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Effect of Naloxone and Naltrexone on the Development of Satiation Measured in the Runway: Comparisons With d-Amphetamine and d-Fenfluramine

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KIRKHAM, T. C. AND J. E. BLUNDELL. *Effect of naloxone and naltrexone on the development of satiation measured in the runway: Comparisons with d-amphetamine and d-fenfluramine.* PHARMACOL BIOCHEM BEHAV **25**(1) 123–128, 1986.—A straight runway was used to monitor changes in measures of food motivation and food consumption in order to track and to characterise the development of satiation following administration of equianorectic doses of naloxone (5.0 $mgkg^{-1}$), naltrexone (2.5 $mgkg^{-1}$), dexfenfluramine (1.5 $mgkg^{-1}$) and d-amphetamine (1.0 $mgkg^{-1}$). Naloxone and naltrexone did not reduce motivational measures or block food consumption during the early trials. These drugs brought about a prompt cessation of intake only after some food had been consumed. Dexfenfluramine displayed an early effect on motivation and hastened the onset of satiation. The anorexic activity of d-amphetamine was virtually abolished. These results indicate that the runway is a useful device for analysing the effects of drugs on eating motivation. This study has further characterised the anorexic actions of naloxone and naltrexone; the profiles of these agents can be distinguished from both dexfenfluramine and d-amphetamine. The suppressive action on food intake exerted by these particular opioid antagonists appears to arise from an intensification of the feedback from food ingestion. The mechanisms through which this effect is achieved are not known.

Opioid antagonists Naloxone Naltrexone Fenfluramine Amphetamine Anorexia Feeding Satiation Runway

ENDOGENOUS opioid peptides have been implicated in the physiological processes that are responsible for the regulation of ingestive behaviours. Administration of opioid receptor agonists or antagonists produce, respectively, reliable elevation or attenuation of food intake. These effects have been replicated in a number of species (including man) and under a variety of experimental conditions (for reviews see: [8, 20, 22, 23]).

Considering the nature of opioid antagonist-induced anorexia, there is good evidence that these agents do not reduce intake through non-specific effects such as the production of taste aversion, motor debilitation or sedation (e.g., [5, 13, 16, 17]). Rather, the antagonists appear to produce their intake-suppressant effects through some action on normal satiation processes [7,15]. Indeed, detailed behavioural analyses reveal that naloxone (NX) and naltrexone (NTX) act to reduce the duration of feeding episodes by promoting an early termination of eating [15,16]. Moreover this action of the antagonists is associated with the occurrence of a post-prandial behaviour sequence [15,16] that is characteristic of the development of satiation [3, 26, 30].

In the present study the possibility that NX and NTX reduce food intake by advancing the onset of satiety is further investigated. We report the consequences of antagonist administration in rats performing a highly trained, food-rewarded behaviour, but given sufficient food to allow satiation to occur under control conditions. Rats were trained to negotiate a simple runway for food. This method allows the detailed observation of the anorexic effects of NX and NTX over successive trials, in terms of both motivation to eat (level of runway performance) and quantity of food consumed [27,28]. Moreover, by allowing access to food even in the absence of the instrumental response, the development of satiation may be accurately monitored under each condition. Additionally, the effects of NX and NTX were compared to those of the anorexic agents d-amphetamine (AMPH) and d-fenfluramine (FF). Since these latter drugs are believed to reduce food intake via actions on aminergic systems [11], their effects on food motivated behaviour may

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be expected to differ qualitatively from those of the opioid antagonists. Such distinctions are important in determining the specificity of action of NX and NTX.

METHOD

Animals

Ten male Lister-hooded rats initially weighing 368–372 g were selected for training. All animals were individually housed and maintained on a reversed 12:12 hr light-dark cycle (lights-off at 09.00 hr). Once habituated to housing conditions, animals were given only restricted access to food. At 16.00 hr each day animals were weighed and given sufficient chow to maintain them at 85% of normal body weight. This regime was maintained throughout the course of training and testing.

