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Noradrenergic Receptor Interactions in Feeding Elicited by Stimulation of the Para-Ventricular Hypothalamus

ANTHONY TOWELL,[1] RICHARD MUSCAT AND PAUL WILLNER

Psychology Department, City of London Polytechnic, Old Castle Street, London E1 7NT

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TOWELL, A., R. MUSCAT AND P. WILLNER. *Noradrenergic receptor interactions in feeding elicited by stimulation of the para-ventricular hypothalamus.* PHARMACOL BIOCHEM BEHAV 32(1) 133–139, 1989.—Food intake and feeding behaviour were examined after the administration of noradrenaline (NA) or clonidine to the para-ventricular nucleus of the hypothalamus, or after systemic administration of clonidine. In 20-hr deprived animals all treatments dose-dependently reduced pellet consumption; however, at a low dose (2–5 μg) central clonidine increased eating time and bout length. In 4-hr deprived animals all treatments increased sucrose consumption. Clonidine (peripheral and central) increased feeding time but did not alter feeding rate; NA did not alter feeding time, but did increase feeding rate; NA also increased activity and decreased resting. The effects of NA on feeding rate, activity and resting were blocked by propranolol; however, the propranolol-NA combination increased feeding time. Thus, NA and clonidine increased feeding by different mechanisms, but after propranolol pretreatment the effects of NA were similar to those of clonidine. It is concluded that clonidine enhances feeding by inhibiting satiety and that the feeding stimulant effect of NA is mediated by a complex interaction of alpha- and beta-receptors.

Feeding Satiety Eating time Feeding rate Clonidine Noradrenaline Propranolol Para-ventricular hypothalamus Alpha- and beta-receptors Rats

INTRAHYPOTHALAMIC administration of noradrenaline (NA) to rats causes a robust feeding response (3, 6, 10, 11). It has been found using dietary preference paradigms that NA specifically increases the consumption of diets rich in carbohydrate, but not fat or protein (16, 17, 31, 32). Intrahypothalamic NA can also suppress food intake (10). This effect may require larger doses of NA (30) and appears to arise from a different anatomical locus: the most sensitive site for adrenergic suppression of feeding is the perifornical area of the lateral hypothalamus (11), while the area most sensitive to adrenergic facilitation of feeding is the paraventricular nucleus (PVN) in the medial hypothalamus (13,20). As NA release in the medial hypothalamus is elevated following a period of food deprivation (19), it is assumed that adrenergic mechanisms in the PVN are involved in the physiological control of food intake (8,15).

Analysis of meal patterns has consistently shown that NA increases the size of meals without changing their frequency (24,29). These data suggest that the effect of NA is primarily to maintain feeding and delay satiety, rather than to initiate a feeding response. However, in the most detailed meal pattern study to date, NA was also found to increase the rate of eating (29), suggesting that adrenergic feeding might result in part from nonspecific arousal effects. The first of the present experiments addressed these issues by using a microstructural paradigm (33,34) to examine bouts of feeding within a meal, the whole session being brief enough to assume that the contribution of postabsorptive responses would be minimal. It was hypothesised that if NA specifically maintains (but does not initiate) feeding, then NA should increase the length of feeding bouts without altering the length of interbout intervals (gaps).

The alpha-adrenergic receptor agonist clonidine also elicits feeding when administered systemically (4, 18, 27) or directly to the PVN (17, 18, 32). Administration of an alpha receptor antagonist or the catecholamine synthesis inhibitor, α-MpT to the PVN has been shown to block both of these effects (5,32). Similarly, alpha-receptor antagonists have been found to antagonise NA-elicited feeding (5,12), while beta-receptor antagonists appeared to be ineffective (15,17). These data strongly suggest that NA elicits feeding from the PVN via alpha-adrenergic mechanisms. However, in the first of the present experiments, the effects of NA and clonidine on feeding microstructure were found to be somewhat different. As NA, unlike clonidine, stimulates both alpha- and beta-receptors, a difference between NA and clonidine might reflect a contribution of beta-receptors to the action of NA that had previously been overlooked. A second experiment was therefore carried out in which the beta-receptor antagonist propranolol was used to reexamine role of beta-

[1]Present address: Medical Research Council, National Hospital, Queen Square, London WC1N 3BG.

