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N-Allylnormetazocine (SKF-10,047): The Induction of Feeding by a Putative Sigma Agonist

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GOSNELL, B. A., A. S. LEVINE AND J. E. MORLEY. *N-allylnormetazocine (SKF-10,047): The induction of feeding by a putative sigma agonist.* PHARMACOL BIOCHEM BEHAV **19**(5) 737–742, 1983.—Several distinct classes of opiate receptors have been postulated. It has been suggested that two of these, the kappa and sigma, may play a role in the initiation of feeding. The putative sigma receptor agonist N-allylnormetazocine increased food intake at doses of 0.1 and 1 mg/kg, whereas higher doses caused a decreased intake under some conditions. This stimulatory effect increased after repeated injections and was naloxone reversible. After repeated injections of N-allylnormetazocine, the feeding response to ketocyclazocine, but not morphine, appeared at an earlier point than in naive rats. These experiments support the suggestion that the sigma receptor may play some role in the initiation of feeding.

N-allylnormetazocine Sigma agonist SKF-10,047 Food intake

OPIATE agonists increase food intake induced by a variety of conditions [5, 13, 14, 23]. These findings coupled with the demonstrations that the opiate antagonist, naloxone, reduces intake [2, 9, 25], have led to the suggestion that endogenous opioid peptides play a role in the regulation of appetite [16,22].

There are a variety of opiate receptors [4, 15, 21, 29, 30] and different opiate agonists bind more readily to one type of receptor than to the others. For example, morphine is referred to as a mu receptor agonist, while ketocyclazocine (KC) is consisdered to be a kappa receptor agonist [4,15]. The preferential kappa agonists ketocyclazocine and ethylketocyclazocine (EKC) are more potent stimulators of feeding than morphine [19]. This suggests that the kappa receptor may play a more central role than the mu receptor in the regulation of appetite. Additionally, food intake is increased by the central injection of dynorphin [12, 17, 18], a peptide believed to be an endogenous ligand for the kappa receptor [3].

Recently, we have shown that butorphanol tartrate is a potent stimulator of feeding [14]. Butorphanol is believed to possess both kappa and sigma receptor agonist properties [11]. Though there is some question as to whether the sigma receptor is a true opiate receptor [29,30], the potent feeding effect of butorphanol suggests that the sigma receptor may also play a role in the regulation of feeding. Because N-allylnormetazocine is believed to be primarily a sigma agonist [4, 15, 20], we examined its effects on food intake in rats.

METHOD

Male Sprague-Dawley rat (230–355 g; n=59) were housed in individual wire mesh cages and maintained on ad lib food and water with lights on from 0700–1900 hours. Within 3 hours after the onset of the light cycle, rats were injected SC with (±)N-allylnormetazocine HCl (NANM 0.1, 1, 5, or 10 mg/kg) or saline (NaCl). NANM was obtained from the Research Triangle Institute, Research Triangle Park, NC. Pre-weighed food pellets were placed into the cages immediately after injection and were weighed and replaced after 1, 2, 3, 4, and 6 hours. In a second dose-response experiment, male naive rats (245–330 g; n=52) were injected SC with NANM (0.001, 0.01, 0.1 or 1 mg/kg) or saline. Intake was measured at 1, 2, 3, 4, and 6 hours after injection.

To determine whether rats develop a tolerance to the feeding effects of NANM, animals in the NaCl, 1 and 10 mg/kg groups from the first experiment were given once daily injections of the same doses for 5 days immediately following the day of the first feeding measure. On the fifth day, food intake was measured at 1, 2, 3, and 4 hours after injection. For analysis, the mean intake of the saline group was subtracted from the amounts consumed in the 1 and 10 mg/kg groups. These values (experienced condition) were compared with similarly derived values from the first feeding measures (naive condition) with a *t*-test for repeated measures (two-tailed) at each hour.