Runway Apparatus

A wooden runway was constructed which consisted of an alley 2.4 m long, separating a start box and a goal box each measuring 35 by 16 cm. The alley (internal width and height: 16 cm) and start box were painted matt black, while the goal box was painted white. Clear perspex roofed the entire apparatus, allowing the animals to be clearly seen while minimising extraneous stimuli. Access to the runway from the start box was controlled by a hand-operated wooden guillotine gate. Set into the walls of the alley, 20 cm from the gate and 5 cm from the goal box entrance, were two sets of infrared photocells. These, in conjunction with an electronic timer, allowed accurate measurement of running times. Two hand-held stop watches were used to time exit latency (i.e., time from the gate being lifted until rat's whole body was in the alley) and latency to eat on reaching the goal box. A video-camera and monitor allowed the experimenter to observe activity within the goal box. Food (45 mg Noyes pellets), contained in a glass dish, was placed within the goal box, 12 cm beyond the second photocell.

Training

Once 85% body weight had been attained, animals were habituated to the runway. Rats were individually given 10 min daily access to all components of the runway (including food). After 5 days habituation, training proper began using a method previously described by Thurlby, Grimm and Samanin [27]. Over 10 consecutive days rats were given 30 individual trials (3 trials per day with 5 min separating each trial). On each trial the rat was placed in the start box with the gate being opened after 10 sec. Once the animal had entered the goal box, it was allowed 30 sec to eat. On each of the last 3 days of training, rats were sham injected 20 min before the first trial. After this training period, 6 rats were selected whose starting and running speeds were both high and consistent.

Drugs

Naloxone HCl (Endo), naltrexone HCl (Endo), d-amphetamine (Sigma) and d-fenfluramine (Servier) were dissolved in 0.9% saline. The following doses were used: NX=5.0 $mgkg^{-1}$; NTX=2.5 $mgkg^{-1}$; AMPH=1.0 $mgkg^{-1}$; FF=1.5 $mgkg^{-1}$. All drugs were administered intraperitoneally at a volume of 1 ml kg^{-1}, 20 min before testing. These equianorectic doses were chosen on the basis of previous work showing that each produces an approximate 50% reduction of food intake in a 1 hr nocturnal test (6 hr food deprived rats).

Test Procedure

Following injection of vehicle or drug, each animal was given 15 consecutive trials in the runway. Each rat was first placed in the start box for 30 sec before the gate was opened and running allowed. Upon reaching the goal box rats were given 2 min access to food before being removed to the start box. Thirty seconds separated each trial. Animals which failed to leave the start box 30 sec after the gate was opened were placed directly in the goal box and allowed to feed for 2 min. Individual sessions lasted approximately 45 min. Each animal received all 5 treatments according to a counterbalanced design. At least 72 hr separated successive treatments. On non-experimental days training was resumed in the manner described above. All testing occurred under low-level red light, each animal being tested at the same time on each test day.

Data Collection and Statistical Analysis

Starting and running times, latency to eat on reaching the goal box and weight of food eaten were recorded for each trial. In addition to the individual runway performance indices an overall latency to eat (i.e., time from access to runway becoming available to onset of eating) was computed. Cumulative food intake over the course of the 15 trials was also calculated. In order to normalize data, starting and eating latencies were reciprocated to provide starting speed and speed to eat (1/latency, sec^{-1}). Running times are expressed as velocities ($msec^{-1}$). For trials on which rats failed to leave the start box, run or eat, minimum values of 0.01 sec^{-1} for starting speed and speed to eat and 0.01 $msec^{-1}$ for running speed were assigned. Data were initially analysed using analysis of variance (one-way, repeated measures). Subsequent comparisons between treatments were made using Newman-Keuls test for multiple comparisons.

RESULTS

Starting Speed, Running Speed, Speed to Eat and Food Intake

Data for each of these parameters were consolidated into five blocks, each representing the average response of 6 rats within successive groups of 3 trials. These consolidated data are summarised in the graphs in Fig. 1. Analysis of variance revealed a significant main effect of treatment on starting speed over blocks 3, $F(4,20)=3.715$, $p<0.05$ and 5, $F(4,20)=2.965$, $p<0.05$. Significant effects of drug treatment on running speed occurred only within block 3, $F(4,20)=3.019$, $p<0.05$, while speed to eat was only markedly affected in the final block, $F(4,20)=2.970$, $p<0.05$. In contrast, a significant effect on food intake was apparent across the whole session (block 1, $F(4,20)=6.939$, $p<0.01$; block 2, $F(4,20)=5.267$, $p<0.01$; block 3, $F(4,20)=3.675$, $p<0.025$; block 4, $F(4,20)=3.030$, $p<0.05$; block 5, $F(4,20)=5.322$, $p<0.01$).

