Pharmacology Biochemistry & Behavior, Vol. 18, pp. 19–23, 1983. Printed in the U.S.A.

Effect of Centrally Administered Neurotensin on Multiple Feeding Paradigms

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Received 6 July 1982

LEVINE, A. S., J. KNEIP, M. GRACE AND J. E. MORLEY. *Effect of centrally administered neurotensin on multiple feeding paradigms.* PHARMACOL BIOCHEM BEHAV **18**(1) 19–23, 1983.—Recent studies have suggested that the tridecapeptide, neurotensin, may be an endogenous satiety factor. The present study was undertaken to examine the effects of neurotensin on multiple paradigms known to stimulate feeding. Following a 30 hour starvation period, neurotensin suppressed feeding at the 20 μg and 10 μg dose, but not at the 1 μg dose when compared to saline controls. Norepinephrine (20 μg ICV) induced feeding was suppressed at the 20 μg neurotensin dose but not at the 10 μg or 1 μg dose. In contrast, neurotensin did not suppress muscimol induced feeding at any of the doses. Insulin induced feeding (10 units SC) also was not suppressed by neurotensin. Neurotensin suppressed dynorphin induced feeding at the 20 μg and 10 μg but not at the 1 μg dose. Neurotensin suppressed spontaneous feeding ($p<0.01$) in vagotomized rats (2.5±0.3 g/2 hr) when compared with saline controls (4.2±0.5 g/2 hr) suggesting that an intact vagus is not necessary for neurotensin's anorectic effect. We conclude that neurotensin may play a role in short-term appetite regulation by a complex interaction with monoamines and neuropeptides, particularly norepinephrine and the kappa opiate agonist, dynorphin.

Neurotensin Eating Multiple feeding paradigms

THE tridecapeptide, neurotensin (NT) which was first isolated from bovine hypothalamus [7] and later from bovine and human intestine [6, 14, 18], possesses a wide variety of effects. Peripheral administration of NT does not induce the same effects as central administration, even at high doses, suggesting that NT does not readily cross the blood-brain barrier. Given intravenously, it produces hypotension [7], hyperglycemia associated with decreased plasma insulin and increased plasma glucagon concentrations in the rat [5,38], an increase in both insulin and glucagon in dogs [16,52], an increase in the concentration of somatostatin in the portal vein of the rat [47], and has a variety of effects on pituitary hormone release [24, 25, 45, 53]. When injected centrally, NT induces hypothermia [37, 39, 40], and analgesia [8,43], diminishes spontaneous locomotor activity [54], antagonizes several effects of thyrotropin releasing hormone [42], increases plasma somatostatin concentration in the rat hypophyseal portal blood [1], and inhibits activation of the hypothalamic-pituitary-thyroid axis [24,42].

As plasma concentrations of NT are markedly increased after eating [26] and as NT has major effects on gastrointestinal motility [3,12], it appears that this neuropeptide may play a role in feeding behaviors. Intraventricular administration of NT has been reported to suppress feeding in food-deprived rats [23] and intrahypothalamic injection of NT has been shown to attenuate intrahypothalamic norepinephrine induced feeding [51]. Also, Gibbs, *et al.* [12] have reported that intraperitoneal administration of NT suppressed feeding in 3 hour deprived rats although this appeared to be due to a wheezing and other disruptions of normal behavior.

We have previously postulated that dopamine and the endogenous opiates acts as a tonic signal for the induction of feeding, being held in check by monoamines (e.g., serotonin) and neuropeptides [27,29]. Using multiple pharmacological feeding paradigms including spontaneous feeding [19], muscimol [34], and norepinephrine induced feeding [36], insulin induced feeding [21] and dynorphin induced feeding [31], our laboratory has been investigating the anorectic effects of various putative satiety agents. In the present study, we evaluate the effects of central administration of NT on food intake induced by various pharmacological agents.

