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Effects of Naloxone and Naltrexone on Meal Patterns of Freely-Feeding Rats

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KIRKHAM, T C AND J E BLUNDELL *Effects of naloxone and naltrexone on meal patterns of freely-feeding rats* PHARMACOL BIOCHEM BEHAV **26**(3) 515–520, 1987 —The effects of naloxone and naltrexone on the night-time meal patterning of freely-feeding male rats were investigated using a Kissileff-type eatometer Naloxone (5 0 mg/kg) and naltrexone (2 5 mg/kg) reduced intake for two hours after IP injection This effect resulted from a shortening of duration of meals and an extension of postmeal intervals Unlike other anorexic agents neither drug affected meal frequency or the eating rate within meals These particular opioid antagonists therefore appear to produce anorexia by advancing meal termination and extending the inhibition of feeding which follows a meal These specific changes in the structure of the meal pattern consolidate previous findings and support the hypothesis that naloxone and naltrexone reduce food intake in rats by promoting satiation and prolonging satiety

Opioid antagonists Naloxone Naltrexone Anorexia Satiety Feeding behaviour Meal patterns

IN recent years considerable empirical evidence has accrued to support a role for endogenous opioid peptides in mechanisms governing eating and drinking behaviours. While administration of opioid receptor agonists has been found to promote hyperphagia, a key strategy in this field of research has been the analysis of the anorexia induced by variety of opioid antagonists [9, 26, 31, 32]. Certain of these antagonists (e.g , naloxone and naltrexone) influence feeding behaviour in a relatively specific manner [7, 12, 16, 23] through a suppressive action on food intake via an intensification of the feedback from food ingestion Evidence from behavioural and motivational analyses reveal that NX and NTX do not block the initiation of feeding but advance eating termination in a manner consistent with the early onset of satiety [15–18]. Moreover, the anorexia induced by NX and NTX is attenuated by severe food deprivation and is unattainable in situations in which the normal development of satiation is prevented [5, 10, 11, 18, 33].

In many studies the effects of NX and NTX on food intake have been tested over brief periods using food-deprived animals. However, such short-session, high motivation designs have limited utility since the behaviour of food-deprived and normal free-feeding animals may be controlled by qualitatively different variables [8, 25, 27] Consequently, there is a requirement that effects obtained under rather extreme physiological conditions should be demonstrated using nondeprived subjects under more natural circumstances Here we report the effects of opioid antagonists in an experimental situation which permits a detailed analysis of feeding behaviour in the home environment with disturbance and extraneous variables reduced to a minimum. The automatic technique employed enables the continuous monitoring of feeding patterns over long periods and precise measurement of food intake over short intervals. The procedure incorporates the use of a pellet detecting eatometer [19], which delivers a small (45 mg) food pellet to replace one eaten by the subject animal and provides a record of every pellet consumed during the experimental period Meal pattern analysis is a valuable tool for disclosing the processes through which experimental manipulations influence overall intake and has been used many times to investigate physiological and environmental influences on eating (e.g., [3, 8, 13, 34]). The influence of the drugs on meal patterns is assessed by analysing effects on meal frequency, meal size, intermeal intervals and the relationships between these indices. A similar procedure has been used previously to investigate the effects of naloxone in lean and genetically obese Zucker rats [24]. In the following study this analysis is extended to include naltrexone-induced alterations to the meal patterning of normal, lean rats within their home environment.

METHOD

Animals

Twelve male hooded rats (two groups of N=6) weighing 310–365 g at start of procedure were selected for testing. Animals were housed singly, within the apparatus described below, and maintained on a reversed 12·12 hr light-dark cycle (lights-off at 10 00 hr)

