

Effects of Naltrexone on Food Intake and Changes in Subjective Appetite During Eating: Evidence for Opioid Involvement in the Appetizer Effect

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YEOMANS, M. R. AND R. W. GRAY. *Effects of naltrexone on food intake and changes in subjective appetite during eating: evidence for opioid involvement in the appetizer effect.* *PHYSIOL BEHAV* **62**(1) 15–21, 1997.—The effects of 50 mg naltrexone on eating and subjective appetite were assessed in a double-blind placebo-controlled study with 20 male volunteers. Appetite was monitored using a disguised digital balance connected to a micro-computer, which constantly monitored the amount of food remaining, and which automatically interrupted feeding for 30 s after every 50 g consumed to allow appetite ratings to be made. Half the subjects ate pasta with a cheese sauce, and the remainder pasta with a tomato sauce. Subjects ate significantly less of both foods after 50 mg naltrexone than in either the placebo condition or on the initial (familiarisation) day. Naltrexone also reduced the rated pleasantness of both foods, and reduced overall eating rate. When best-fit quadratic functions were used to describe changes in rated hunger in relation to intake within the meal, naltrexone abolished the positive linear component reflecting the initial stimulation of appetite without altering either intercept or the negative quadratic function. Although mood ratings suggested that naltrexone had a mild sedative effect, mood changes alone could not explain the effects of naltrexone on appetite. Overall, these data suggest a specific role for opioids in the stimulation of appetite through palatability. © 1997 Elsevier Science Inc.

Feeding Naltrexone Palatability Opioids Hunger

OPIOID peptides have been shown to play an important role in the control of food intake (see 4,6 for reviews), based largely on studies employing opioid antagonists and agonists. Although it is likely that opioids are involved in a number of physiological systems which can modify feeding, a variety of evidence suggests that opioids play a key role in those aspects of feeding related to reward. In this paper we explore further this idea using a micro-structural analysis of eating in human volunteers.

It is now widely accepted that opioid antagonists reduce feeding in most species (see reviews by 4,18), including humans (1,20,21,25). In humans, the acute reduction in meal-size with opioid antagonists does not appear to result in sustained weight loss (15,17), suggesting that opioids play a role more in the short term modulation of eating than in the longer term control of energetic intake. In studies with rats also, the reduction in food intake by naloxone appears to be due to modulation of meal-size once feeding has started, rather than any reduction in motivation to initiate feeding (11). Consequently, recent research has concentrated on the detailed analysis of feeding behaviour following

opioid antagonism, leading to the suggestion that opioids play a role in orosensory reward mechanisms in feeding (12,14,25).

One of the most influential ideas in our understanding of the control of food intake is that the underlying structure of meal-taking can be described in terms of two opposing feedback loops, one representing the stimulation of appetite by taste and other sensory factors, and one representing the processes underlying satiation. Support for this type of model has come from detailed analyses of the microstructure of feeding in rats (e.g. 5), and from studies of the micro-structure of eating in humans (13). In both cases, the decrease in eating rate over the course of a meal is best described by a quadratic function, with a combination of a positive linear component reflecting the stimulatory effects of the food, and the negative quadratic function relating to satiation. Recently, we have extended this approach further by examining changes in subjective appetite within a meal (22). Again, a quadratic function was the best descriptor of changes in appetite, indexed as ratings of subjective hunger, and we also found that manipulation of palatability by altering the sensory quality of the

TABLE 1
NUTRIENT CONTENTS OF THE TWO FOODS USED IN THE STUDY

Food Item	Nutrient Content (per 100 g)			
	kJ	Fat (g)	Protein (g)	Carbohydrate (g)
Cheese sauce	871	10.7	7.1	20.8
Tomato/tuna sauce	665	1.5	5.3	34.2

* Value given is for non-sweet carbohydrate.

food altered the positive linear component of this relationship without affecting any other component. Thus, ratings of subjective hunger increased in the early stages of a meal when the food was palatable, but not when the food was either bland or unpleasantly strong tasting. If, as has been suggested, opioids are involved in this stimulation of appetite by palatability (the “appetizer effect,” 22), it would be predicted that opioid antagonists should alter this component of the relationship between subjective hunger and intake without modifying any other component.