On day 6, rats which had received repeated injections of saline or 10 mg/kg NANM were injected SC with approximately equimolar doses of either ketocyclazocine (KC, 10 mg/kg) or morphine sulfate (25 mg/kg). Rats which had received repeated 1 mg/kg NANM injections served as controls and were injected SC with either saline or KC buffer (1:1 methanol:0.1 N HCl). Food intake was measured at 1, 2, 3, 4, and 6 hours. This experiment compared the effects of KC

TABLE 1

EFFECT OF N-ALLYLNORMETAZOCINE (NANM) ON CUMULATIVE FOOD INTAKE (GRAMS) IN SPONTANEOUS DAYTIME FEEDING RATS

Dose of NANM (mg/kg)	n	Time (Hours) 1	2	3	4	6
NaCl	12	0.54 ± 0.31	1.03 ± 0.31	1.48 ± 0.32	1.70 ± 0.32	2.10 ± 0.34
0.1	11	1.12 ± 0.34	2.05 ± 0.25	2.15 ± 0.26	2.55 ± 0.28	3.00 ± 0.41
1	12	1.46 ± 0.44*	1.66 ± 0.46	1.73 ± 0.47	1.87 ± 0.49	1.97 ± 0.49
5	12	0.31 ± 0.17	1.59 ± 0.32	2.29 ± 0.47	2.92 ± 0.46	3.11 ± 0.46
10	12	0.13 ± 0.03	0.90 ± 0.23	1.84 ± 0.30	2.40 ± 0.28	2.78 ± 0.41
F(4,54)=		2.96†	2.09	0.84	1.74	1.52

*$p<0.05$, one-tailed LSD procedure.
†$p<0.05$, one-way ANOVA.

and morphine on feeding in naive and NANM-experienced rats.

We have previously shown that KC and morphine decrease rather than enhance nocturnal feeding [19]. To determine the effects of NANM on spontaneous nocturnal feeding, the rats used in the second dose-response experiment were injected SC with NANM (1 or 10 mg/kg) or saline at the beginning of the dark cycle. Food intake was measured at 1, 2, 3, 4, and 6 hours after injection. Food had been removed 1 hour prior to injection.

As naloxone has been shown to reduce intake induced by a variety of opiates [13, 18, 24], a third group of rats (approximately 150 g; n=43) was used to determine whether naloxone could block the feeding response to NANM. Because the time course of the feeding effect of NANM (1–3 hours) was similar to that seen for the effects of naloxone in other studies (up to 4 hours [2, 24, 25]), both injections were given simutaneously. Each rat received two SC injections within 5 minutes of each other, forming the following groups: saline + saline, NANM + saline, NANM + naloxone (1 mg/kg), NANM + naloxone (10 mg/kg), saline + naloxone (0.1 mg/kg), saline + naloxone (1.0 mg/kg), and saline + naloxone (10 mg/kg). The NANM dose in all cases was 1 mg/kg. Food intake was measured at 1, 2, 3, 4, and 6 hours.

All experiments, except the one in which nocturnal feeding was measured, began within three hours after the onset of the light cycle (0700 hours). In all experiments, food intake was corrected for spillage at each measurement. Except where noted above, data in each experiment were analyzed with a one-way analysis of variance (ANOVA) at each time point, followed by the least significance difference (LSD) procedure (one or two-tailed) when the overall F-value was significant. One-tailed tests were used only when previous experience or the literature allowed a clear prediction about the direction of the effects.

RESULTS

In the first dose-response experiment (0.1–10 mg/kg), there was a significant drug effect only within the first hour, $F(4,54)=2.96$, $p<0.05$. Further analysis (LSD procedure) indicated that only the 1 mg/dose significantly increased food intake (Table 1). The second dose-response experiment extended the dose range to include smaller doses. In this experiment, there was a significant effect at 2 and 3 hours, $F(4,47)=3.40$ and 4.99, respectively, $p<0.05$. The LSD procedure indicated that the 0.1 and 1.0 mg/kg doses significantly increased intake at 2 and 3 hours (Fig. 1).