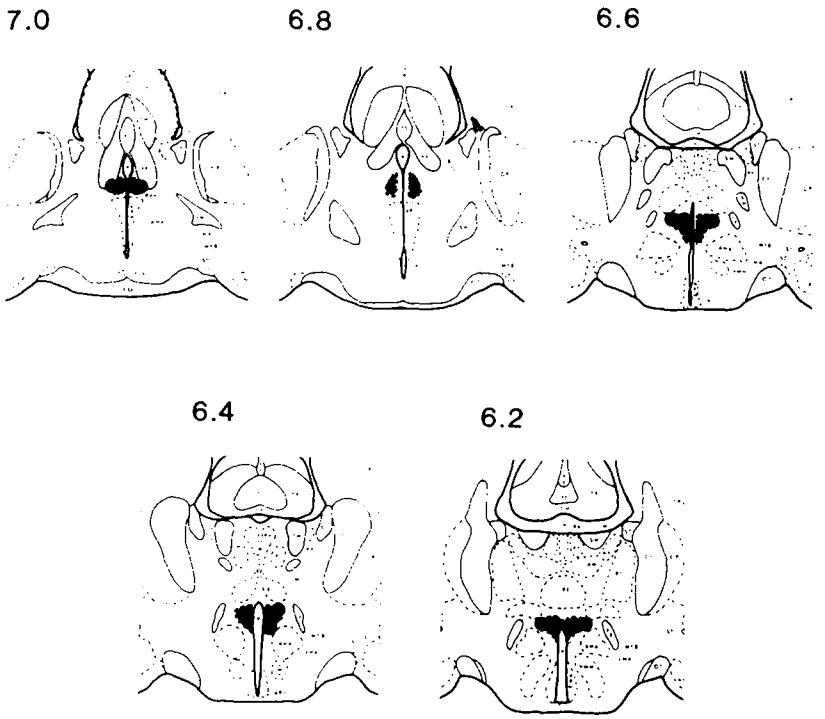

FIG. 1. Serial sections through the rat brain, from the atlas of Pellegrino and Cushman (22). The position of the PVN is shown by shading; black circles show cannula placements.

receptors in the feeding elicited by adrenergic stimulation of the PVN.

METHOD

Subjects

Central drug effects were tested on six adult male Lister hooded rats (NIMR, Mill Hill, England) weighing approximately 320 g at the time of surgery. A second group of animals (n=12) were tested after peripheral administration of clonidine. Animals were housed individually under conditions of controlled temperature and humidity, on a 12-hr light-dark cycle (09.00 hr to 21.00 hr light). Behavioural testing was carried out betweeen 13.00 and 14.00 hr.

Surgery

The animals used for central drug administration were implanted bilaterally under halothane anaesthesia (28) with cannulae aimed at the PVN. The coordinates, chosen according to the atlas of Pellegrino and Cushman (22), were: anterior 6.6 mm, medial −0.5 mm and ventral −1.0 to −1.5 mm. The cannulae were of 26-gauge stainless steel (Arnold and Howell, London); injections through them were made using a microsyringe with a 33-gauge needle (V. A. Howe, London). At the end of the experiment, cannula placements were verified histologically. All cannulae were located within the PVN (Fig. 1). No evidence of gross tissue damage in the vicinity of the cannula tip was apparent on microscopic examination. The functional integrity of the PVN is suggested by the fact that robust feeding responses were elicited even at the very end of the experiment (see below).