Runway performance under control conditions. Starting speed gradually declined across the session while running speed remained essentially stable, with only a marginal reduction between the first (0.33 $msec^{-1}$) and final blocks (0.27

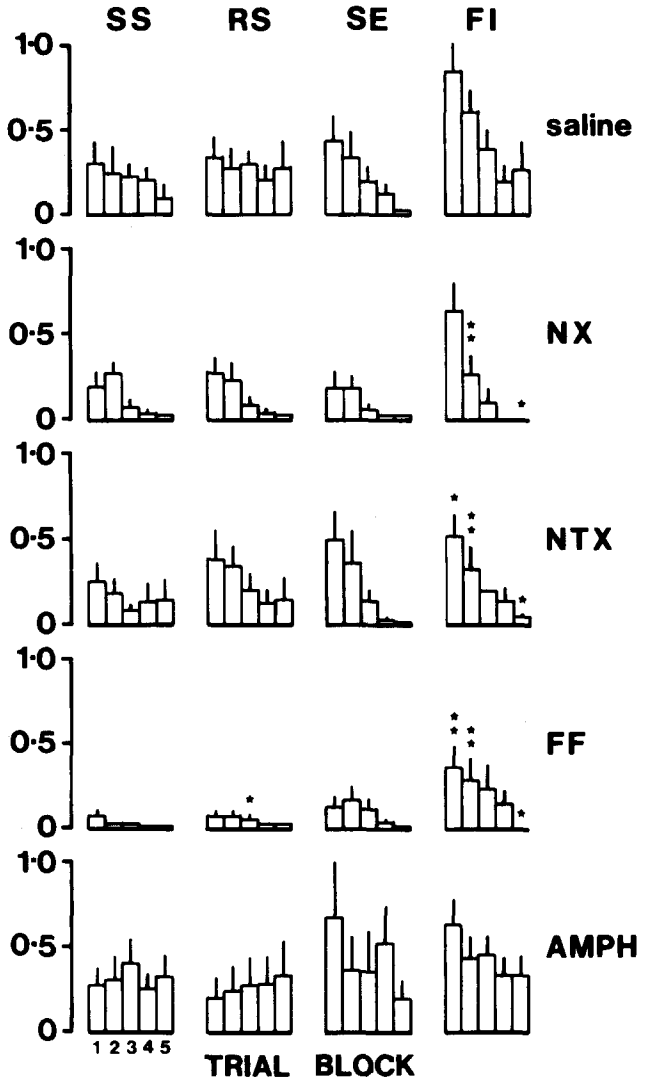

FIG. 1. Effects on starting speed (SS, sec^{-1}), running speed (RS, $msec^{-1}$), speed to eat (SE, sec^{-1}) and food intake (FI, g) of 5 $mgkg^{-1}$ naloxone (NX), 2.5 $mgkg^{-1}$ naltrexone (NTX), 1.5 $mgkg^{-1}$ d-fenfluramine (FF) and 1 $mgkg^{-1}$ d-amphetamine (AMPH). Each bar represents data from six rats (mean±SEM) consolidated into 5 blocks of 3 trials. ★$p<0.05$, ★★$p<0.01$: difference from saline values (Newman-Keuls test).

$msec^{-1}$). Speed to eat (SE), the time elapsed from entering the goal box to initiation of eating, was much more markedly altered: there was an almost linear decline of this measure from a mean value of 0.43 sec^{-1} (i.e., a latency of 2.33 sec) in block 1 to only 0.02 sec^{-1} over the final block. Food intake also showed a steady decline, with mean intake over block 5 falling to approximately 30% of that recorded over block 1.

Effects of drug treatments. After NX administration runway performance measures and levels of food intake were initially very similar to those found after saline injection. However, later stages of testing were characterised by a far more rapid decline of runway performance; no NX-treated rat exited the start box after trial 10. In particular, there was a marked downward trend in weight of food consumed after block 1. Over block 2 NX produced intake levels that were significantly lower than saline values ($p<0.01$). By the third block intake was further reduced (mean=0.09 g), although no longer significantly less than control intake. No eating occurred beyond this point (trial 9).

The effects of NTX on runway behaviour were somewhat milder than those described for NX. However, significant alterations to food intake were produced by this drug at an early stage. Over block 1 mean intake was significantly less than the saline mean ($p<0.05$) and remained lower than control levels throughout. Over the final block mean intake was only 0.04 g which amounts to only a single pellet. Eating was thus effectively abolished during this latter stage of testing.