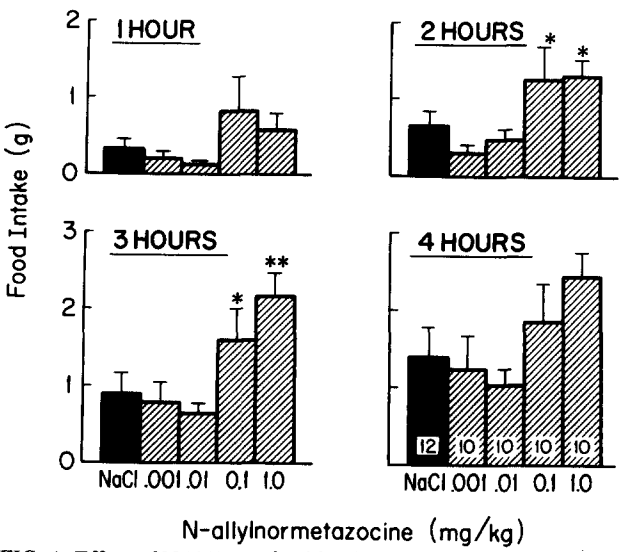

FIG. 1. Effect of NANM on food intake. There was significant drug effect on 2 and 3 hour cumulative intakes, $F(4,47)=3.40$ and 4.99, respectively, $p<0.05$, one way ANOVA. Numbers inside bars (4 hour intake) indicate the number of animals used at each dose. Conditions marked with asterisks are significantly different from the NaCl condition ($p<0.05$, $^{**}p<0.01$, one-tailed LSD procedure).

The feeding effects of 1 and 10 mg/kg doses of NANM in naive animals (data from first experiment) were compared to the effects of the same doses after the rats had received multiple injections of these doses. At the 2, 3, and 4 hour measures, the amount of food ingested above baseline (saline condition) was significantly greater in NANM-experienced rats than in naive rats for both doses (Fig. 2).

Figure 3 illustrates the feeding effects of morphine in naive and NANM-experienced rats. There was no significant effect of morphine except in the 6 hour cumulative intake, $F(2,14)=4.63$, $p<0.05$. At this point, the NANM-experienced but not the naive rats had consumed significantly more than rats receiving saline. However, there was no significant difference in the mean intakes of the naive and experienced rats.

Figure 4 illustrates the feeding effects of ketocyclazocine (KC) in naive and NANM-experienced rats. There was a signif-

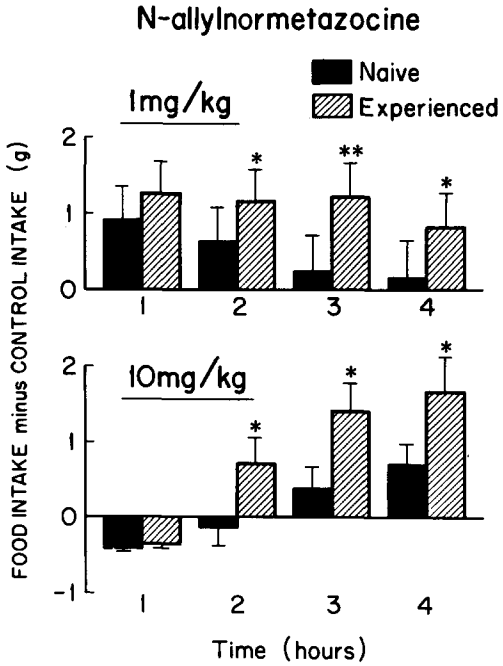

FIG. 2. Effect of repeated injections of NANM on the amount of food consumed above control intake. Rats were injected with either NaCl, 1 or 10 mg/kg of NANM (n=12 in each group) once daily for 5 days. Bars indicate mean intake above control on Day 1 (naive) and Day 5 (experienced). Conditions marked with asterisks are significantly different from corresponding naive condition (*$p<0.05$, **$p<0.01$, t-test (two-tailed) for repeated measures).

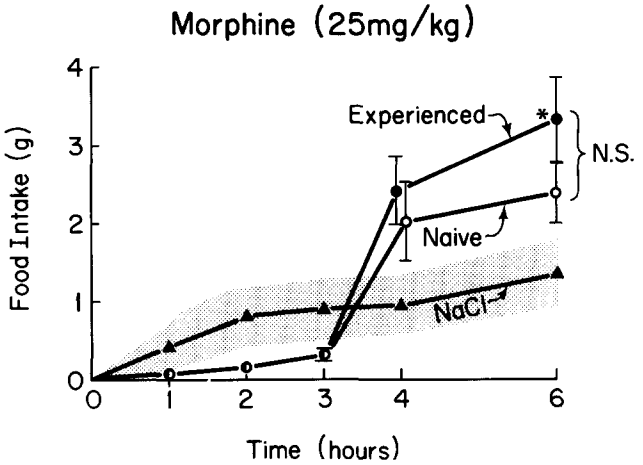

FIG. 3. Effect of morphine on food intake in NANM experienced and naive rats. Experienced (n=5) and naive (n=6) rats were injected SC with 25 mg/kg of morphine sulfate and compared to saline-injected controls (n=6). The stippled area represents (±)1 standard error from the control means. There was a significant effect of morphine only at 6 hours, $F(2,14)=4.63$, $p<0.05$, one way ANOVA, where morphine significantly increased intake in experienced but not naive rats (*$p<0.05$, two-tailed LSD procedure).