Previously, we have reported that the opioid antagonists nalmefene (24,25) and naltrexone (23) both reduce the rated pleasantness of food items, and have suggested that the reduction in food intake seen with these drugs may be a consequence of their effect on palatability. While several other studies have also reported reductions in rated food pleasantness with opioid antagonists (e.g. 8,16), not all have found this effect (9). Moreover, opioid antagonists have been reported to specifically reduce intake of fat in humans (3,7,25), and this effect has not always correlated with alterations in food pleasantness. Because of the food-specific nature of the effect of opioid antagonists in other studies, two foods varying on a number of dimensions including energetic density, macronutrient content and sensory properties were tested to see how general the effects on appetite were under these circumstances. Since some authors have suggested that the effect of opioid antagonists on eating may be secondary to side-effects such as induced nausea (3), reported side-effects were collated both from a double-blind structured interview at the end of each test session, and from a series of mood ratings made before and after drug administration, although previously we found no evidence to support this contention (23). The drug used in this study was naltrexone, which has previously been shown to reduce food intake in acute studies with humans in this laboratory (23) and elsewhere (3,15,19).

METHOD

Subjects

Twenty male volunteers were recruited from an existing subject database, mainly students and staff at Sussex University.

Potential subjects were non-smoking, non-dieting, non-vegetarian males who gave consent for the investigators to approach their general practitioner for medical screening. They were screened to include only subjects who had normal medical histories, with histories of drug abuse, eating disorders and liver dysfunction as specific exclusion criteria. The 20 participants (mean age 24, range 19 to 36; mean BMI 22.4, range 19.4 to 25.2) came from a screened sample of 25 potential subjects, and were paid for their participation. Subjects were informed that the first test session would not involve any drug testing, but that on the subsequent two sessions they would be given either naltrexone or placebo. They were also informed that previous studies had reported a low incidence of side-effects, and a full list of possible side-effects were provided on the subjects information sheet as part of the standard Informed Consent conditions for this study. However, while subjects were aware that the study investigated the effects of naltrexone on appetite, no indication was given of what the nature of these effects might be.

Appetite Tests

In this study, food intake was continuously monitored using a disguised balance (Sartorius, Model BP 4100), located in a modified table so that the balance surface protruded 3 mm above the table surface, but no part of the balance was visible. The balance had a white plastic cover shaped like a place mat (dimensions 267 mm wide $\times$ 318 cm long $\times$ 4 mm thick), with the leading edge 10 mm from the table edge. The balance was connected to a Macintosh computer (model LCII) via the printer port. The computer was custom-programmed (in QuickBasic) to read the balance weight (to 0.1 g accuracy) at 2 s intervals throughout each meal. The eating test started with the subject rating hunger using a computerised visual analogue rating (see below), followed by the instruction to ask their experimenter to provide the food. Subjects were then instructed to taste a forkful of the food (weighed by the computer), after which they rated hunger, fullness and food pleasantness. They then ate at their normal rate, with the following restrictions: they were only to take food onto their fork when ready to ingest it, and they were not to leave their fork in the bowl with their food at any stage. Although subjects were not told explicitly that their eating would be monitored, the restrictions on eating style are likely to have made subjects aware that this was so. Once the meal had started, the computer gave a signal (2 second buzz accompanied by on-screen instructions) for the subjects to pause after every 50 g consumed (referred to here as an eating bout), taken as the first measurement where the decrease in weight of food from the start of each bout was at least 50.0 g. In practice, since bite-size was not controlled, this meant some slight variations in the 50 g bout sizes, with an average across all bouts and subjects of 58.8 ± 0.3

TABLE 2
EFFECTS OF NALTREXONE ON OVERALL INTAKE AND EATING RATE FOR THE TWO GROUPS OF SUBJECTS EATING PASTA WITH DIFFERENT SAUCES

Food Group	Baseline		Placebo		Naltrexone	
	Cheese	Tomato	Cheese	Tomato	Cheese	Tomato
Intake (g)	561.3 $\pm$ 71.0 (8)	806.8 $\pm$ 63.8 (8)	588.8 $\pm$ 82.5 (9)	828.7 $\pm$ 81.2 (9)	483.6 $\pm$ 72.0 (9)	595.3 $\pm$ 59.5 (9)
Intake (kJ)	4887 $\pm$ 619 (8)	5371 $\pm$ 425 (8)	5128 $\pm$ 719 (9)	5516 $\pm$ 541 (9)	4211 $\pm$ 627 (9)	3962 $\pm$ 396 (9)
Eating rate (g/min)	54.6 $\pm$ 5.8 (8)	53.1 $\pm$ 3.9 (7)	48.9 $\pm$ 7.2 (9)	53.4 $\pm$ 3.2 (9)	39.8 $\pm$ 6.2 (9)	50.4 $\pm$ 3.2 (9)
Meal duration (s)	652 $\pm$ 63 (9)	930 $\pm$ 91 (8)	810 $\pm$ 106 (9)	980 $\pm$ 89 (9)	786 $\pm$ 97 (9)	697 $\pm$ 82 (9)

Values are mean $\pm$ SEM, (n). See text for statistical analysis.

