	0.8 and 1.6 mg bolus	dose-related decrease max at 2.5 h	no effect	—	—	none
Cohen et al. (5)	Normal Wt. n=7	2 mg/kg bolus	decreased (28%) 2.75 and 7.75 h later	no effect	—	—	nausea: n=1 stomach ache: n=1
Wolkowitz et al. (28)	Obese n=9	0.5–2.0 mg/kg bolus	decreased 2.75 and 7.75 h later	decreased	—	—	0.5 and 1.0 mg/kg nausea and vomiting
Drewnowski et al. (6)	Normal Wt. n=9	6 mg bolus then 0.1 mg/kg/h for 2.5 h	decreased fat intake	—	decreased	—	—
Naltrexone: Oral Administration							
Atkinson et al. (3)	Obese n=60	50 and 100 mg for 8 weeks	—	—	—	no effect	nausea and vomiting: n=3
Malcolm et al. (15)	Obese n=41	200 mg for 8 weeks	—	—	—	no effect	diarrhea and dysphoria: n=5
Maggio et al. (14)	Obese n=8	100, 200, 300 mg for 3 days each	no effect	—	—	no effect	GI distress: n=2
Fantino et al. (7)	Normal Wt. n=8	60 mg	—	no effect	decrease for glucose and food odors	—	none
Mitchell et al. (19)	Obese n=33	300 mg for 8 wk	—	—	—	no effect	nausea, dysphoria, etc.: n=7
Spiegel et al. (25)	Obese n=17	25–200 mg increasing over 4 days	decreased after day 1	decreased	decreased	no effect	nausea, etc.: n=7
Melchior et al. (17)	Normal Wt. n=14	25 mg	—	no effect	potentiated glucose alliesthesia	—	—
Jonas and Gold (13)	Bulimics n=16	50–300 mg high or low dose over 6 weeks	decreased frequency of binges and purges	—	—	—	nausea: n=5 liver problems: n=1
Nalmefene: Oral Administration							
Yeomans et al. (30)	Normal Wt. n=20	2.5 mg at 1 h before lunch	22% decrease in lunch intake of most palatable foods	no effect	—	—	minor
Yeomans and Wright (29)	Normal Wt. n=24	2.5 mg at 1 hour before lunch	20% decrease in lunch intake of most palatable foods	no effect	decreased	—	minor

*Acute unless stated otherwise.

Before the study began all subjects came to the laboratory to have the procedure explained, to familiarize them with the laboratory setting and to give written, informed consent. Finally, a taste test was conducted to ensure that all the foods used in the experiments were liked (i.e., above neutral on visual analog scales).

Procedure

In Experiment 1, subjects attended the laboratory on two separate occasions. They were instructed to eat the same meal on the evening before each session. They fasted from 8:00 p.m. the previous evening and drank only water until the test session.

On both test days, subjects came to the laboratory at 10:30 a.m. At that time, visual analog scales (VAS) were presented on a computer screen to the subjects who were instructed to rate gastric, somatic, cerebral and mood variables (20). Following these baseline ratings, ratings of eight sample foods were made on the pleasantness of taste and texture and the sweetness and intensity of flavor. Subjects were then given 60 g of water and a capsule containing either placebo (sucrose) or 50 mg of naltrexone. Forty minutes later subjects were again given the VAS and asked to re-rate hunger, fullness, and mood. Subjects were also given another sample tray and asked to reassess the foods. Following this series of ratings, subjects were given a self-selection meal, instructed that this was lunch and asked to eat as much as they wanted from the tray. After consuming this meal, subjects completed a final series of ratings of hunger, fullness and mood.

Sample foods were given to subjects on a tray in 20 ml clear, plastic containers. The foods offered in the sample tray consisted of salty and sweet foods, which were rated in the following order: tomato soup (salty), corn chips (salty), diet Coke (sweet), lettuce and Italian dressing (salty), butter cookies (sweet), strawberry yogurt (sweet), cheddar cheese (salty), crackers (salty) and chocolate (sweet).

The self-selection meal consisted of 450 g of tomato soup (0.352 kcal/g), 75 g of corn chips (5.5 kcal/g), 354 ml of diet Coke (0.003 kcal/g), 150 g of lettuce and Italian dressing (0.184 kcal/g), 87 g of butter cookies (5.06 kcal/g), 450 g of strawberry yogurt (1.11 kcal/g), 125 g of cheddar cheese (4.07 kcal/g), 64 g of crackers (5.4 kcal/g) and 84 g of chocolate (5.4 kcal/g).