GENERAL METHOD

Animals and Chemicals

Male Sprague-Dawley rats (150–275 g), kept under standard lighting conditions (12 hr/day artificial light, 6 a.m. to 6 p.m.) and given free access to Purina rat chow and water were used in all experiments. In the rats receiving intraventricular agents or saline, stainless steel guide tubes were stereotactically implanted into the lateral ventricle under nembutal anesthesia at least 5 days prior to the commencement of the experiments. Drugs and peptides were administered in a 5 μl volume of saline when given intraventricularly, or in a 0.2 cc volume of saline subcutaneously. A separate group of rats was used for each experiment.

All substances were purchased commercially: insulin (Iletin U-100, Eli Lilly and Co.), muscimol, norepinephrine and dynorphin (Sigma Chemical Co., St. Louis, MO) and neurotensin (Vega Chemicals, Reno, NV).

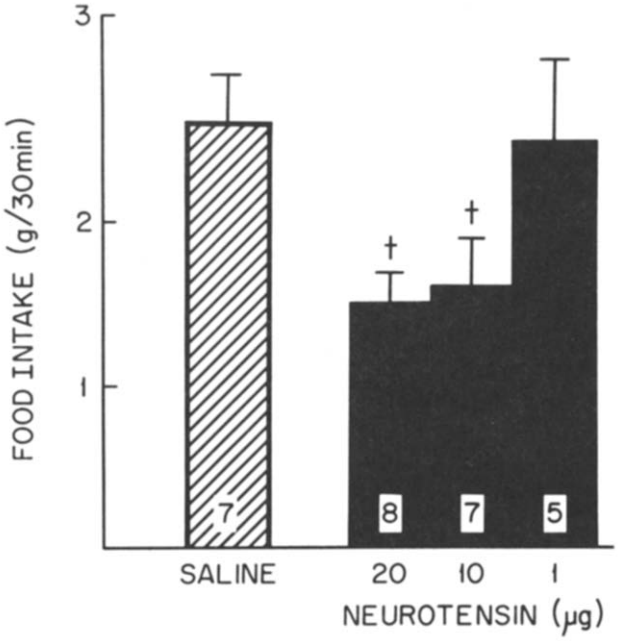

FIG. 1. Effect of neurotensin on food deprivation induced feeding. $F=3.94$, $p<0.025$, $^{\dagger}p<0.05$ compared with saline control. Numbers at the base of each figure represent number of animals/group. Error bar represents standard error of the mean.

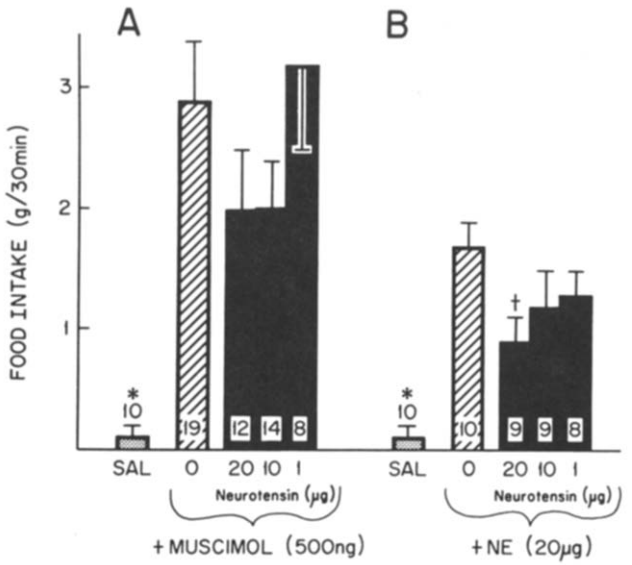

FIG. 2. Effect of neurotensin on muscimol (A) and norepinephrine (B) induced feeding. (A)$F=4.94$, $p<0.005$. (B)$F=9.93$, $p<0.005$, $^{\dagger}p<0.05$ compared with 0 dose of neurotensin; $^{*}p<0.05$ compared with 0 dose of neurotensin.

Statistics

All results are expressed as the mean±SEM. Results were compared using one way ANOVA and the protected least significance test.