Drugs

All drugs were dissolved in sterile physiological (0.9%) saline. Intracranial (IC) injections of l-noradrenaline-d-bitartrate (Sigma, Poole, Dorset) and clonidine hydrochloride (Sigma) were made bilaterally at a volume of 0.44 μl (delivered as two 0.22 μl pulses) immediately prior to testing. Intraperitoneal (IP) injections of dl-propranolol hydrochloride (Sigma) and clonidine were made at a volume of 1 ml/kg. A minimum of two drug-free days was allowed between successive treatments (which is sufficient time for the agents used in this study to be cleared from the body).

Experiment 1

Eight identical operant chambers (Campden Instruments Ltd., London), from which the levers had been removed, were programmed to deliver a 45-mg food pellet whenever the Perspex food tray door was pressed, subject to the constraint that presses spaced less than one second apart were ineffective. Each response on the tray door was logged (to the nearest 0.1 sec) by a Cromemco Z2 microcomputer. Test sessions were 30 min in duration. Measures of eating rate, eating time and other microstructural parameters were derived from log survivor analysis of the frequency distribution of interresponse times (IRTs), as described in more detail elsewhere (33,34). Briefly, the distribution of IRTs is expressed as the logarithm of the number of IRTs greater than any given IRT. This "log survivor function" falls linearly at low IRTs until a point is reached at which the slope suddenly decreases. There is a very high probability that IRTs smaller than this "break-point" come from bouts of continuous feed-

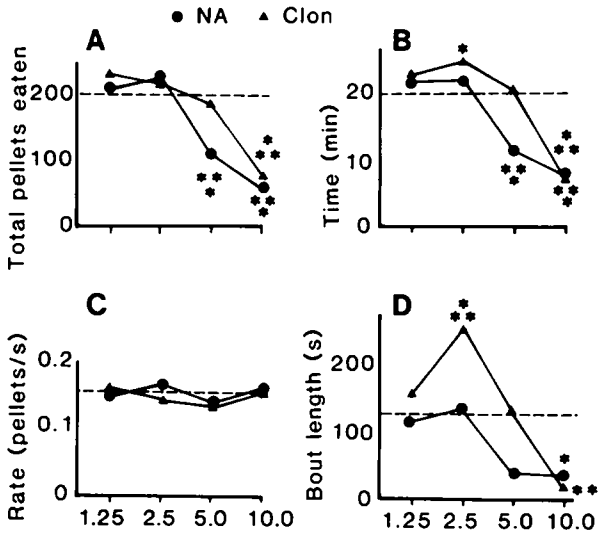

FIG. 2. Microstructural analysis of the effects of PVN administration of NA and clonidine on pellet consumption. Values are means; dashed lines show the means of the two vehicle sessions. Asterisks show significant differences from vehicle: *$p<0.05$; **$p<0.01$; ***$p<0.001$. (A): Total food intake; (B): Eating time; (C): Eating rate; (D): Bout length.

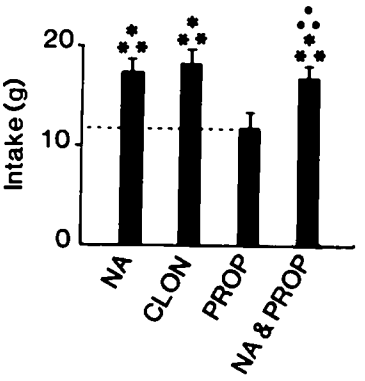

FIG. 3. Drug effects on sucrose consumption: NA—noradrenaline; CLON—clonidine; PROP—propranolol. Values are means (+standard error); dashed lines show the mean of the two vehicle sessions. Asterisks show significant differences ($p<0.001$) from vehicle and dots show significant differences from propranolol.

ing, whilst IRTs greater than the break-point represent intervals between feeding bouts (33).

The animals were maintained on 20 hr food deprivation, with free access to food between 14.00 and 17.00 hr. Prior to surgery, they received extensive training in feeding from the pellet dispensers; following surgery, pharmacological studies were not initiated until they had reattained asymptotic performance. Five doses each of NA and clonidine (0–10 μg IC) were administered to the operated animals in a repeated measures counterbalanced design; the unoperated animals received seven doses of clonidine systemically (0–80 μg/kg IP).