In contrast to the opioid antagonist drugs, FF was found to have very marked effects on all aspects of runway behaviour from the earliest stages of testing. Within block 1, for instance, starting speed was reduced to less than a quarter of the mean speed observed after saline. Over the next 2 blocks starting speed fell to only 0.02 sec^{-1}, indicating a tendency of FF-treated rats not to run, even at this early stage. Indeed, food intake was markedly suppressed from trial 1, although it subsequently declined more gradually than under the previous conditions. Thus, mean intake for blocks 3 and 4, although low, were not significantly less than for saline. However, after this stage eating was discontinued.

The behavioural changes induced by AMPH provide a clear contrast to the previously noted findings. Rather than following the more typical across-session decline, starting and running speeds and speed to eat generally remained stable. Thus, AMPH-treated rats approached food and initiated eating significantly faster than rats in any other condition during the final block ($p<0.05$). The pattern of food intake after AMPH was also unlike that occurring in other conditions: at no time did AMPH produce a significant reduction. The level of consumption remained relatively stable and by block 5 AMPH levels were higher than those induced by NX ($p<0.01$), NTX ($p<0.01$) and FF ($p<0.01$).

Overall Latency to Eat and Cumulative Intake

Figure 2 demonstrates the close relationship between overall eating latency (LE) and food intake on each trial, with shorter values of LE being associated with the higher intake levels (note that a maximum value of 100 sec was assigned for trials on which animals failed to initiate eating). This inverse relationship exists for each treatment and, with the exception of the AMPH condition, a significant negative correlation was obtained between LE and food intake. It may be concluded that LE represents a useful indicator of motivational strength within the current paradigm. The combination of this measure with that of cumulative intake (Fig. 2) illustrates more clearly the development of satiety under control conditions and the adjustments to this process induced by the anorectic drugs.

Latency to eat and cumulative intake under control conditions. Under control conditions LE was initially stable, but from trial 4 (T4) increased in a progressive fashion, reaching a maximum on the final trial. Cumulative intake increased in a regular manner, albeit with a tendency for increments to be smaller on later trials. By T7 saline-treated rats had consumed some 74% of their total intake. Subsequently, the cumulative intake curve flattened, with successive increments being less than 5% of total intake (compared with over 13% on trials 1 and 2). Total intake in this condition (6.41 g) was of the same order as that found in home-cage intake tests

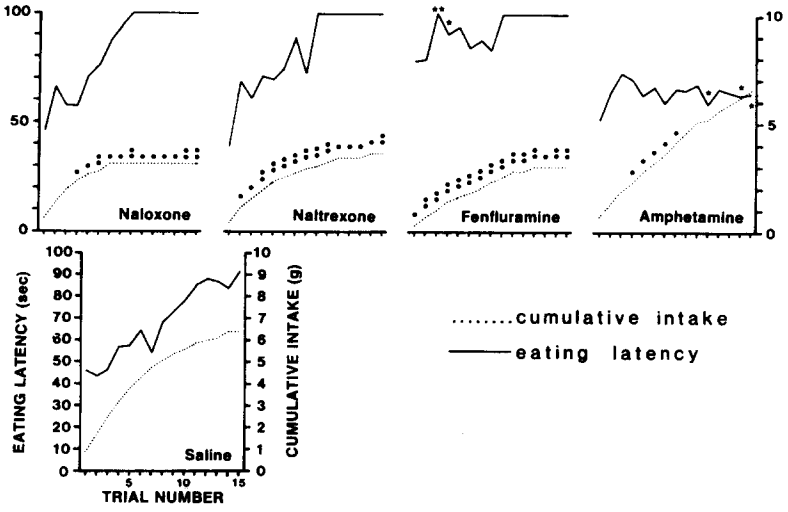

FIG. 2. Overall latency to eat (——) and cumulative food intake (·····) over 15 runway trials after saline, naloxone, naltrexone, fenfluramine and amphetamine administration. Values represent means of six rats. ★$p<0.05$, ★★$p<0.01$ (latency); ●$p<0.05$, ●●$p<0.01$ (intake): significantly different from saline values (Newman-Keuls test). N.B. A latency value of 100 sec was assigned to rats failing to eat on any trial.

performed after mild food deprivation (unpublished data). This suggests that the runway enabled the successful monitoring of the development of satiation in non-drugged rats: indeed the intake data shown in Fig. 2 form a classical satiation curve.