TABLE 3

RATINGS OF FOOD PALATABILITY AT THE START (45 min POST-DRUG) AND END OF LUNCH, AND HUNGER AND FULLNESS BEFORE AND AFTER DRUG ADMINISTRATION AND AFTER LUNCH FOR THE TWO GROUPS OF SUBJECTS EATING PASTA WITH DIFFERENT SAUCES

Rating	Condition	Food Group	Time of Rating		
			Pre-Drug	Pre-Lunch	Post-Lunch
Palatability	Baseline	Cheese	—	338.4 ± 34.6	230.2 ± 39.1
		Tomato	—	407.1 ± 18.3	339.6 ± 27.2
	Placebo	Cheese	—	354.7 ± 30.0	228.7 ± 36.2
		Tomato	—	434.9 ± 16.5	312.4 ± 36.3
	Naltrexone	Cheese	—	316.1 ± 33.3	222.0 ± 41.0
		Tomato	—	389.3 ± 14.5	313.7 ± 40.3
Hunger	Baseline	Cheese	373.0 ± 19.8	419.4 ± 17.2	84.9 ± 24.2
		Tomato	385.9 ± 24.3	416.6 ± 21.0	76.4 ± 19.9
	Placebo	Cheese	359.0 ± 24.4	393.2 ± 14.5	95.9 ± 33.6
		Tomato	389.2 ± 33.8	419.7 ± 23.1	89.8 ± 15.9
	Naltrexone	Cheese	346.3 ± 19.0	398.8 ± 20.7	81.4 ± 21.0
		Tomato	365.7 ± 14.8	395.2 ± 16.6	95.7 ± 17.8
Fullness	Baseline	Cheese	99.1 ± 24.1	77.9 ± 25.7	383.3 ± 21.7
		Tomato	111.1 ± 34.1	104.7 ± 33.7	425.7 ± 16.4
	Placebo	Cheese	103.7 ± 28.7	94.1 ± 16.0	412.3 ± 19.7
		Tomato	108.7 ± 34.6	70.2 ± 22.4	409.3 ± 10.1
	Naltrexone	Cheese	120.2 ± 21.9	101.0 ± 24.5	394.7 ± 21.2
		Tomato	124.1 ± 24.5	86.8 ± 19.1	402.7 ± 20.2

Values are mean ± SEM, $n = 9$.

g ($n = 547$, minimum = 50.0, maximum = 86.4). Each bowl contained between 500 and 510 g of food. To reduce the impact of portion size on intake, the food bowl was replaced during the first pause in eating after the point where the total weight had fallen by at least 400 g, which ensured that no subject could complete their meal simply by emptying their bowl. This gave a maximum of eight 50 g eating bouts with each bowl of food. Subjects could end their meal at any time during an eating bout by using the computer mouse to click in a dialogue box with the legend "Please press the mouse button when you have finished eating", but were also asked the specific question "Do you wish to continue eating?" at the end of each 50 g bout. Subjects made visual analogue ratings of hunger, fullness and food pleasantness during each pause within the meal, and the total pause between instructions to stop and restart eating was 30 s.

Computerised Ratings

All visual analogue ratings were made using the same computerised scales as used previously in this laboratory (23), using a single horizontal line positioned centrally on a VDU screen. The line was anchored with the words "Not at all" and "Very," and the polarity was randomised between trials. The specific attribute to be rated was presented as an appropriate question positioned immediately above the line. Ratings were made by the accurate positioning of a vertical bar on the horizontal line. This bar was initially presented in the centre of the line, and could then be dragged to the appropriate point using the computer mouse. All ratings were scored automatically by the computer on a scale of zero (Not at all) to 500 (Very), with subjects instructed to treat the centre of the scale (250) as neutral. Subjects completed a battery of ten ratings before drug administration, and again before and after lunch. The ratings used were for hunger, fullness, thirst, nausea, light-headedness, alertness, anxiety, drowsiness, tiredness and elation. Additional ratings of hunger,

fullness and palatability were made periodically throughout the meal.