Experiment 2

Following the end of Experiment 1, the animals were given free access to food, and exposed for 48 hr to a sucrose solution (10% w:v) in place of water. Subsequently, animals were tested for their consumption of 10% sucrose solution following 4 hr food and water deprivation. Animals were habituated to these changes over two weeks. Over a 60-min testing period, the animals were observed every 15 sec, and their behaviour recorded in one of four mutually exclusive categories (drinking, activity, grooming and resting), using a BBC B+ microcomputer. The 'resting' category was used when an animal was motionless; usually it would be lying down, but occasionally animals 'rested' while standing.

The operated animals received NA and clonidine at 0 and 2.5 μg IC. In addition, propranolol (5 mg/kg IP) was administered 60 min before the test session, prior to IC injection of NA or vehicle. The six treatments were administered in a counterbalanced order. Effects of systemically administered clonidine (0 and 5 μg/kg IP) were tested in the unoperated animals.

Analysis

Data were subjected to analysis of variance, supplemented where appropriate by tests of simple main effects and planned comparisons. In neither experiment were there any significant differences in the effects of the two central vehicle treatments. The two vehicle sessions were therefore combined for subsequent analysis and presentation. Separate analyses were performed on the two groups of experimental animals.

RESULTS

Experiment 1

In 20 hr food-deprived animals, neither NA nor clonidine, administered to the PVN, significantly increased food intake at any dose [max, $F(1,45)=3.81$, N.S.], and indeed, at higher doses food intake was significantly reduced by both drugs (Fig. 2A). Clonidine also suppressed food intake on systemic administration at doses of 10 μg/kg, $F(1,66)=7.9$, $p<0.001$, or higher (results not shown). However, microstructural analysis revealed that at the 2.5 μg central dose, clonidine did increase eating time, $F(1,45)=5.2$, $p<0.05$, and the length of eating bouts [$F(1,45)=12.1$, $p<0.001$, relative to vehicle; $F(1,45)=8.9$, $p<0.01$, relative to NA]. NA did not have these effects (Fig. 2B,D).

Experiment 2

With a shorter deprivation period and a more palatable diet (sucrose), both NA and clonidine (2.5 μg) produced a reliable and robust increase in consumption when administered to the PVN, $F(1,25)=75.7$ and 95.8, $p<0.001$, respectively. The effect of NA was equally strong after propranolol pretreatment, $F(1,25)=59.1$, $p<0.001$. Propranolol alone had no effect on sucrose consumption (Fig. 3). All animals commenced feeding immediately in every session.

These data suggest that the effects of NA and clonidine were similar, and that propranolol was inactive. However, analysis of drug effects on consumption time and rate shows that in fact clonidine and NA increased consumption by different behavioural mechanisms, and that the effects of NA were significantly modified by propranolol.

Consumption time was estimated in two ways: a) as the frequency of observations of drinking and b) as the time