Drugs

Naloxone HCl and naltrexone HCl (Endo) were dissolved

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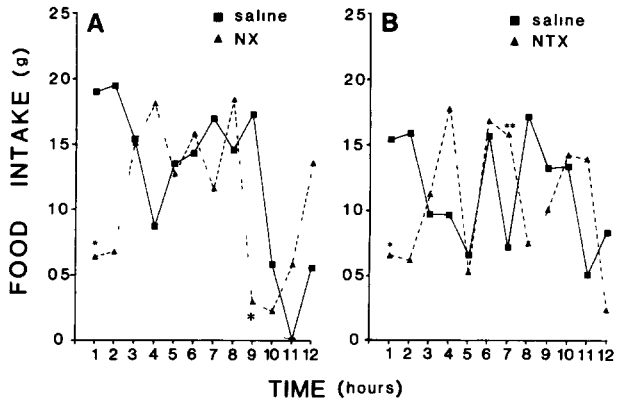

FIG 1 Effects of naloxone (A) or naltrexone (B) on hourly nighttime food intake Each point represents the mean for six rats *$p<0.05$—difference from saline (t-test)

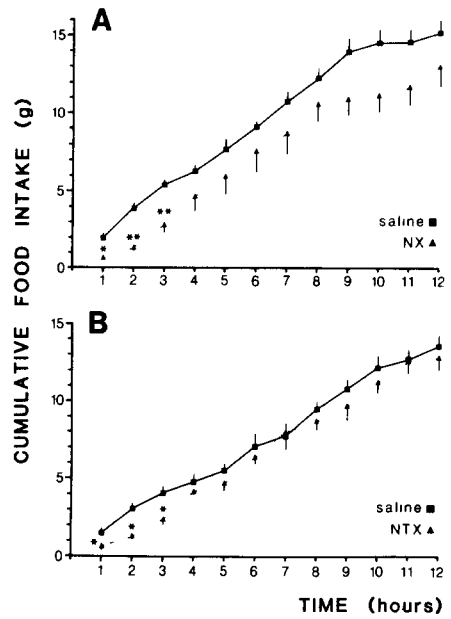

FIG 2 Cumulative food intake during the dark phase after naloxone (A) or naltrexone (B) administration Each point is the mean (±SEM) for six rats *$p<0.05$, **$p<0.01$—difference from saline (t-test)

in 0 9% saline Doses of 5 0 mg/kg NX and 2 5 mg/kg NTX were administered by IP injection at a volume of 1 ml/kg These equi-anorectic doses were chosen on the basis of previous tests showing that each produces an approximate 50% reduction of intake over 1 hr in mildly food-deprived rats

Apparatus

Throughout all phases of experimentation rats were housed in ventilated, sound attenuating automatic feeding chambers. These chambers (of wooden construction) contained a living area (42×39×36 cm) together with an automatic pellet dispenser, water bottle and extractor fan The living area was separated from all electrical and mechanical hardware by a removable aluminium divider Internal lighting was provided by a single fluorescent strip (4 watts) Periodicity of lighting was controlled by external electromechanical timers. One corner of each chamber was provided with a shade, allowing the animal to withdraw from direct light at will. Food (45 mg Noyes precision pellets), was continuously available from a pellet detecting eatometer consisting of a V-shaped trough, at opposite ends of which were positioned an infra-red light emitting diode (LED) and a photosensor Removal of a pellet allowed the LED to activate the photosensor, leading to the delivery of the next pellet Delivery of each replacement pellet was triggered within 0 5 sec of photosensor activation. Water was obtained from a spout set into an aperture in the partition. Feeding activity sent a discrete electronic signal via an interfacing system to a micro-computer running a data acquisition program This program recorded the source and exact (real) time of each signal, and also calculated the elapsed time between last and previous activation of each signal source Inputted data were continuously displayed on a VDU, allowing events to be monitored without interrupting the data collection process. These data were then automatically transferred to disc and stored prior to analysis.