In Experiment 2, instead of giving a variety of foods, a highly palatable, single food (chocolate ice cream) was given. The test meal was offered after lunch, with a considerably shorter period of prior deprivation than that of Experiment 1. In addition, food intake and ratings were assessed in the evening following drug administration, to investigate later effects of naltrexone.

In this experiment, subjects came to the laboratory on two occasions separated by at least one week. On each occasion they were instructed to have their normal lunch at noon and to come to the laboratory at 2:00 p.m. On arrival at the laboratory subjects completed ratings as in Experiment 1 (20). They also rated the pleasantness of the taste of eight sample foods and their desire to eat these foods. The sample foods consisted of tomato soup, potato chips, regular Coke, chocolate ice cream, banana, cheddar cheese, ham and chocolate.

After this, subjects were given 60 g of water and a capsule containing either placebo or 50 mg of naltrexone. Subjects then left the laboratory with the explicit instruction to refrain from eating or drinking anything but water and to return to the laboratory in eighty minutes. Subjects returned, completed the VAS and reassessed the sample foods. They were then offered a test meal consisting of 500 g of chocolate ice cream (Breyers, Kraft, Inc., Philadelphia, PA 19103: 2.406 kcal/g). Subjects were instructed to eat as much chocolate ice cream as they wanted. Two minutes after finishing the ice cream, a further series of VAS were completed, including ratings of sample foods. After this, subjects were given a set of VAS to take away with the instruction to rerate the variables at 5:00 p.m. In addition, they were given a food diary to record the type and quantity of foods consumed at dinner and any snacks eaten that evening. Instructions on how to complete a food diary were given by a trained nutritionist (N.V.). The completed scales and diary were returned to the investigators the next morning.

One day after the final test session, subjects were interviewed by telephone using a standard questionnaire to assess whether they had guessed the purpose of the experiment, to record any adverse reaction to drug administration and to discover whether subjects could correctly discriminate the active drug from the placebo condition. At this time, subjects were debriefed and payment was mailed to subjects for their participation.

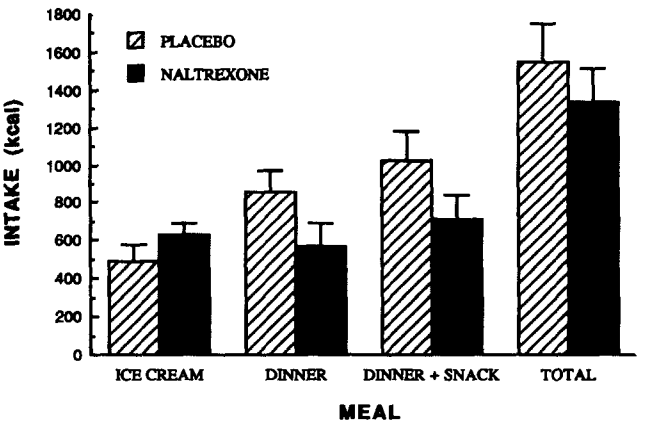

FIG. 1. Mean (±SEM) energy intake of ice cream, dinner, dinner and snacks and total energy intake, Experiment 2.

Measurements and Data Analyses

In both experiments, food intake was calculated as the weight offered minus the weight left over, both the weight of food consumed and caloric intake were determined. In Experiment 2, the weight and calories consumed in the evening were calculated from food diaries using a nutrient analysis program (IBM: Nutritionist III).

Changes in ratings (hunger, fullness, mood and pleasantness, sweetness, intensity of the taste of the foods) following the drug administration were measured by subtracting the ratings made after the drug or placebo (premeal ratings) from the baseline ratings. Changes in ratings following the meal were determined by subtracting postmeal ratings from premeal ratings.

Analyses of variance were conducted to test the effect of the drug and the effect of order of administration on food intake. The effect of session (i.e., the order effect) and the interaction between session and drug condition were assessed using a two-way analysis of variance with session and condition as factors.

In Experiment 2, evening food intake was compared across conditions using a repeated-measures analysis of variance. Evening intake was divided into weight and calories consumed during the evening meal alone, evening meal and snacks combined, and total intake (ice cream, evening meal and snacks).

Absolute ratings and changes in ratings were analysed using a two-way analysis of variance with condition (drug/placebo), and time (baseline, postdrug, postmeal, final) as factors. Post hoc tests on significant effects were conducted using the Scheffé test.

RESULTS

All results are expressed as means (±SEM).

Food Intake

In Experiment 1, the weight of food consumed in the self-selection meal after placebo was 943.3±97.1 g and after naltrexone was 954.1±117.3 g. The caloric intake following placebo was 1091.8±108.9 kcal and following naltrexone was 1020.3±123.8 kcal. No statistically significant differences in intake as a result of naltrexone administration were found. The

interaction between session and drug administration was not significant. Energy intakes in the first and second sessions were equivalent (1054 ± 129.8 kcal; 1058 ± 102.8 kcal, respectively).