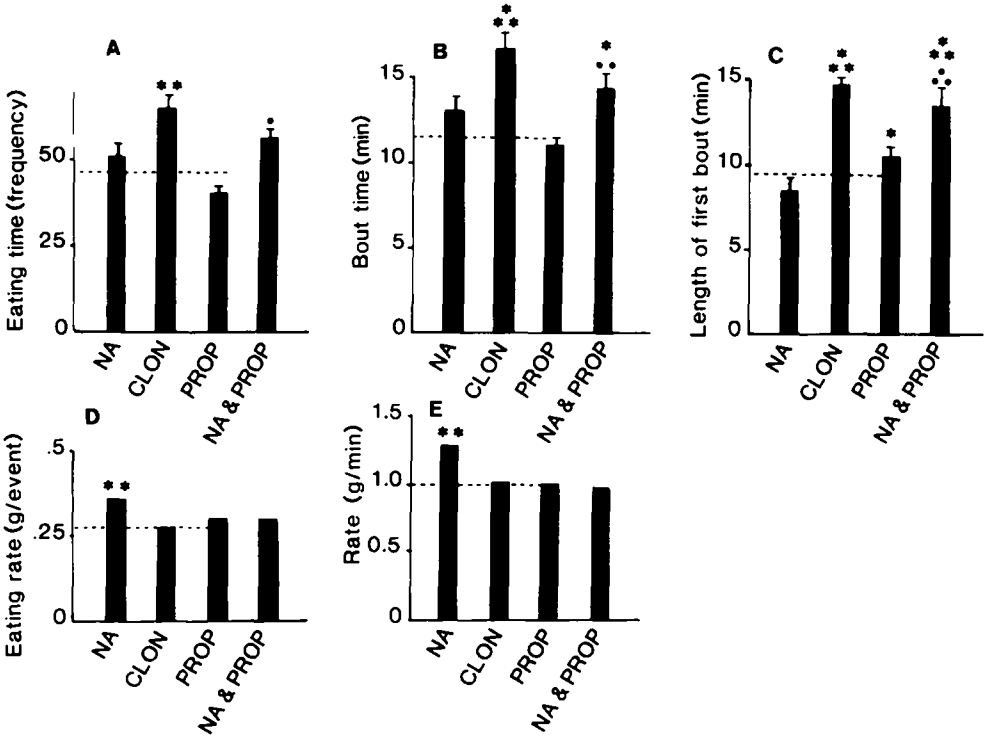

FIG. 4. Drug effects on parameters of sucrose consumption: (A and B): feeding time; (C): length of first bout; (D and E): feeding rate. NA—noradrenaline; CLON—clonidine; PROP—propranolol. Values are means (+standard error); dashed lines show the mean of the two vehicle sessions. Asterisks show significant differences from vehicle and dots show significant differences from propranolol: one symbol, $p<0.05$; two symbols, $p<0.01$; three symbols, $p<0.001$.

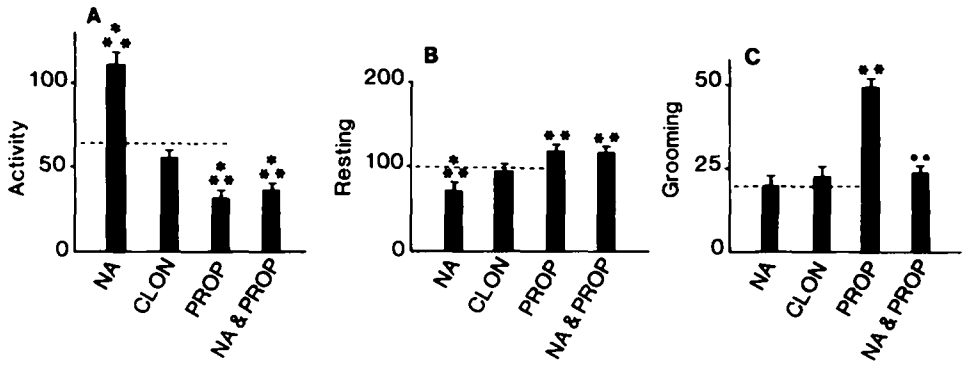

FIG. 5. Drug effects on the frequency of other behaviours: (A): activity; (B): resting; (C): grooming; NA—noradrenaline; CLON—clonidine; PROP—propranolol. Values are means (+standard error); dashed lines show the mean of the two vehicle sessions. Asterisks show significant differences from vehicle and dots show significant differences from propranolol: one symbol, $p<0.05$; two symbols, $p<0.01$; three symbols, $p<0.001$.