Effects of drug treatments. In NX-treated rats, LE was initially identical to the control value. Subsequently, however, the rate of increase of LE was accelerated, with maximum values being recorded at T9. Cumulative intake increased in a regular manner over early trials, although successive increments were smaller than those occurring in the saline condition. By T4 intake was significantly less than control intake ($p<0.05$) and remained so until the end of the session: most animals ceased eating after T5; intake recorded on T6–T9 being due to only two rats.

Initial LE for NTX-treated rats was again similar to the saline value, but from T2 was markedly increased, reaching a maximum on T9. As after NX, cumulative intake increased in a regular fashion on the earliest trials, but from T6 onwards successive increments were reduced. Generally, eating persisted for longer after NTX than NX. However, by T9 only 50% of rats were consuming any food and from T12 eating was effectively abolished, with a single rat eating on T12 and two rats only on T14.

The effects of FF on LE and cumulative intake were clearly distinguished from those of NX or NTX. Even on T1 LE was considerably higher (78.44 sec) than control values, corresponding with values obtained at T10 of the saline condition and T6 of the NX and NTX conditions. Cumulative intake increased particularly slowly after FF administration; successive increments were small from the earliest stages. Food intake at T1 was significantly lower than control levels and was also the lowest of all recorded intakes at this stage of testing ($p<0.05$).

Latency to eat after AMPH administration exhibited a remarkable constancy over the course of testing, such that by T11 AMPH-treated rats were initiating eating significantly faster than controls ($p<0.05$). Cumulative intake after AMPH was similarly stable. Thus AMPH failed to exert its usual anorexic action. This lack of suppressive effect was not an artifact caused by a few animals failing to respond to the drug. Rather, unlike the other drug treatments, the majority of rats ate throughout the test. On every trial at least 4 out of the 6 rats initiated eating.

DISCUSSION

The method employed in this study proved an effective strategy for monitoring the development of satiation in non-drugged rats. This process was represented by a regular decline in the quantity of food consumed on successive trials and is consistent with previous observations (e.g., [25, 27, 28]). Moreover, this technique was able not only to distinguish between the behaviour of drugged or non-drugged rats, but also to clearly discriminate between the actions of individual drugs. Although NX, NTX and FF each produced a similar degree of intake suppression (51, 44 and 54%, respectively), this reduction was obtained through distinct alterations to behaviour.

As mentioned earlier, it has been argued that the actions of NX and NTX upon eating parameters (reduced meal size and early termination of eating) indicate an action of these drugs to advance satiety [7, 15, 24]. The present paradigm enabled this hypothesis to be more directly investigated. Satiation refers to the termination of food consumption resulting from the act of food ingestion itself [1]. Thus, according to the present hypothesis, NX and NTX should not reduce the motivation to eat before feeding has been initiated, but may accentuate the motivational diminution that accompanies the development of satiation. Initial runway performance should therefore remain unaffected by these agents, and early consumption levels ought to remain close to control levels.

The present data are thus consistent with an action of NX

and NTX to advance the onset of satiety. Clearly, neither NX nor NTX produced any significant immediate decrement in runway performance. There was no evidence of any motivational deficit that might have reduced the tendency to initiate the primary instrumental or consummatory response. Since, as in observational analysis [15,16] these drugs exhibited no tendency to impede the onset of eating, NX and NTX appear to act to reduce motivation to eat subsequent to, rather than prior to the commencement of feeding. Only at the point when, in saline-treated rats, intake starts to decline (as the process of satiation begins) do the effects of NX and NTX become apparent: the recession of running and eating was accelerated, with motivation to eat falling to a minimum some 40% earlier than under control conditions. Certainly, these findings confirm that we are dealing with some specific action on feeding behaviour: there was no evidence that NX or NTX had any general debilitating effects. The ability to run for food was unimpaired by either drug. Similarly, the specific motor acts involved in the act of eating were unaffected. The anorexia produced by NX and NTX would therefore appear to constitute a natural, rather than unnatural, inhibition of intake.