EXPERIMENT 1

Food deprivation for various time periods can induce feeding in rats. The present study was conducted to evaluate the effect of NT on feeding induced by a 30 hour food deprivation.

Method

Food intake was induced by depriving naive rats of food for 30 h (water given ad lib). At the time of the study, rats were removed from their home cages, given an intraventricular (ICV) injection of NT (dissolved in 5 μl saline) or saline (5 μl) and returned to their home cage (containing 7–10 g of Purina rat chow). Food intake was measured for the ensuing 30 minute time period (in all studies food remaining, including spillage beneath cages, was subtracted from the starting weight to quantify food intake).

RESULTS AND DISCUSSION

Following the 30 hour starvation period, NT suppressed feeding at the 20 μg and 10 μg dose, but not at the 1 μg dose compared with saline controls (Fig. 1). Luttinger, *et al.* [23] previously reported that centrally administered NT suppressed food intake following a 24 hour food deprivation at a dose as low as 3.3 μg. In our study there was still a tendency for a reduction in food intake at the 1 μg dose although it was not significant. Luttinger, *et al.* [23] used rats which were habituated to a food deprivation schedule which may explain the slight discrepancy in dose response. We have previously failed to find an effect of a 1 μg dose of neurotensin ICV on stress-induced eating when using the mild tail pinch model [30]. These results suggest that relatively high concentrations of neurotensin (2 or 6 nmol) ([23] and present study) are required to suppress feeding compared to some other neuropeptides, e. g., bombesin (0.06 nmol) [30], calcitonin (0.012 nmol) [9] (0.0003 nmol) [22] and CRF (0.21 nmol) [28].

EXPERIMENT 2

Intraventricular administration of the GABA agonist, muscimol, has been reported to induce feeding in rats, possibly by binding to GABA receptors within satiety areas and exerting an inhibitory effect on the system [29]. Norepinephrine has also been shown to be an important hypothalamic factor in the initiation of feeding, although it has been reported that norepinephrine may suppress feeding following injections into some areas of the lateral hypothalamus [30]. Previous studies from our laboratory have suggested that norepinephrine induced feeding is dependent on activation of a GABAergic system [34]. The purpose of this study was to evaluate the effect of NT on muscimol and norepinephrine induced feeding.

METHOD

Feeding was stimulated by ICV administration of muscimol (500 ng/5 μl saline) or norepinephrine (20 μg/5 μl slightly acidified saline). Muscimol or norepinephrine was administered followed immediately by an ICV injection of NT or saline. Rats were then returned to their home cage containing 7–10 g of rat chow and food intake was quantified for a 30 minute period.

RESULTS AND DISCUSSION

Neurotensin did not suppress muscimol induced feeding at any of the administered doses, but attenuated norepi-

TABLE 1
EFFECT OF NEUROTENSIN ON INSULIN INDUCED FEEDING

		n	Food Ingested (g/90 min)
Saline		6	3.6 ± 0.3
Neurotensin	(20 μg ICV)	6	4.3 ± 0.5
	(10 μg ICV)	5	2.6 ± 0.5
	(1 μg ICV)	5	3.6 ± 0.4

nephrine induced feeding at the 20 μg dose (Fig. 2). Hoebel [15] and Stanley, Eppel and Hoebel [51] reported that NT injected directly into the paraventricular hypothalamic area suppressed feeding resulting from paraventricular administration of norepinephrine. We have previously reported [34,36] that many known satiety factors fail to inhibit muscimol induced feeding, including CCK-8, bombesin, somatostatin, quipazine, TRH, isoproterenol and phentolamine. However, bombesin and CCK-8 do reduce norepinephrine induced feeding [36]. Thus, NT joins bombesin and CCK-8 as satiety factors which appear to suppress norepinephrine induced feeding without having a significant effect on muscimol induced feeding.

EXPERIMENT 3

It is well established that peripheral administration of insulin will induce eating in rats consistently, with a resultant increase in body weight. This study was conducted to investigate the effect of NT on insulin induced feeding.