occupied by bouts of drinking; a bout was deemed to begin at the start of four consecutive observations (i.e., 1 min) of drinking, and to end at the start of four consecutive observations of other behaviours (Fig. 4A,B). On both of these measures, clonidine significantly increased consumption time, $F(1,100)=7.8$, $p<0.01$, and, $F(1,25)=29.9$, $p<0.001$, respectively, but NA did not [NA vs. CLON: $F(1,25)=12.2$, $p<0.01$]. However, NA did increase consumption time after propranolol pretreatment [$F(1,100)=4.9$, $p<0.05$, and, $F(1,25)=7.6$, $p<0.01$, for the two measures, respectively]. Clonidine and NA (after propranolol) also increased the length of the first bout of drinking, $F(1,25)=82.8$ and 47.3, $p<0.001$, respectively; again, NA alone was without effect [Fig. 4C: NA vs. CLON: $F(1,25)=89.0$, $p<0.001$]. The length of subsequent bouts appeared to be unchanged by drug treatments, but these data could not be analysed as approximately half of the sessions involved only a single bout. This fact also precluded analysis of interbout intervals.

TABLE 1
EFFECTS OF SYSTEMIC CLONIDINE ON SUCROSE CONSUMPTION*

	Vehicle	Clonidine	
Sucrose consumed (g)	10.9 (±0.5)	15.1 (±0.7)	$t=4.8$, $p<0.001$
Consumption time			
Events	36 (±1.3)	43 (±1.1)	$t=3.0$, $p<0.05$
Min	8.3 (±0.4)	10.9 (±0.4)	$t=3.8$, $p<0.01$
First bout (min)	7.9 (±0.4)	9.6 (±0.6)	$t=2.3$, $p<0.05$
Consumption rate			
g/event	0.31 (±0.002)	0.36 (±0.002)	$t=1.5$, N.S.
g/min	1.18 (±0.08)	1.35 (±0.07)	$t=1.5$, N.S.

*Values are means (±standard error). Results analysed by two-tailed t-test ($df=11$). See text for start and end of bout criteria.

Consumption rate was also estimated in two ways, corresponding to the two measures of consumption time (Fig. 4D,E). The rate measure based on frequency of observations is simply total consumption/observations (i.e., g/observation); to calculate rate from bout data (g/min) we used the formula (total consumption/bout time) × (observations occurring within bouts/total observations). On both of these measures, NA increased consumption rate, $F(1,25)=17.1$, $p<0.001$ and 9.3 $p<0.01$, respectively. However, clonidine did not affect either measure of rate [NA vs. CLON: $F(1,25)=10.1$, $p<0.01$ and 4.7, $p<0.05$]. The effects of NA on rate were blocked by propranolol, $F(1,25)=0.0$ and 0.6, N.S.

Clonidine had no significant effect on activity, resting or grooming (Fig. 5A–C). However, NA significantly increased activity [$F(1,100)=57.6$, $p<0.001$, relative to vehicle; $F(1,100)=56.5$, $p<0.001$, relative to clonidine] and decreased resting [$F(1,100)=42.9$, $p<0.001$, relative to vehicle; $F(1,100)=27.3$, $p<0.001$, relative to clonidine], whilst propranolol had the opposite effects (Fig. 4A,B). As in the case of consumption rate, propranolol abolished the effects of NA on activity and resting (Fig. 5A,B): effects of the NA/propranolol combination did not differ significantly from those of propranolol alone, $F(1,100)=0.7$ and 0.1 N.S.

The effects of systemic clonidine were exactly comparable to those seen following administration to the PVN. Systemic clonidine (5 μg/kg) significantly increased sucrose consumption, consumption time and the duration of the first feeding bout, but clonidine did not significantly alter consumption rate (Table 1).

DISCUSSION

Adrenergic stimulation of the PVN, or systemic administration of clonidine, did not increase food intake in hungry animals at any dose, and decreased food intake at higher doses (Experiment 1). Previous studies have uniformly demonstrated increased feeding in satiated animals (see Introduction). The failure to observe such an effect presumably results from the use of 20 hr food deprivation. This procedure was necessary in order to generate sufficient data to analyse: unfortunately, satiated animals produced insufficient feeding responses to apply the method of log survivor analysis to data from brief experimental sessions. However, it seems to us likely that the suppression of feeding at high doses of NA and clonidine, in deprived animals, results from nonspecific causes and is of little physiological significance.