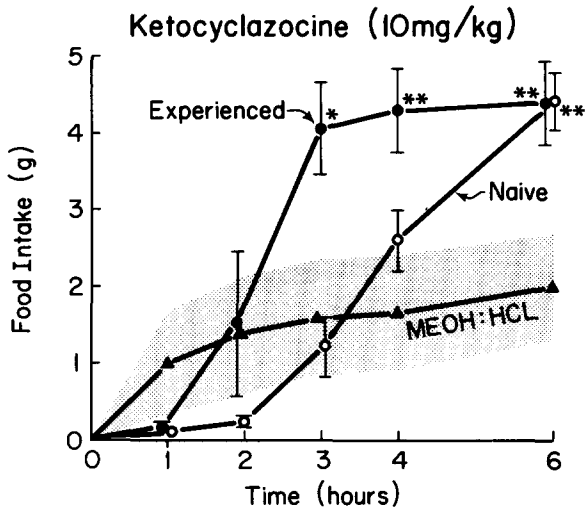

FIG. 4. Effect of ketocyclazocine (KC) on food intake in NANM-experienced and naive rats. Experienced (n=6) and naive (n=6) rats were injected SC with 10 mg/kg of KC and compared to (MeOH:HCl) buffer-injected controls (n=6). The stippled area represents (±)1 standard error from the control means. KC significantly increased intake in experienced rats at 3, 4, and 6 hours, whereas the intake of naive rats was significantly greater than control only at 6 hours (*$p<0.05$, **$p<0.01$, two-tailed LSD procedure).

icant overall effect of KC at 3, 4, and 6 hours, $F(2,15)=6.74$, 5.2 and 6.37, respectively, all p's<0.05. At 3 hours, the intake of the experienced rats was significantly greater than that of both the naive (KC injected) and vehicle-injected rats. At 4 hours, intake of the experienced rats was significantly greater than that of vehicle-injected but not KC-injected naive rats. At 6 hours, the intakes of the experienced and naive rats were almost identical, with both amounts being significantly greater than control.

Though not systematically observed, it was noted during feeding changes that rats receiving morphine (25 mg/kg) were immobilized and appeared catatonic for as long as three hours. To a lesser degree, rats receiving KC (10 mg/kg) were also immobilized. No such effects were noted in rats given the highest dose of NANM (10 mg/kg, Experiment 1). However, a slight ataxia was observed in some of these animals.

Results from the nocturnal feeding experiment are summarized in Table 2. There was a significant effect of NANM at 1, 2, 3, 4, and 6 hours. Subsequent analysis indicated that at each time point, rats receiving the 10 mg/kg dose ate significantly less than saline controls. The intakes of rats receiving the 1 mg/kg dose were not significantly different from controls at any time point.

Table 3 summarizes the results from the experiment to determine whether naloxone could block the feeding effects of NANM. As indicated, NANM-treated rats consumed significantly more food at 1, 2, and 3 hours. Naloxone at the 1 and 10 mg/kg doses blocked this effect at the same time points.

DISCUSSION

Results from the first dose-response experiment suggest that NANM in the 0.1–1 mg/kg dose range causes an early (within the first hour) increase in food intake. The slight decrease in intake seen in the first two hours with higher doses is possibly due to psychomimetic or disorienting effects of the sigma receptor agonists [4, 15, 29]. In the second experiment, a lower range of doses was used. Again, the 0.1 and 1 mg/kg doses significantly increased intake, though in this case the effect occurred at 2 and 3 hours. This increased intake is in disagreement with the results of Vaupel and Morton [27], who found that NANM in a comparable dose range decreased 1 hour intake in food-deprived dogs. The species