When food intake was analysed according to calories derived from sweet versus salty foods, no significant differences were recorded in relation to the drug administration. No selection differences across conditions were observed, and there were no significant differences in the amount of individual foods consumed. No effect of the order of drug administration was found.

In Experiment 2, analysis of ice cream intake across conditions, $F(1,13)=4.86$, $p<0.05$, suggested a significant difference in intake, such that less ice cream was consumed following placebo (456.7 ± 79.2 kcal) relative to naltrexone (599.3 ± 67.6 kcal). The mean increase in intake of ice cream was 81.4 kcal (18.7% increase). Although the effect of session overall was not significant, the session by condition interaction was significant, $F(1,12)=4.5$, $p<0.05$. Ice cream intake was significantly less in the placebo condition (275.8 ± 89.4 kcal) when naltrexone was given first relative to ice cream intake in the placebo condition (703.0 ± 93.0 kcal) when naltrexone was given second.

Intake of ice cream was influenced by the order of drug administration. When subjects were given the naltrexone first, five out of seven subjects ate less in the second session when placebo was administered. When the naltrexone was given second, subjects ate similar amounts on both drug and placebo days. This suggests that receiving naltrexone first had an impact on subsequent intake of ice cream in the second or placebo condition.

The rate of ice cream consumption was not influenced by administration of naltrexone. Subjects consumed the ice cream at approximately the same rate across conditions (placebo: 22.6 ± 2.3 g/min, naltrexone: 23.3 ± 1.2 g/min).

Intake of the evening meal recorded in food diaries following test sessions revealed a significant effect of condition. When naltrexone was administered, subjects consumed fewer calories in the evening meal (571.3 ± 114.7 kcal) relative to placebo administration (854.8 ± 117.6 kcal) and this was significantly different, $F(1,12)=7.5$, $p<0.02$. A session by condition analysis indicated a significant interaction, $F(1,12)=11.1$, $p<0.01$. Post hoc tests demonstrated an effect of naltrexone administration on the first session (419.1 ± 139.8 kcal) compared to placebo administered on the first session (1046.3 ± 189 kcal). Thus subjects had a smaller evening meal following naltrexone if this was given on the first session compared to placebo given first. When naltrexone was administered on the second session, dinner intake (723.4 ± 172.4 kcal) was equivalent to intake following placebo on the second session (663 ± 107.7 kcal) and appeared to be less than that following placebo on the first session, however, this difference was not significant. Therefore, food intake later in the day was also influenced by the order of naltrexone administration. Subjects who received drug first tended to eat less than subjects given placebo first and may be accounted for reports of aversive experiences with the drug given first.

When energy intake from the evening meal was combined with that from snacks eaten later in the evening, average intake in the naltrexone condition (710.4 ± 126.9) was less than that in the placebo condition (1023.5 ± 159.2), however, this result failed to reach significance, $t(13)=2.04$, $p=0.06$. The caloric intake from late evening snacks alone did not differ when naltrexone was given (139.1 ± 60.7) relative to placebo (168.7 ± 71.0). Similarly, weight of foods consumed in the evening (dinner and snacks combined) was less following naltrexone (682.2 ± 121.9 g) than placebo (842 ± 99.0 g), however, this trend also failed to reach statistical significance.

When the total caloric intake from the ice cream test meal, evening meal and snacks was calculated, no significant difference across conditions was observed (see Fig. 1).

Visual Analog Scale Ratings

Analyses of the changes in ratings of hunger, fullness and mood indicated no significant effects of naltrexone in both experiments. The greatest differences in ratings were observed following consumption of the test meal for both drug and placebo conditions in both experiments. Thus hunger ratings decreased and fullness ratings increased following food intake regardless of drug condition. Ratings of nausea, depression and anxiety were not influenced by naltrexone or food intake. Similarly, ratings of the pleasantness, sweetness and intensity of the flavor of the foods were not influenced by naltrexone.

In Experiment 2, ratings of hunger and fullness recorded later in the evening (5:00 p.m.) did not differ as a result of naltrexone administration.

No specific effect of naltrexone administration on ratings of the sample foods was found and no specific effect of naltrexone administration on the pleasantness of the sweet foods was observed.