The results described here also provide a clear distinction between the effects of NX and NTX upon food-oriented behaviour and those resulting from the administration of AMPH or FF. Fenfluramine, in contrast to NX and NTX, produced a marked depression of runway performance and feeding on trial 1, equivalent to control levels recorded from T10 onwards. Identical alterations to runway behaviour following FF treatment have been reported by Thurlby, Grimm and Samanin [27]. These authors suggested that FF induces a behavioural state comparable to control rats at the end of testing. Such data are consistent with the suggested action of this drug to induce a degree of satiation similar to that occurring in the latter stages of a normal meal [21]. Further, allowing rats to eat several grammes of food before being tested in the runway has been shown to produce identical behaviour to that observed after FF administration [28].

The effects of AMPH on runway behaviour were also dissimilar to those of NX and NTX. In particular, feeding levels remained stable over the test period: monitoring behaviour in the runway completely eliminated the anorexic action of the drug. In the absence of the expected anorexic effect of AMPH, or even of the normal (control) pattern of satiation, it is inappropriate to equate runway performance with motivation for food in this instance. (Note also that the motivational index of overall latency to eat shows no direct relationship with food intake for this condition.) Indeed, much evidence suggests that AMPH anorexia involves, not an intervention in an endogenous mechanism regulating food intake, but rather a more generalised action of the drug upon other behavioural systems. Amphetamine may, in fact, produce hyperphagia in certain situations [10,14]. Additionally, doses of AMPH that reduce overall food intake may simultaneously stimulate the motor acts involved in feeding [2]. Irrespective of its effects on food intake, common to all these situations is the ability of AMPH to stimulate particular aspects of behaviour [29].

It has been proposed [19] that the probability of different behaviours being emitted when AMPH takes effect is the major determinant of the predominant AMPH-induced behaviour. Thus, when tested in the home cage AMPH is likely to stimulate behaviours (such as rearing, sniffing and locomotion) which naturally precede the initiation of eating, to the detriment of the feeding response. In the runway a combination of reinforcement and strong environmental stimuli determine the probability of occurrence of behaviours: in this case running and eating predominate. In the absence of competing behaviours, both the instrumental and consummatory responses are thus likely to be enhanced by AMPH.

The importance of situational variables to the expression of AMPH anorexia (and the apparent satiety enhancing action of the opioid antagonists) is confirmed by contrasting the present data with those from a simple intake test carried out in the home cage (data not shown). In mildly (6 hr) deprived rats 5 $mgkg^{-1}$ NX, 2.5 $mgkg^{-1}$ NTX, 1.5 $mgkg^{-1}$ FF and 1.0 $mgkg^{-1}$ AMPH were found to exhibit a similar anorectic potency (approximately 50% reduction) in the course of a 30 min test. However, in the animals prepared for runway testing (given only restricted access to food and maintained at 85% of free-feeding body weight) but tested in the home cage, only AMPH retained the ability to significantly reduce food intake (54.5% reduction) over the same period. The intakes of NX-, NTX-, and FF-treated rats were equivalent to control values. Thus, an identical dose of AMPH, administered to identical animals, produced sharply contrasting effects on food intake in two distinctly different environments (runway and home cage).

These latter observations (lack of effect of NX and NTX) are again consistent with the view that the opioid antagonists (and possibly FF) reduce food intake by an action on satiation. The 85% body weight animals were clearly hyperphagic and, under control conditions, were observed to eat throughout the 30 min test period. Thus, NX and NTX fail to attenuate food intake in a situation in which saline-treated rats display no signs of satiation. These observations are also reflected in the reports of other investigators. For example, it has been reported that prolonged food deprivation can reduce the magnitude of the anorexic effect of NX [4]. Similarly, in an analogous situation—that of restricted daily access to food—NX has been found to have no significant effect upon intake [9, 12, 24]. That similarly severely food deprived rats exhibited signs of satiation in the runway may be due to the exaggerated intervals between successive bouts of feeding. Such a reduced rate of intake may allow satiation to develop more effectively than when there is unrestricted access to food, since a low rate of eating has been associated with reduced meal size [6]. Moreover, there is evidence that the rate of eating declines after deprivation-induced weight loss [18].

These results suggest, therefore, that NX and NTX will only exert their effects on feeding in situations in which the normal development of satiation is permitted. The present data therefore provide considerable support for the hypothesis that NX and NTX reduce food intake via a facilitation of the physiological consequences of food ingestion that lead to the termination of eating. This, in turn, supports the implication of endogenous opioid peptides in the mechanisms controlling ingestive behaviour. More specifically, these substances may have a role in the maintenance of eating by exerting some influence on the development of satiation.

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