Procedure

For two weeks prior to testing animals were habituated to the feeding chambers, they were housed in them permanently and removed only briefly on every second day for cleaning and maintenance of apparatus Food and water were replenished daily at 09 00 hr On the last three days of habituation each animal received a single IP injection of saline. At the end of this period all animals displayed stable feeding patterns. On test days each animal received injection of test solution 15 min before onset of dark period. Each rat served as its own control receiving both saline and NX (Group 1) or saline and NTX (Group 2) according to a counterbalanced schedule Following each treatment, feeding patterns were continuously monitored for 24 hr At least 72 hr separated successive treatments

Data Analysis

A separate computer program analysed the collected data according to the following criteria. A meal was defined as the removal of 5 or more pellets separated from any number of 5 or more pellets by an interval of at least 5 minutes (the validity of these criteria have been discussed elsewhere, [3]). The number of meals, the duration (minutes) and size (grammes) of each meal were determined. Additionally, the rate of eating (g/min) within each meal was computed. Finally, intermeal intervals and satiety ratios (meal size/duration of postmeal interval) were calculated. For each parameter the significance of drug-induced changes occurring over the 12 hr of the dark period were analysed using the Student's t-test (two-tailed) for repeated measures.

RESULTS

1 General Pattern of Food Intake

Naloxone produced clear alterations to the pattern of intake over the early stages of testing (Fig. 1A) The drug produced a considerable depression of intake over the two

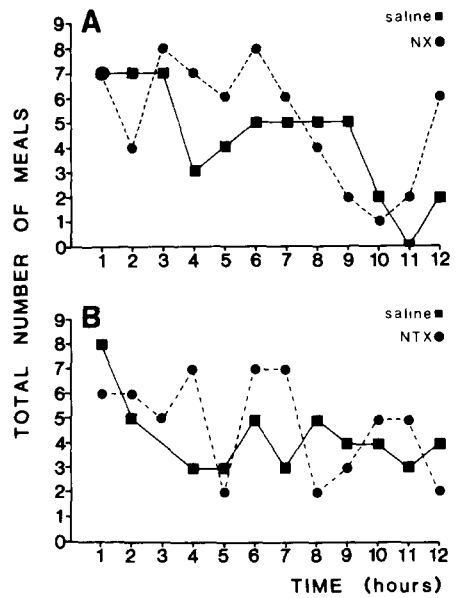

FIG 3 Meal frequency after naloxone (A) or naltrexone (B) administration Each point represents total number of meals eaten by 6 rats within each hour of the dark phase

hours subsequent to administration, effectively abolishing the dusk eating peak. Over this period mean intake was less than 50% of control values, and was significantly reduced over the first hour, $t(5)=3\ 570$, $p<0.05$. Recovery of intake was apparent over hours 3 and 4, so that by the end of hour 4 the cumulative intake of NX rats was no longer significantly different from control levels (Fig 2A). Whether in response to any remaining (albeit small) energy deficit, or to an endogenous circadian entrainment of meal taking [36], NX-treated rats continued to eat at high levels over the following four hours Over this period mean hourly intake paralleled that occurring under control conditions (i e , during mid-phase eating). Finally, after two hours of minimal intake, levels rose again over hours 11 and 12 to coincide with the dawn eating peak Thus, the normal features of nocturnal eating had been restored in the NX-treated rats, despite a slight desynchronisation of the normal eating pattern [which accounts for the marked difference between saline and NX intake levels during hour 9, $t(5)=3\ 830$, $p<0.05$]

The effects of NTX (Fig 1B) were similar to those occurring after NX administration. The dusk eating peak was again abolished, with NTX producing a 57% reduction of intake over the 1st hour, $t(5)=4\ 024$, $p<0.02$ A similar reduction was obtained over the 2nd hour. Over the next 2 hours NTX-treated rats showed a marked recovery of intake, so that at the end of the 4th hour cumulative intake for the NTX-treated rats matched control levels (Fig 2B). Over the 5th hour NTX intake fell to control levels and from this point NTX rats displayed a pattern of intake similar to that of controls The initial anorexia and subsequent restorative feeding again gave rise to a slight desynchronisation of intake patterning (Fig. 1B) Thus dawn eating was found to be delayed by 1 hr in NTX-treated rats.