METHOD

Insulin (10 U/kg) was administered subcutaneously to induce feeding. ICV NT or saline was administered 90 minutes following insulin administration and rats were then placed in unfamilar plastic boxes containing 7–10 g of rat chow. Food intake was quantified for a 90 minute period.

RESULTS AND DISCUSSION

Insulin induced feeding was unaltered by NT injection (Table 1). We have previously shown that CCK-8 (5 μg/kg) and bombesin (5 μg/kg) [21] as well as calcitonin, naloxone and prostaglandins [20] suppressed insulin induced feeding.

EXPERIMENT 4

The opiate kappa receptor agonist, dynorphin-(1–13) has recently been demonstrated to stimulate food ingestion in sated rats [17, 31, 33]. Recent data has suggested [32,48] that the kappa opioid receptor may be pivotal to the initiation of feeding. The purpose of this study was to evaluate the effect of NT on dynorphin-(1–13) induced feeding.

METHOD

Animals were housed in individual cages and all testing was conducted in their home cages. Use of the home cage is important for dynorphin-(1–13) induced eating, as in a previous experiment [31] only one of eight animals given 10 μg of dynorphin-(1–13) ICV ate when placed in a novel environment. Testing was carried out between 0800–1000 hr. Immediately following drug or vehicle (50:50, v/v; 1N HCl:MeOH) administration, animals were returned to their cage together with 7–10 g of Purina rat chow and food intake was measured for 60 minutes (since the maximal rate of food intake occurs 60 minutes following administration of dynorphin).

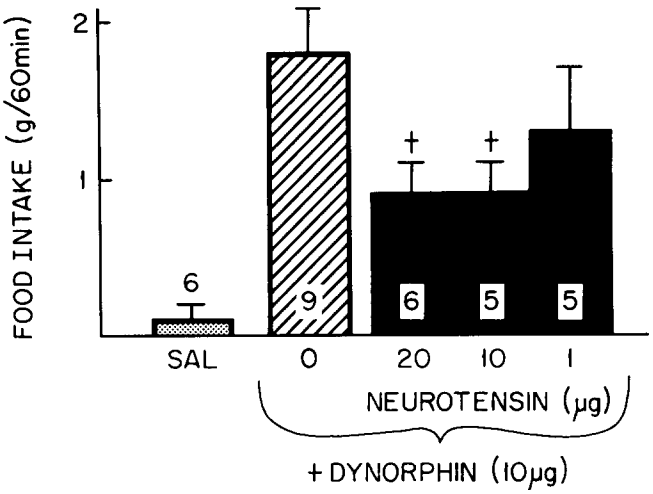

FIG. 3. Effect of neurotensin on dynorphin-induced feeding. $F=5.67$, $p<0.005$, $^{\dagger}p<0.05$.

RESULTS AND DISCUSSION

Dynorphin induced feeding was attenuated at the 20 and 10 μg dose (Fig. 3). We have recently observed that CCK-8 (10 μg/kg) and somatostatin (10 μg/kg) do not suppress dynorphin-(1–13) induced feeding, whereas bombesin (10 μg/kg) suppressed such feeding [19,33].

EXPERIMENT 5

It has been shown that several anorectic peptides, including CCK [35,50] and somatostatin [19] suppress feeding after peripheral administration through a mechanism involving the vagus and that an intact vagus is necessary for the expression of norepinephrine induced feeding [49]. The present study was conducted to evaluate the effect of NT on spontaneous feeding in vagotomized rats.

METHOD

The effect of NT on spontaneous food intake in vagotomized rats was measured following a two hour period during which time rats normally ingest food (2000–2200 hr). NT was administered in a separate room using limited light and rats were returned to their home cages containing pre-weighed rat chow (lights off). Following the two hour period the remaining food, including spillage, was measured.