Procedure

The study combined a placebo-controlled double-blind cross-over design to examine the effects of naltrexone on appetite with a between-groups comparison of two foods (pasta with one of two sauces, hereafter referred to as "food group"). Pasta shells (Sainsbury's) were freshly prepared daily by boiling for 10 min in salted water. The cooked pasta was subsequently mixed with one of two sauces, either a cheese sauce (Sainsbury's 4-cheese pasta sauce) or tomato sauce (Sainsbury's "Pomodori" sauce) with added tuna and maltodextrin so that the sauces had similar protein content and energy content (see Table 1 for nutrient content of the 2 foods). Subjects were randomly assigned to one of these two food conditions, and were tested alone in cubicles in the Human Psychopharmacology Unit at Sussex University on three occasions. The purpose of the first session was to familiarise subjects with the experimental procedures and to obtain baseline measures of appetite and ingestion, and no drug was included. There was a minimum of 7 days between sessions, and subjects received a single tablet containing either 50 mg naltrexone or a placebo (containing 50 mg paracetamol to mimic the bitter taste of naltrexone), with the order of naltrexone and placebo counterbalanced across subjects and sessions. Paracetamol has been the placebo condition in all previous studies of the effects of naltrexone on appetite (e.g. 2,15,17), including work in this laboratory (23), and it has been generally accepted that at this low dose paracetamol has little pharmacological activity.

On the day before testing, subjects were required to eat normally, but abstain from all alcohol. On each test day, they reported to the laboratory between 0830 and 0930 h where they were given a standard breakfast of cereal and orange juice (390 kcal, 4.7 g fat, 8.7 g protein, 77.0 g carbohydrate). They were

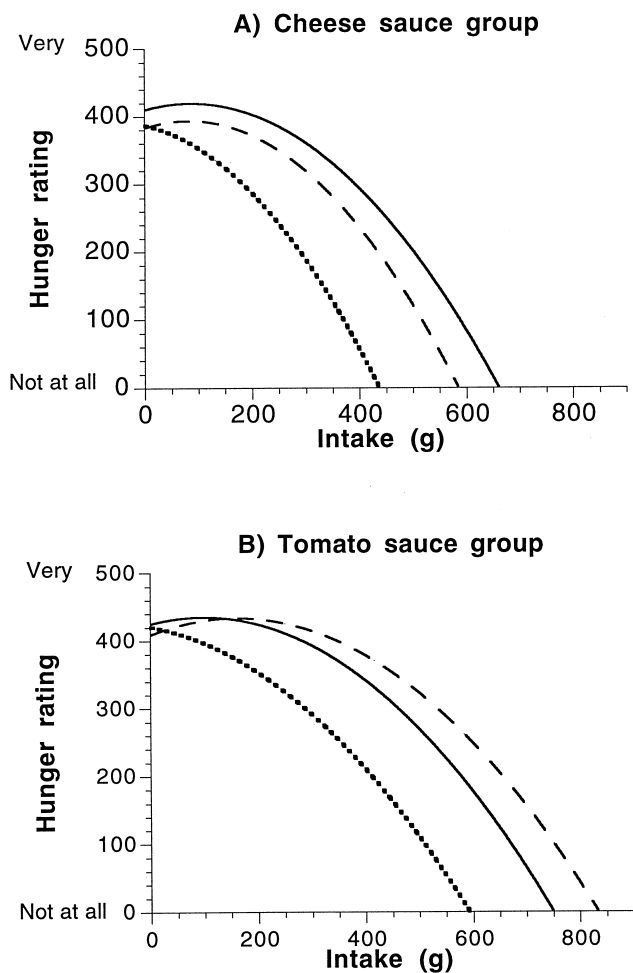


FIG. 1. Best fit quadratic functions between ratings of hunger and actual intake in the meal for the baseline (—), placebo (---) and naltrexone (·····) conditions for the two groups of subjects with different foods. See text for statistical analyses.

then instructed to refrain from eating until they returned for lunch, and to drink only water during this time. They returned three hours later, and completed a series of baseline ratings of appetite and mood. On test days, they then received the appropriate drug treatment, and were then required to rest for 30 min before a second set ("Pre-Meal") of mood and appetite ratings. The main appetite tests started 45 min after drug administration, with unlimited intake of the appropriate test food interspersed with appetite ratings at 50 g intervals. Further appetite and mood ratings were completed after the end of the intake test ("Post-Meal"), and the session ended with a structured interview in which subjects were asked to report any side-effects, and indicate whether they believed they had received drug or placebo.