2 Meal Frequency

When meal frequency is plotted (Fig. 3A and B) a similar pattern is found to that observed for hourly intake During the course of the dark period saline-treated Group 1 rats consumed an average of 8 33 (±0 42) meals, saline-treated Group 2 rats ate 8.5 (±0 67) meals. When meals taken over the following 12 hr of the light period are included, 24 hr averages of 11.5 (±0 88) and 10.67 (±0 71) are obtained for saline treatments in groups 1 and 2, respectively. This conforms with the early finding [28] that rats will satisfy their nutritional requirements by consuming 8 to 13 separate meals over 24 hr

Whereas NX reduced food intake significantly during the first hour of testing, there was no effect upon the number of meals taken during this period (Fig. 3A) Clearly, therefore this intake reduction was not due to a failure of NX-treated rats to commence eating However, during the 2nd hour NX-treated rats initiated fewer meals than under control conditions (see discussion of intermeal interval data in section 3, below) Beyond hour 2 the number of meals engaged in by NX rats rose above control levels and subsequently followed a pattern similar to that described for hourly intake. At the end of the dark period the total number of meals eaten by NX-treated rats (9.67±1.36) equalled those occurring under control conditions Total meals over 24 hr were similarly comparable after NX (11.17±1.40) and saline (11.5±0.88) treatments.

Generally, the plot of meal frequency of NTX-treated rats corresponds to the pattern of hourly intake and exhibits similar adjustments to those induced by NX In particular, while NTX produced marked a reduction of intake over the first hour, the number of meals was not appreciably altered (Fig. 3B) As for Group 1, the total number of meals occurring in the 12 hr after NTX administration (mean=8.5±1.18) was equivalent to the saline total Over 24 hr 10.67±0 71 and 11.00±1 44 meals were consumed after saline and NTX treatments respectively

3 Drug Effects on Individual Meals

Tables 1 and 2 show the effects of NX and NTX on specific parameters related to the first three meals occurring in the test period Since each animal took only a single meal (and rarely two) within any hour, these data thus encompass the period during which the drugs exerted their major anorexic action (hours 1 and 2), and also the subsequent period when recovery from the effects of the drugs was occurring.

Naloxone exerted particularly strong effects upon both the length and size of the first meal. Duration was reduced by approximately 60%, $t(5)=5\ 491$, $p<0.01$, and mean intake by 67%, $t(5)=11.135$, $p<0.001$. Naloxone had no effect upon eating rate Following NX administration there was a 44% increase in the length of the first postmeal interval. The satiety ratio (meal size/postmeal interval) was significantly reduced by NX, $t(5)=3.197$, $p<0\ 05$, indicating that the power of a given quantity of food to inhibit further eating was greater after NX administration than under control conditions.

Considering the normal half-life of NX *in vivo* [37] and the long intermeal interval noted above (mean=78 min), the drug might not be expected to produce very marked effects upon 2nd meal parameters However, meal size was again reduced by some 60%, $t(5)=4.552$, $p<0\ 01$. Again, NX had no effect upon eating rate. Postmeal interval was slightly extended and the satiety ratio was again lower in NX-treated rats, but these differences were not significant

TABLE 1

NALOXONE-INDUCED ALTERATIONS TO MEAL PARAMETERS OF FREE-FEEDING RATS DURING DARK PHASE (MEALS 1–3)

Meal Number	Treatment	Meal Duration (min)	Meal Size (g)	Eating Rate (g/min)	Postmeal Interval (hr)	Satiety Ratio
1	saline	6 12 ± 0 87	1 62 ± 0 08	0 34 ± 0 03	0 90 ± 0 12	1 92 ± 0 26
	naloxone	2 39 ± 0 68†	0 54 ± 0 08‡	0 30 ± 0 03	1 30 ± 0 39	0 60 ± 0 27*
2	saline	7 69 ± 2 71	1 71 ± 0 20	0 33 ± 0 04	0 74 ± 0 14	2 62 ± 0 52
	naloxone	5 28 ± 1 66	0 68 ± 0 06†	0 25 ± 0 03	0 96 ± 0 18	1 18 ± 0 38
3	saline	7 40 ± 3 74	1 35 ± 0 37	0 33 ± 0 02	2 45 ± 0 91	1 07 ± 0 20
	naloxone	6 74 ± 1 94	0 84 ± 0 15	0 32 ± 0 04	0 71 ± 0 16	1 43 ± 0 43