After reducing the length of food deprivation and introducing a more palatable diet (Experiment 2), substantial increases in intake were observed in all three drug conditions. Under these experimental conditions the onset of consumption is almost immediate; therefore, drug effects on the initiation of feeding could not be determined. Clonidine had no effect on the rate of consumption when given either centrally or peripherally. However, after both peripheral and central administration, clonidine increased consumption time (Experiment 2) primarily by prolonging the duration of the first drinking bout. Even in deprived animals (Experiment 1), where clonidine failed to increase food intake, a significant increase in the length of eating bouts was apparent after central administration, with no change in the interbout interval. These effects of clonidine are compatible with the hypothesis that clonidine enhances eating by suppressing satiety (29). As, in hungry animals, feeding is still in progress after 30 min exposure to pellets, a desatiating effect of clonidine would not have been readily apparent in Experiment 1. The suppression of feeding by higher doses may simply reflect the well-established sedative effect of clonidine (4).

Like clonidine, NA also enhanced sucrose consumption on administration to the PVN. However, the underlying mechanisms clearly differ: clonidine increased consumption time but not the rate of sucrose consumption, while NA increased consumption rate but not consumption time. These differences were extremely robust, and were present irrespective of the methods used to calculate time and rate. The effect of NA on eating rate may reflect a nonspecific behavioural stimulation since NA (but not clonidine) also increased activity and decreased resting. The fact that NA and clonidine increase sucrose consumption by different behavioural mechanisms has not previously been reported.

The effects of NA on activity, resting and eating rate were all abolished by propranolol pretreatment. However, following propranolol pretreatment, NA did increase eating time; and in fact, the effects of NA after propranolol pretreatment were indistinguishable from those of clonidine. If sucrose consumption is the only measure considered, the effect of NA was unaffected by propranolol. However, this first impression is highly misleading. Following propranolol pretreatment NA continued to enhance sucrose consumption, but by a quite different behavioural mechanism. The most likely explanation is that an alpha-receptor-mediated stimu-

lation of eating time was unmasked by the beta-receptor blockade; concurrent beta-receptor stimulation (by NA, but not clonidine) apparently causes a nonspecific behavioural stimulation which prevents the expression of the alpha-adrenergic specific stimulation of feeding.

Although administered as a beta-receptor antagonist, it must be recognised that dl-propranolol also has a number of other actions, including antagonism of 5-HT receptors (26) GABA agonist properties (2) and local anaesthetic effects (1). The latter can probably be discounted as an explanation of the present data, as propranolol was administered systemically. There are two reasons for thinking that 5-HT, GABA or other nonspecific effects probably do not contribute either: firstly these other effects of propranolol are usually seen in a higher dose range, and secondly propranolol antagonised the NA-induced increase in the rate of sucrose consumption but had no effect on the basal rate, suggesting a specific interaction with NA. Beta-receptor agonists are usually sedative on systemic administration (23), but activating effects of stimulating central beta-receptors have also been described (21).

These results suggest that NA infusions into the PVN may stimulate feeding by two independent mechanisms: a nonspecific activation which is probably mediated by beta-receptors, and a specific enhancement of eating time which we assume is mediated by alpha-receptors. Adrenergic mechanisms in the PVN appear to be involved in the physiological control of food intake (15,29). However, the present results suggest the need for reexamination of the assumption that these effects are mediated solely by alpha-receptors (11, 15, 16). Under the present experimental conditions the effects of NA were mediated primarily by beta-receptors and the effects of alpha-receptor stimulation was only revealed by concurrent beta-receptor blockade. Nevertheless, alpha-receptor antagonists are known to abolish the stimulation of food intake by PVN administration of NA (5,11). These data suggests that alpha-receptor stimulation is fundamental in eliciting a feeding response. If NA causes a beta-receptor-mediated behavioural activation following alpha-receptor blockade, this alone is insufficient to elicit feeding. Clearly, further studies of the behavioural microstructure of adrenergic feeding will be necessary to resolve the nature of this complex interaction.

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