Data Analysis

One subject was taken ill on his last session, and all data for that session were excluded from analysis. All data from a second subject were excluded since he failed to follow the experimental instructions making it impossible to calculate total intake on any session, even though he was given extra training with the meal-pattern monitor after the baseline session. Problems with the labo-

rance system also occurred with 4 other subjects, and although subjective ratings at the start and end of eating were available on all days for these subjects, it was impossible to calculate total intake on the baseline day for two subjects, and detailed records of eating were available for one of the three test days only for one subject, and for two days for 3 subjects. Where at least 2 days data were available for any one subject, their data were included in analysis and degrees of freedom automatically adjusted by the number of missing data points to reduce the likelihood of type 1 errors (see 10). Total intakes were compared between experimental sessions by mixed analyses of variance with three treatment conditions (within-subjects) and the two food groups (between subjects), and similar analyses of variance were also used to compare changes in subjective appetite and mood between the start and end of the meal. Specific planned contrasts between naltrexone and the other two conditions were made only where the relevant main effect or interaction was significant. The specific relationship between rated appetite (hunger, fullness and desire to eat) and actual food intake was assessed by fitting individual best-fit quadratic functions for each subject's data, and then contrasting the three coefficients from these best-fit functions between treatment conditions, also using mixed analyses of variance. Analyses were conducted using Super-Anova and Statview (Abacus) run on Macintosh computers, with best-fit functions calculated using the least squares method, run on Kaleidagraph (Abelpeck).

RESULTS

Intake and Feeding Micro-Structure

Naltrexone caused a significant reduction in energetic and total intake in both food groups (Table 2: energy, main effect of treatment, $F(2, 30) = 10.38, p < 0.001$, contrasts of naltrexone with placebo $F(1, 30) = 19.59, p < 0.001$, and with baseline $F(1, 30) = 9.40, p < 0.01$; volume, main effect of treatment $F(2, 30) = 9.69, p < 0.001$, contrasts of naltrexone with placebo $F(1, 30) = 17.44, p < 0.001$, baseline $F(1, 30) = 8.68, p < 0.01$). It was also noteworthy that energetic intake did not differ between the two groups ($F(1, 16) = 0.08$, NS), despite the pasta with the tomato sauce having a lower energetic density: thus the group with this sauce ate a greater volume overall (main effect of sauce: $F(1, 16) = 4.67, p < 0.05$). However, the effect of naltrexone on intake was independent of subject group (energy, $F(2, 30) = 0.94$, NS; volume $F(2, 30) = 1.66$, NS), and treatment order had no significant effect on intake. Naltrexone also suppressed the overall rate of eating (main effect of condition $F(2, 29) = 9.98, p < 0.001$: contrast of naltrexone with placebo $F(1, 29) = 8.51, p < 0.01$, and baseline $F(1, 29) = 18.96, p < 0.001$), with similar eating rates in the two food groups, and a tendency for greater suppression of eating rate for the group with the cheese sauce (interaction of food group $\times$ treatment $F(2, 29) = 2.45, p = 0.10$). Meal duration varied depending on food group and treatment (interaction of food group $\times$ treatment $F(2, 31) = 3.62, p < 0.05$), with the group with the tomato sauce finishing their meal sooner after naltrexone (contrast of naltrexone and placebo, $F(1, 31) = 9.74, p < 0.001$, baseline and naltrexone $F(1, 31) = 4.04, p < 0.05$), but the group with cheese taking similar amounts of time in placebo and naltrexone conditions. Thus, the reduction in overall intake was achieved by eating for less time in one group of subjects, and eating slower by the other group.

Subjective Appetite

Rated palatability at the start of feeding (Table 3) differed significantly between treatment conditions ($F(2, 32) = 8.75, p$

TABLE 4

BEST-FIT COEFFICIENTS FOR QUADRATIC FUNCTIONS RELATING RATINGS OF HUNGER AND FULLNESS AGAINST INTAKE DURING THE COURSE OF THE LUNCH FOR THE TWO GROUPS OF SUBJECTS EATING PASTA WITH DIFFERENT SAUCES