For vagotomy, rats (n=12) were anesthetized with nembutal, a midline incision was made, and vagal trunks were visualized. Bilateral vagotomy was performed according to the method as previously described [50]. Briefly, each vagal trunk was transected and all neural tissue surrounding the esophagus was removed. Vagotomies were verified anatomically under 5X magnification. Shams (n=12) were prepared using the above procedure except for the transection and neural stripping. Animals were allowed to recover at least 7 days before being used in the study.

RESULTS AND DISCUSSION

Neurotensin significantly suppressed ($p<0.01$) spontaneous feeding in vagotomized rats (2.5±0.3 g/2 hr) when compared with saline controls (4.2±0.5 g/2 hr) suggesting that an intact vagus is not necessary for neurotensin's anorectic effect. As peripheral administration of somatostatin does not inhibit feeding when the vagus is transected [19] it does not appear that neurotensin's anorectic effect is secondary to the neurotensin induced release of somatostatin. Studies on gastric acid secretion have suggested that neurotensin may inhibit acid secretion by effecting central release of norepinephrine [44]. Furthermore, Garcia-Seville, *et al.* [10] have reported that ICV administration of neurotensin increased the turnover of monoamines in rat brain. Thus, neurotensin might inhibit feeding by interacting with adrenergic feeding mechanisms. Recently it has been reported that norepinephrine induced eating is abolished in rats with complete subdiaphragmatic vagotomy [49]. Since neurotensin blocked feeding in rats with an intact as well as a transected vagus it seems that neurotensin's inhibitory effect on feeding is independent of the previously reported vagal-norepinephrine mechanism of feeding induction.

GENERAL DISCUSSION

Neurotensin affects various systems known to be involved in the regulation of food intake. In addition to the increased plasma levels of NT which occur postprandially [26], peripherally administered NT results in hyperglycemia, decreased plasma insulin and decreased plasma glucagon concentrations [5,38] as well as increased somatostatin concentration in the portal vein of the rat [47]. Central administration of neurotensin increases the somatostatin concentration in rat hypophyseal portal blood [1], interacts with the dopaminergic system [42] and influences the turnover of monoamines [10]. It now seems clear that centrally administered neurotensin suppresses feeding stimulated by a variety of conditions including food deprivation, norepinephrine-induced feeding, dynorphin induced feeding and in vagotomized rats during nocturnal feeding.

There appears to be many similarities between NT and the putative satiety peptide, bombesin: (1) both result in hyperglycemia following peripheral administration [4, 5, 38], (2) both induce hypothermia, decrease conditional avoidance responding, and enhance ethanol induced sedation [37,41], (3) both result in reduction in food intake following central or peripheral administration [11, 12, 23, 30, 51], (4) both inhibit feeding in vagotomized rats [13,35], (5) neither suppress muscimol induced feeding yet both suppress norepinephrine induced [34,36] feeding, (6) both suppress dynorphin induced feeding [31], (7) neither appear to result in a generalized disruption of behavior [11,23], and finally, as is true for many peptides, (8) they are both found in the brain and the GI tract [41]. However, they do appear to be different in that a much smaller concentration of bombesin on a molecular basis is necessary to inhibit feeding compared to neurotensin. It should also be noted that intravenous administration of bombesin to rats results in the release of neurotensin [46].

The use of multiple feeding paradigms is important to the understanding of the delicate balance which exists between monoamines and peptides in the regulation of food intake. For example, NT is known to increase somatostatin concentrations [47] and thus one might hypothesize that NT suppresses feeding indirectly via somatostatin. However, in contrast to NT, peripherally administered somatostatin does not inhibit norepinephrine induced, dynorphin induced or food deprivation induced feeding, but does inhibit insulin induced feeding and requires an intact vagus to produce its effect. Thus, it is unlikely that neurotensin's satiety effect results from release of peripheral somatostatin. It seems reasonable to propose that NT inhibits feeding at two sites; by inhibiting norepinephrine induced feeding through a non-vagally related mechanism and by blocking the postulated opioid signal responsible for the feeding drive.

ACKNOWLEDGEMENTS

This research was supported by the Veterans Administration and by General Mills, Inc. We thank JoAnn Tallman for secretarial assistance.

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