TABLE 2

EFFECT OF N-ALLYLNORMETAZOCINE (NANM) ON CUMULATIVE FOOD INTAKE (GRAMS) IN SPONTANEOUS NOCTURNAL FEEDING RATS

		Time (Hours)				
Dose of NANM	n	1	2	3	4	6
NaCl	10	2.31 ± 0.24	3.61 ± 0.38	5.52 ± 0.47	6.96 ± 0.32	10.01 ± 0.23
1 mg/kg	10	2.29 ± 0.10	3.95 ± 0.42	4.68 ± 0.41	5.73 ± 0.54	8.64 ± 0.64
10 mg/kg	10	0.33 ± 0.11‡	1.67 ± 0.35‡	3.90 ± 0.41*	5.28 ± 0.42*	8.17 ± 0.55*
F(2,27)=		36.84†	10.11†	3.56†	3.98†	3.58†

*$p<0.05$, ‡$p<0.01$, two-tailed LSD procedure.
†$p<0.05$, one-way ANOVA.

TABLE 3

EFFECT OF NALOXONE ON N-ALLYLNORMETAZOCINE-INDUCED CUMULATIVE FOOD INTAKE (GRAMS) IN SPONTANEOUS DAYTIME FEEDING RATS

		Time (Hours)				
	n	1	2	3	4	6
Saline + saline	8	0.14 ± 0.09	0.15 ± 0.09	0.44 ± 0.27	0.49 ± 0.26	0.90 ± 0.43
NANM + saline	8	0.86 ± 0.27‡	0.98 ± 0.25‡	1.49 ± 0.38*	1.56 ± 0.39	1.84 ± 0.52
NANM + naloxone (1 mg/kg)	6	0.03 ± 0.02	0.08 ± 0.05	0.32 ± 0.18	0.33 ± 0.20	0.37 ± 0.21
NANM + naloxone (10 mg/kg)	6	0.07 ± 0.07	0.07 ± 0.07	0.07 ± 0.07	0.23 ± 0.21	0.83 ± 0.39
Saline + naloxone (0.1 mg/kg)	5	0.26 ± 0.16	0.26 ± 0.16	0.66 ± 0.38	0.98 ± 0.38	1.82 ± 0.58
Saline + naloxone (1 mg/kg)	5	0.0 ± 0.0	0.16 ± 0.16	0.42 ± 0.27	0.70 ± 0.40	0.84 ± 0.48
Saline + naloxone (10 mg/kg)	5	0.18 ± 0.12	0.18 ± 0.12	0.26 ± 0.10	0.92 ± 0.34	1.50 ± 0.38
F(6,36)=		4.31†	5.10†	3.18†	2.30	1.58

*$p<0.05$, ‡$p<0.01$, two-tailed LSD procedure.
†$p<0.05$, one-way ANOVA.

difference, along with the fact that we measured spontaneous rather than deprivation induced feeding, prohibits a direct comparison of the discrepant results. After food deprivation, the intake of control animals is usually fairly large; the initial disorienting or dysphoric effects of NANM in such a condition might be manifested as a relative reduction in intake, as we report here for nocturnal feeding (where control intake is also fairly large). We and others have found a similar initial reduction in intake following morphine injections in food-deprived rats [19,23]. When food was withheld for 2 or 4 hours after the injection, however, there was no initial decrease, presumably because the sedative effect of morphine had dissipated [19].

N-allylnormetazocine is often referred to as a sigma opiate receptor agonist [4, 15, 20]. However, because of its psychotomimetic actions and its generalizability to the non-opiate phencyclidine in discrimination trials, along with its ability to displace bound ^{3}H-phencyclidine [10, 15, 31], it has recently been suggested that the sigma receptor is not an opiate receptor [29,30]. The present demonstration of a naloxone antagonism of the feeding effects of NANM is therefore difficult to explain. However, naloxone has also been found to reduce NANM-induced analgesia [20].

It has been suggested that there are multiple binding sites in the brain for NANM [20,28]. It is therefore possible that the increased feeding caused by NANM may be due to its

action on receptors other than the sigma. For example, Herling and Shannon [8] found that the discriminative effects of *d-l*-EKC partially generalized to the *l*-isomer of NANM, which is consistent with the suggestion that NANM may be a partial kappa agonist [26]. On the other hand, we have found that NANM, but not the kappa-sigma agonist butorphanol, induces feeding in the diabetic Chinese hamster [1]. This discrepancy suggests that the feeding response to NANM may not be a kappa-mediated effect.