Rating	Condition	Food Group (n)	Best-fit Function		
			Y-intercept	Linear Coefficient	Quadratic Coefficient
Hunger	Baseline	Cheese (8)	409.8 ± 11.4	0.22 ± 0.12	-0.0013 ± 0.0003
		Tomato (7)	424.6 ± 25.5	0.20 ± 0.11	-0.0010 ± 0.0003
	Placebo	Cheese (9)	382.8 ± 13.1	0.26 ± 0.11	-0.0016 ± 0.0005
		Tomato (8)	408.7 ± 26.0	0.31 ± 0.20	-0.0010 ± 0.0003
	Naltrexone	Cheese (8)	386.5 ± 9.9	-0.17 ± 0.15	-0.0016 ± 0.0007
		Tomato (8)	420.1 ± 15.1	-0.14 ± 0.20	-0.0007 ± 0.0002
Fullness	Baseline	Cheese (8)	86.4 ± 21.0	0.44 ± 0.22	0.0001 ± 0.0004
		Tomato (7)	63.1 ± 27.4	0.09 ± 0.15	0.0004 ± 0.0002
	Placebo	Cheese (9)	97.8 ± 13.0	0.26 ± 0.19	0.0009 ± 0.0003
		Tomato (8)	45.6 ± 22.8	0.00 ± 0.22	0.0007 ± 0.0004
	Naltrexone	Cheese (8)	122.0 ± 26.6	0.31 ± 0.27	0.0006 ± 0.0006
		Tomato (8)	82.1 ± 21.3	0.03 ± 0.15	0.0014 ± 0.0005

Values are mean ± SEM, with *n* in brackets after the relevant food subject group.

< 0.001), with lower ratings in the naltrexone condition with both foods than in placebo ($F(1, 32) = 17.49, p < 0.001$) or baseline conditions ($F(1, 32) = 4.98, p < 0.05$), and lower overall ratings for the group with the cheese-sauce ($F(1, 16) = 4.54, p < 0.05$). The interaction of food group and treatment condition was not significant ($F(2, 32) = 0.17, NS$). There was no effect of treatment condition on rated palatability at the end of the meal, although ratings for the group with the cheese sauce still tended to be lower than for those with the tomato sauce ($F(2, 32) = 3.76, p = 0.07$).

Ratings of hunger before and after drug administration, and after lunch (Table 3) did not differ between treatment conditions (no significant main effect or interaction involving treatment). However, naltrexone altered significantly the relationship between rated hunger and food intake within the meal (Fig 1). Neither the intercept or quadratic component of the best-fit function were altered significantly by treatment condition, but the linear component was significantly reduced by naltrexone compared with both placebo and baseline conditions (main effect of condition, $F(2, 26) = 9.37, p < 0.001$, contrast of naltrexone with placebo $F(1, 26) = 16.79, p < 0.001$ and with baseline $F(1, 26) = 10.90, p < 0.01$). Indeed, whereas there was a significant positive linear coefficient in both placebo and baseline conditions (Table 4), this function did not differ significantly from zero in the naltrexone condition. These effects were independent of food group ($F(1, 16) = 0.02, NS$). Actual hunger ratings at the start of the meal and the values for best-fit Y-intercept differed slightly, which was a consequence of the averaging procedure in the curve-fitting process. Naltrexone had no effect on ratings of fullness before and after lunch (Table 3), nor did it alter the relationship between rated fullness and intake within a meal (Fig. 2). The best-fit functions for fullness were more variable than for hunger, suggesting that subjects found this measure harder to rate consistently. Thus, although there was a trend for faster satiation in the naltrexone condition for the tomato sauce group, the effect of treatment was not significant ($F(2, 26) = 0.35, NS$). Rated thirst was unaffected by naltrexone.

Mood Changes and Side-Effects

Although rated nausea varied between treatment conditions ($F(2, 32) = 3.48, p < 0.05$), there was little evidence that nal-