All values are the mean (±SEM) of six rats

*$p<0$ 05, †$p<0$ 01, ‡$p<0$ 001 significantly different from control values using t-test for repeated measures (two-tailed)

TABLE 2

NALTREXONE-INDUCED ALTERATIONS TO MEAL PARAMETERS OF FREE-FEEDING RATS DURING DARK PHASE (MEALS 1–3)

Meal Number	Treatment	Meal Duration (min)	Meal Size (g)	Eating Rate (g/min)	Postmeal Interval (hr)	Satiety Ratio
1	saline	8 77 ± 3 06	0 92 ± 0 17	0 34 ± 0 03	0 60 ± 0 13	1 70 ± 0 39
	naltrexone	4 93 ± 1 43	0 71 ± 0 15	0 29 ± 0 04	1 23 ± 0 24*	0 55 ± 0 09
2	saline	15 36 ± 4 79	2 05 ± 0 31	0 34 ± 0 05	1 45 ± 0 23	1 47 ± 0 25
	naltrexone	7 19 ± 3 34	1 16 ± 0 31	0 34 ± 0 06	0 95 ± 0 19†	1 12 ± 0 13
3	saline	9 42 ± 4 96	1 37 ± 0 39	0 32 ± 0 03	1 74 ± 0 36	0 75 ± 0 18
	naltrexone	12 33 ± 7 27	1 37 ± 0 40	0 28 ± 0 05	0 87 ± 0 19	1 72 ± 0 65

All values are the mean (±SEM) of six rats

*$p<0$ 05, †$p<0$ 01 significantly different from control values using t-test for repeated measures (two-tailed)

Consistent with the fact that the third meal was predominantly consumed when the main intake-reducing effect of NX had abated, third meal size was not significantly affected by the drug Again, neither meal duration nor eating rate were affected Note also that the postmeal interval was, for the first time, shorter than the control interval. Consequently, meal 3 satiety ratio was marginally higher than the control value As a larger value for this ratio suggests less inhibition of feeding per unit of food ingested, this measure is in agreement with the observed increase in meal frequency exhibited by NX rats from the third hour of testing.

Naltrexone reduced first meal duration by some 44%, although the effect was not significant Alteration to first meal size was more modest, with NTX bringing about only a 23% reduction. Eating rate was unaffected by NTX. In contrast, NTX produced a two-fold increase in the length of the first postmeal interval, $t(5)=2$ 957, $p<0$ 05 Associated with this action to delay subsequent eating was a reduction of the satiety ratio. Although this effect was clearly apparent in 5 out of 6 rats, the difference between the means following control and NTX treatments just failed to reach significance, $t(5)=2$ 507, $p>0$ 05 In addition to delaying subsequent eating, NTX also reduced second meal duration and size by 53% and 43%, respectively, although these effects were not significant Eating rate was again unaffected. Consistent with the data in Fig. 1B, these effects seem to mark the termination of NTX's anorexic action

GENERAL DISCUSSION

Many aspects of the data from these experiments are in agreement with previous observations, especially those from the only previous study of opioid antagonist effects on meal patterns [24]. The generality of those earlier findings has been extended by the demonstration that these effects on meal patterning (and particularly the marked short-term anorexia) may be obtained in freely-feeding rats within their home environment Of particular importance is the reduction of meal duration, indicative of an early termination of eating, which follows NX treatment A tendency for meal duration to be reduced by NTX is also suggested by the data, although the effect failed to achieve significance Observational studies have shown an early cessation of eating in NX and NTX-treated rats to be accompanied by the behavioural sequence typical of post-prandial satiety [15,16]. In arguing that opioid antagonists reduce intake through a specific ac-

tion on the processes involved in meal termination, it is important to rule out potential effects of these drugs on other aspects of feeding behaviour So far there has been little indication that NX or NTX might interfere with eating initiation [16]. The present data also fail to provide evidence of such an effect. Meal frequency was not reliably altered by either drug over the period when maximum intake reduction was evident. In particular, the number of meals occurring during the first hour of testing was similar under both drug and saline conditions. A similar lack of effect on meal frequency after NX administration has also been reported in lean and obese Zucker rats [24]. Thus, NX and NTX appear to influence food intake only after eating has commenced. Indeed, tracking the development of satiation using a runway paradigm [17,18] revealed that NX and NTX did not reduce motivational measures or block food consumption during early stages of testing Rather, these drugs brought about a prompt cessation of intake only after some food had been eaten.