In addition to sigma and possible kappa receptor effects, NANM is thought to be a partial mu receptor antagonist [15]. Though opiate receptor blockade is generally associated with decreased feeding, it has been suggested [19] that some degree of mu receptor blockade might enhance the feeding induced by agonists at other receptor sites by reducing the effects typically associated with mu agonists, such as sedation, catatonia, and indifference [7, 15, 30]. Interestingly, it has been suggested that butorphanol, a potent inducer of feeding [14], may also be a mu receptor antagonist [6].

The effectiveness in stimulating feeding of two doses of NANM (1 and 10 mg/kg) significantly increased after repeated injections of the drug. The animals thus displayed a "reverse tolerance" in relation to food intake. We have previously noted this phenomenon with the kappa and mu agonists, ketocyclazocine and morphine [19]. This effect was interpreted as indicating the development of tolerance to the sedative effect of the drugs.

The development of tolerance to some opiate-like effect of NANM might also explain the increased effectiveness of KC to stimulate intake in NANM experienced rats. The experienced rats ate a significantly greater amount of food than controls by 3 hours, whereas the intake of the naive rats was not significantly greater than control until the 6 hour measurement. That the experienced and naive rats had consumed nearly the same amount by 6 hours indicates that KC stimulated feeding in both groups to an approximately equal degree; possibly a tolerance to sedative or disorienting effects allowed this feeding to occur much earlier in the experienced rats. This suggests that there may be some cross-reactivity between KC and NANM. As discussed earlier, it has been suggested that NANM may be a partial kappa agonist [26].

On the basis that NANM may be a partial kappa agonist and mu antagonist and that chronic NANM treatment potentiated the feeding effect of KC (a kappa agonist), it might be predicted that chronic NANM treatment would not potentiate the feeding effects of the mu agonist, morphine. Indeed, repeated exposure to NANM had little, if any, effect on the response to morphine sulfate (25 mg/kg). We have found, however, that morphine is a relatively weak stimulator of intake in naive rats [19], though its effect appears to increase with repeated injections [7,19]. In this experiment, morphine did not significantly increase intake at any time point in naive rats. Experienced rats ate significantly more than controls only at 6 hours, and their intake did not significantly differ from that of naive animals. If any slight tolerance to the effect of opiates resulted from NANM injections, the effect was probably obscured by the strong sedative effect of morphine.

NANM was not effective in stimulating intake when tested during the first half of the dark cycle, and in fact significantly depressed food intake during this time. We have found that the feeding reponses to ketocyclazocine and morphine display a marked circadian rhythm with no effect or a suppression of feeding during the noctural part of the cycle [19]. This lack of effect was interpreted as indicating a near maximum saturation of opiate receptors at this time, such that exogenous opiates can do little to enhance the already stimulated feeding system. Decreases in intake were interpreted as being secondary to sedative effects. The suppression of intake by the 10 mg/kg dose of NANM in this report may be due to dysphoric or disorienting effects of the drug, as was noted by Martin *et al.* [15] in dogs, or the slight ataxia noted in the first experiment. Alternatively, in light of the possibility that NANM may also act at receptors other than the sigma (see above), the suppression of nocturnal feeding could be the result of displacement of endogenous opiates.

It should be noted that the time course of this effect of NANM is quite variable. The 1 mg/kg dose was effective only in the first hour in the first dose-response experiment, whereas it was effective only at the 2 and 3 hour measures in the second experiment. In the naloxone blockade experiment, this dose was effective for 3 hours. In one group of rats, NANM (1 mg/kg) significantly increased intake in the first hour (data not reported here). In subsequent tests with animals from this same group, however, this dose had no significant effect on feeding at any point. In our work on feeding and satiety agents, we have found that it is not uncommon to encounter a group of rats that does not respond to various treatments in the manner predicted by preliminary testing and by the literature. When methodological problems can be ruled out, the further study of such anomalies should provide additional insights into the mechanisms of appetite regulation.

We have shown that the preferential sigma receptor agonist, N-allylnormetazocine causes a naloxone-reversible increase in food intake in doses in the range of 0.1–1 mg/kg, whereas the higher doses cause a decreased intake under some conditions. Repeated exposure to NANM increases the feeding effect of ketocyclazocine and of NANM itself, while having little effect on the feeding response to morphine. This enhancement of feeding by NANM suggests that the sigma receptor, like the kappa, may play a role in the regulation of intake.

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