The pleasantness of the taste of the sample foods changed following consumption of the ice cream test meal. When foods were divided into eaten (ice cream) and uneaten foods (all other sample foods) a significant interaction between food and time, $F(2,104)=5.27$, $p<0.01$, indicated that the pleasantness of the ice cream decreased significantly more than the pleasantness of the other foods. Desire to eat ice cream decreased significantly following consumption of the test meal relative to the other foods, $F(2,104)=24.0$, $p<0.001$.

The pleasantness and desire to eat sweet foods decreased more following intake of the ice cream relative to salty foods. Ratings of the pleasantness of ice cream and desire to eat ice cream decreased more than for the other foods (sensory-specific satiety). These changes were independent of naltrexone administration.

In the debriefing interview, subjects were asked on what day the active drug had been given. Of the fourteen subjects, seven reported that they had detected no difference between the two sessions and did not know on which session they had been given the active drug. Seven subjects guessed correctly the day of naltrexone administration. Of these subjects five had been given naltrexone on the first test session. These subjects reported nausea, fatigue and slight malaise following drug administration.

In summary, naltrexone did not influence ratings of hunger, fullness or mood, nor did it differentially influence sensory-specific satiety. However, an order effect was reported by subjects and this may have been attributable to side effects associated with drug administration.

DISCUSSION

Oral administration of 50 mg of naltrexone had no effect on ratings of hunger, fullness, mood and the pleasantness of the taste of a variety of foods and drinks, or on sensory-specific satiety in two separate experiments. The effects on food intake were more equivocal and appeared to depend on aversive side-effects such as nausea. This was shown most clearly in the second experiment in which test meal intake was higher in the naltrexone condition than with the placebo. This effect was due to the order of testing so that subjects who had naltrexone first ate significantly less on their second test with the placebo. Several of these subjects reported increased nausea in the naltrexone condition and the results point to a conditioned aversion to the ice cream. Spiegel et al. (25), in the only other study which has reported a decrease in food intake following naltrexone, also attributed this suppression to a conditioned taste aversion or a conditioned anorexia. That study was also the only one to report a decrease in rated hunger and that too could have been due to aversive effects of the naltrexone.

Consistent with the findings of Fantino et al. (7), we hypothesized that naltrexone would affect both the palatability of foods and the changing pleasantness of the taste of food associated with consumption (sensory-specific satiety). We found no change in the pleasantness of the taste of a variety of foods following naltrexone in either experiment and we found no change in sensory-specific satiety. Spiegel et al. (25) reported that naltrexone decreased the palatability of the foods at the start of meals but this effect developed gradually over days with administration of the antagonists, suggesting that it could have been due to a learned aversion associated with the drug.

The effect of naltrexone may depend on the initial palatability of the food. The sweet solution used by Fantino et al. (7) and the sandwiches in the Spiegel et al. (25) study were only moderately palatable. It is possible that opioid blockers would have more of an effect on moderately palatable foods than on those of higher palatability which perhaps are more resistant to change. Against this idea, however, we did not find that naltrexone had different effects on the palatability of the wide range of foods rated in the two studies. Also, a recent experiment with a long-acting derivative of naltrexone, nalmefene, demonstrated a decrease in food intake due to a decrease in intake of the most palatable foods (29).

Our study indicates that naltrexone is not an ideal substance with which to investigate ingestive behavior. Many of the early studies using naltrexone reported nausea and dysphoria and no effects on food intake and body weight. Other studies have reported aversive effects of naltrexone (12, 16, 18). Nalmefene may be better suited to studies of ingestive behavior, since it has few side effects and reduced food intake and food palatability (29,30).

It seems unlikely that the problem with naltrexone is simply one of not having tested the correct dose. The dose that we used had side effects such as nausea and dysphoria. These effects are worse with higher doses and in chronic studies problems of liver toxicity may be experienced (3, 13, 15, 19). Doses lower than those used here are relatively ineffective. For example, Fantino et al. (7) found that 60 mg of naltrexone decreased the pleasantness of the sweet taste, but Melchior et al. (17) found no effect of 25 mg of naltrexone on the sweet taste unless it was combined with a glucose load.

The endogenous opioid system could be involved in the control of food intake in some situations. It should be noted, however, that food intake has never been depressed more than 20 to 38% with the antagonists currently available. This may reflect the specific contribution that the opioid system makes to eating or it could be that, despite administration of opioid antagonists, other mechanisms compensate for endogenous opioid blockade. Alternatively, it could be that the critical receptors have not been blocked to produce a greater decrease in intake. As a wider variety of antagonists becomes available the specific receptors involved should become clearer.

It seems likely that the opioid system, with its links to pleasure, is involved in the maintenance of food intake and in such phenomena as sensory-specific satiety and alliesthesia, however, further examination of this issue is required.

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