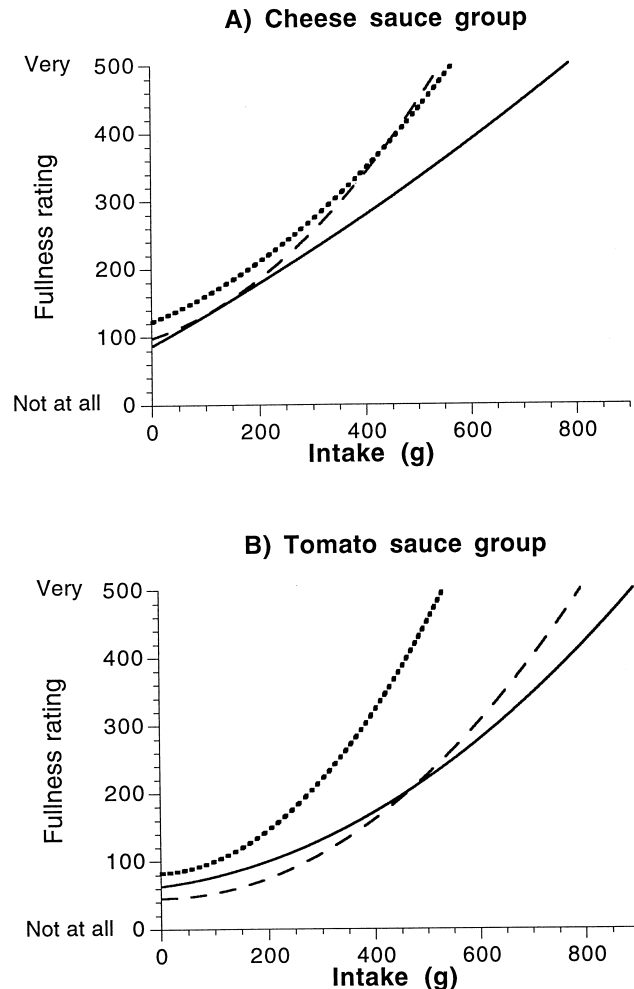


FIG. 2. Best fit quadratic functions between ratings of fullness and actual intake in the meal for the baseline (—), placebo (---) and naltrexone (·····) conditions for the two groups of subjects with different foods. See text for statistical analyses.

TABLE 5
CHANGES IN RATED NAUSEA, DROWINESS AND ANXIETY FOR THE TWO GROUPS OF
SUBJECTS EATING PASTA WITH DIFFERENT SAUCES

Rating	Condition	Food Group	Time of Rating		
			Pre-drug	Pre-lunch	Post-lunch
Nausea	Baseline	Cheese	63.1 ± 13.4	41.1 ± 10.6	80.4 ± 16.6
		Tomato	42.7 ± 17.6	82.6 ± 35.3	58.2 ± 15.3
	Placebo	Cheese	58.2 ± 45.7	63.0 ± 10.7	126.9 ± 27.8
		Tomato	33.4 ± 25.0	87.3 ± 38.0	14.2 ± 31.8
	Naltrexone	Cheese	70.8 ± 30.3	111.1 ± 31.9	111.3 ± 28.5
		Tomato	78.6 ± 30.3	92.7 ± 28.3	130.9 ± 31.0
Drowsy	Baseline	Cheese	198.9 ± 30.3	195.1 ± 36.2	212.7 ± 36.3
		Tomato	203.2 ± 32.5	215.3 ± 30.2	202.7 ± 36.0
	Placebo	Cheese	171.0 ± 34.4	225.8 ± 41.6	264.6 ± 29.0
		Tomato	189.9 ± 41.4	254.1 ± 19.3	269.7 ± 22.8
	Naltrexone	Cheese	216.2 ± 45.2	244.6 ± 46.7	264.0 ± 44.2
		Tomato	185.3 ± 23.6	229.7 ± 25.2	234.7 ± 40.9
Anxiety	Baseline	Cheese	185.8 ± 47.2	179.2 ± 43.8	165.2 ± 34.0
		Tomato	146.0 ± 43.7	81.4 ± 20.4	90.4 ± 17.4
	Placebo	Cheese	130.1 ± 28.6	174.1 ± 35.1	155.3 ± 35.2
		Tomato	86.1 ± 28.1	76.6 ± 24.4	79.9 ± 23.5
	Naltrexone	Cheese	171.6 ± 41.7	131.2 ± 32.3	119.1 ± 32.0
		Tomato	70.0 ± 19.4	51.6 ± 14.8	93.3 ± 30.2

trexone induced nausea: the increase in rated nausea between the pre-drug and pre-lunch period in which the drug would have been absorbed tended to be larger in the placebo than the naltrexone condition, although baseline nausea ratings were slightly higher than placebo. Subjects also tended to have higher nausea ratings at the end of the meal regardless of condition: (main effect of time of rating $F(2, 32) = 5.82, p < 0.01$). There was no significant interaction between treatment condition and time of rating, or any difference between the two food groups (Table 5). Ratings of drowsy and tiredness increased across the lunch period, and alertness fell, but none of these variable differed between drug conditions. Anxiety ratings were higher on the initial, baseline test than in either drug condition, but there was no difference between drug conditions in this or in the other mood ratings (light-headed and elated). Subjects were also unable to identify whether they had received naltrexone or placebo in the debriefing session: 7/18 correctly identified naltrexone, and 9/18 placebo. Three subjects reported feeling nauseous, two after naltrexone and one after placebo, and a further two subjects in the naltrexone condition reported feeling drowsy. To determine whether these effects could account for the reported effects on appetite, overall intake data was analysed further with the change in rated nausea between the pre-drug and pre-lunch sessions as a covariate. The significance of the reductions in energetic and total intake was unaffected, and no effect or interaction involving nausea as a covariate was significant. Thus there was no evidence that effects on appetite were an indirect consequence of induced nausea, or any other indirect effect of naltrexone.