While not preventing meal initiation following food deprivation or a period of naturally occurring abstinence (e g , at the end of the light phase), it is possible that the opioid antagonists may produce some other, less specific effect on eating that could reduce meal size In these experiments, neither NX nor NTX were found to influence eating rate This lack of effect is in marked contrast to the effects of other anorexic drugs For example, fenfluramine reduces meal size and causes early meal termination, but also reduces eating rate [2,6], whilst amphetamine increases intra-meal eating rate [4]. The absence of any alteration to either eating rate or meal frequency following NX treatment but a marked reduction in meal size and length appears to rule out the possibility of non-specific effects of the drug bringing meals to a premature closure

One of the major advantages of the continuous monitoring technique employed in these experiments is that, in addition to data on intrameal parameters, analysis of the temporal relationships of all meals is permitted. Thus, if NX and NTX do influence satiation some alteration to the relationships between intra- and intermeal variables may be expected. It has been proposed that a positive correlation exists between the size of a meal and the time elapsing before the onset of the next meal [21, 22, 35] As satiety may be regarded as a state of inhibition over further eating, in terms of the above relationship, larger meals will normally appear to be more satiating in that they lead to a greater inhibition of subsequent feeding (i e , are followed by a longer postmeal interval)

While NTX produced a significant suppression of intake over the first hour of testing, a reliable reduction of meal size was not obtained However, both the first and second postmeal intervals were significantly extended after NTX injection This effect implies that a quantity of food has a greater capacity to satiate in NTX-treated rats than would a similar amount under control conditions Naloxone failed to produce a reliable extension of postmeal intervals and the small effect that was apparent was limited to the period after the first meal This failure (in the light of the greater effectiveness of NX with respect to meal size and duration) may be due to the shorter half-life of NX, compared to NTX. a tendency for some animals to engage in early rebound feeding could disguise an action of the drug to delay subsequent feeding.

An alternative form of analysis, which takes into account the fact that intermeal intervals may be determined by factors other than meal size, is the satiety ratio (the ratio of meal size to intermeal interval; [27]) Any action of a drug to enhance satiety and thus to increase the satiating capacity of food, should therefore be reflected in an alteration to this ratio Indeed, NX significantly reduced the satiety ratio obtained for the first meal of the test period Thus, compared to control, NX acted to increase the inhibition of feeding per unit of food ingested

The direction of the respective changes to postmeal interval and satiety ratio, together with previous findings, suggests that the narcotic antagonists may both advance meal termination and also extend the inhibition of eating that naturally follows meal taking. These changes would represent effects upon the process of satiation and the state of satiety [1] and such effects are in keeping with recent results on NX suppression of sucrose intake in rats which indicate that NX increases the satiating effect of orosensory and/or postingestive food stimuli [38]

The present results may be usefully compared with the alterations to meal parameters induced, under similar conditions, by central norepinephrine (NE) administration. Evidence suggests that endogenous NE may function in the maintenance of feeding behaviour through the *inhibition* of satiety [20,29] It is interesting, therefore, that injection of NE into the hypothalamic paraventricular nucleus produces effects opposite to those produced by NX/NTX in our experiments, NE increases food intake primarily through a *lengthening* of meal duration, meal frequency being unaffected [34]. These findings suggest that endogenous opioids may exert a similar influence on feeding behaviour to that proposed for NE. Thus, both sets of agents may be related components of a system controlling the onset and development of satiation.

In sum, the data reported here provide support for the hypothesis that opioid antagonists reduce food intake through an enhancement of satiety Although the present data were obtained from single experiments using small numbers of subjects, the fact that NX (and less reliably NTX) produce these effects in free-feeding animals supports the involvement of endogenous opioids in the mechanisms that normally regulate eating behaviour. Possibly, opioid peptides may act to maintain eating by retarding the development of satiation [9]

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