DISCUSSION

In this study, naltrexone was found to reduce food intake in normal volunteers, with an 18% reduction for subjects eating pasta with a cheese sauce and a 28% reduction in a separate group of subjects eating pasta with a tomato sauce. The reduction in intake following naltrexone was associated with a reduction in the overall rate of eating and a reduction in the rated pleasantness

of both foods, but no changes in subjective appetite prior to the meal. The finding of a specific effect of naltrexone on the relationship between intake and rated appetite within the meal, whereby the normal stimulation of rated hunger by food in the initial stages of the meal was abolished by naltrexone in both groups of subjects, lends strong support to the idea that opioids play a role in orosensory reward.

The reduction in the rated pleasantness of the two foods following naltrexone in this study is consistent with other reports on the effects of opioid antagonists (3,8,23–25), and further confirms a role for opioid peptides in hedonic evaluation. What was unclear in previous studies was how this change in the pleasantness of foods prior to ingestion altered subsequent intake, with some studies suggesting that the change in pleasantness alone could account for subsequent reductions in intake (24,25), but others suggesting that other factors might account for the change in intake (7,9,23). The present results suggest that the change in pleasantness is the most important factor determining subsequent intake, based on the specific nature of the effects of naltrexone on the relationship between rated appetite and intake within the meal. These observations were based on a novel method of assessing appetite based on assessing the specific relationship between rated appetite and actual intake within a meal, developed recently in this laboratory (22). We have found that the specific relationship between subjective appetite and intake can be best described by a quadratic function, in much the same way that cumulative intake within meals has been described (13). With both foods, naltrexone abolished the linear function relating rated hunger to intake, without altering either the intercept or quadratic functions. We have previously shown that the linear component of these best-fit functions can be altered by artificial manipulations of palatability (22) in the absence of effects on the other two components of this function (relating to initial motivation and satiation respectively). The fact that naltrexone only affected this linear component is compelling evidence for a specific role of opioids in the stimulation of appetite through palatability. It is also noteworthy that naltrexone caused a larger reduction in

intake of the more palatable food, also in line with the orosensory reward hypothesis, and consistent with other studies (24,25).

A secondary aim of this investigation was to contrast the potential role of opioids in reward mechanisms within feeding with the hypothesised role of opioids in the control of fat intake. It has been suggested that opioids may have a role in intake of sweet and fatty foods independent of their role in palatability (7). Although the fact that similar effects on appetite were seen with the two foods used in this study, it is not possible to draw any strong conclusions about the specific role of fat since the effects of food in this study relied on between-subject comparisons, thus confounding group and food comparisons. Moreover, the two foods differed not only in macronutrient and energetic content, but also on a number of sensory measures. Further studies using similar techniques with foods of equal palatability but markedly different fat content would be needed to evaluate any specific role of opioids in control of fat intake. Since neither of the foods were novel, it is likely that subjects had considerable prior experience with these types of sauces, and this may explain the similarity in energetic intake of the two foods. Alternatively, this similarity may be a fortuitous consequence of the group with the tomato sauce consuming more of the more palatable food.

Any manipulation of appetite which reduces food intake is prone to artefactual results brought about by unpleasant side-effects. In the past, some authors have suggested that the ano-

rectic effect of naltrexone in particular might be attributed to induced nausea (9). However, while there was some evidence for nausea after naltrexone administration in two subjects in this study, there was no evidence that the changes in appetite were dependent on this, in line with other data from this laboratory (23) and elsewhere (3). The surprising increase in rated nausea in the placebo condition could be attributed to demand characteristics, because subjects were informed of nausea as a possible side-effect as part of the informed consent procedure. There was little effect on other mood states, although some suggestion of increased drowsiness/decreased alertness corresponds to previous findings (23). Overall, the low incidence of side effects and lack of correspondence between nausea and altered appetite imply that naltrexone provides a useful assessment of opioid function in appetite control.

In conclusion, naltrexone reduced intake, eating rate and pleasantness, and abolished the stimulation of appetite through palatability. These data clearly implicate opioids in the rewarding aspects of eating, and highlight the value of detailed analyses of eating in dissociating motivational controls.

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