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Effect of nociceptin/orphanin FQ on food intake in rats that differ in diet preference

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Abstract

Nociceptin/orphanin FQ (N/OFQ) is an agonist of the ORL1 receptor. Despite homology with opioids, it does not bind to opioid receptors. Recent studies have shown that centrally administered N/OFQ increases food intake in a manner similar to opioid peptides; its effect is naloxone-reversible. Opioids appear to mediate ''palatability/reward''-dependent feeding: Opioid agonists increase, while antagonists decrease, the intake of preferred diets. The current project was designed to elucidate whether the effect of N/OFQ on the consumption of preferred foods resembles that of opioid peptides. Rats had a constant access for 2 weeks to two palatable (high sucrose and high fat) diets, and their baseline preferences were established. Based on these preferences, animals were divided into three groups: fat preferrers, sucrose preferrers, and ''neutrals''. On the experimental day, rats received an intracerebroventricular injection of N/OFQ. Intriguingly, in fat-preferring rats, N/OFQ stimulated the intake of each of the two diets. It had no effect, however, on the consumption of either diet or cumulative food intake in sucrose-preferring or ''neutral'' animals. Our results reveal that N/OFQ, unlike opioids, does not increase the intake of preferred diets. Thus, it does not seem to mediate ''palatability/reward''-driven feeding. Noteworthy, N/OFQ appears to cause hyperphagia only in fat-preferring rats.

Keywords: Nociceptin/orphanin FQ; Diet preference; Feeding

1. Introduction

Nociceptin/orphanin FQ (N/OFQ) is a heptadecapeptide that binds the opioid-like G-protein-coupled receptor, ORL1 (Reinscheid et al., 1995; Mollereau et al., 1996). N/OFQ and the ORL1-R exhibit striking structural similarities to the large family of opioid peptides and their corresponding receptors, respectively (Bunzow et al., 1994; Civelli et al., 1997). N/OFQ does not, however, activate the kappa, mu or delta receptors, nor does the ORL1 bind kappa, mu or delta ligands (Sim et al., 1996).

N/OFQ has been investigated in relation to its involvement in a variety of mechanisms and processes, including nociception (Mogil et al., 1996; Tian et al., 1997; Taylor and Dickenson, 1998), neuroendocrine control (Bryant et al., 1998), water–electrolyte balance (Kapusta et al., 1997), sexual behavior (Sinchak et al., 1997), learning and memory (Sandin et al., 1997; Manabe et al., 1998), cardiovascular functions (Champion et al., 1998) and locomotion (Devine et al., 1996). The resemblance between N/OFQ and ''classical'' opioid peptides has prompted the question of whether N/OFQ, similarly to opioids, has a stimulatory effect on ingestive behavior. Indeed, studies have shown that N/OFQ injected intracerebroventricularly (icv) (Pomonis et al., 1996) or into specific brain sites (Stratford et al., 1997; Polidori et al., 2000) causes a moderate increase in food intake in sated rats. Feeding response to intracerebroventricular N/OFQ can be observed almost exclusively during the first hour postinjection (Pomonis et al., 1996; Stratford et al., 1997; Polidori et al., 2000).

The magnitude of feeding response evoked by N/OFQ resembles that induced by opioid peptides. N/OFQ-stimulated

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ingestive behavior is sensitive to blockade of "classical" opioid receptors by peripherally injected naloxone, as well as intracerebroventricularly administered naltrexone (Pomonis et al., 1996; Leventhal et al., 1998). In addition, N/OFQ shares with opioid receptor agonists antiaversive properties (Olszewski et al., 2000b). Moreover, similar changes in c-Fos immunoreactivity in some feeding-related brain areas can be detected following administration of N/OFQ and opioids/opiates (Olszewski et al., 2000a; Kim et al., 2001).

One of the most characteristic and well-described functions of opioid peptides, which has not been studied in relation to N/OFQ, is the mediation of "palatability/reward"-dependent feeding. It has been shown that genetic deletion of the opioid receptors leads to a lower saccharin preference in CXBK mice compared to control animals (Yirmiya et al., 1988). Palatability-induced hyperphagia increases hypothalamic dynorphin peptide and mRNA levels in rats (Welch et al., 1996). Blockade of the mu-, kappa- and delta-opioid receptors decreases the intake of palatable foods and solutions (especially of sweet ones or those high in fat) more readily than ingestants of neutral or nonpreferred flavors (Giraudo et al., 1993; Glass et al., 1996). Alternately, opioid receptor agonists are particularly effective in increasing the intake of palatable diets (for a review, see Levine and Billington, 1997). In addition, opioids appear to affect selection of macronutrients. Generally, rats treated with opiates tend to prefer a high-fat diet when high-carbohydrate and high-fat diets are presented concurrently (Welch et al., 1994). However, it should be noted that an initial preference toward a given macronutrient impacts the effect of opiates on macronutrient selection. Gosnell et al. noted that morphine-injected carbohydrate-preferring rats ingested more carbohydrate, whereas fat-preferring animals ate more fat (Gosnell et al., 1990).

The current project was aimed to further clarify whether the nature of the orexigenic action exerted by N/OFQ resembles that of "classical" opioid peptides in rats. Since one of the most characteristic functions of the opioid system in the regulation of ingestive behavior is the mediation of "palatability/reward"-dependent feeding, we assessed the influence of N/OFQ on hedonic-driven food intake as a relatively specific behavioral assay to examine whether the orexigenic action of N/OFQ parallels that of opioids. We determined the effect of intracerebroventricular N/OFQ on the intake of two palatable diets, high in sucrose and high in fat, with both of those diets available ad libitum. This effect was evaluated in relation to initial diet preferences of rats used in the study.

2. Materials and methods

2.1. Animals

Adult male Sprague–Dawley rats (Charles Rivers Laboratories, Portage, MI) weighing approximately 300–380 g at the beginning of the experiment were used in the studies. Animals were housed individually in conventional wire-mesh cages with a 12:12 L/D schedule (lights on at 07:00 h) in a temperature (21–22 °C)- and humidity-controlled room. Food (high-sucrose and high-fat powder diets presented in jars permanently placed in home cages; for diet composition, refer to Table 1) and tap water were available ad libitum.

2.2. Surgical procedures and verification of cannula placement

Rats used in the experiments were equipped with an indwelling stainless-steel cannula (20 gauge) in the right lateral ventricle. The cannula was positioned 1.0 mm lateral to the midline, 1.5 mm caudal to bregma and 3.5 mm below the surface of the skull, according to the atlas of Paxinos and Watson (1986). Dental cement was used to secure the cannula to two screws inserted in the skull. Surgeries were performed under Nembutal anesthesia (50 mg/kg body weight ip). Ten days of postoperative recovery was allowed before the experimental trials began.

Water intake measurement following the administration of angiotensin II (100 ng; Sigma, St. Louis, MO) provided the verification of cannula placement: Those rats that drank less than 6 ml of water within 20 min after the injection of the peptide were excluded from the studies. The angiotensin II test was performed 3 days before the beginning of the studies, as well as 3 days after their completion to ensure that the cannulae remained viable throughout the course of the experiment.

2.3. Drugs and drug administration

N/OFQ was purchased from Phoenix Pharmaceuticals (Belmont, CA). The peptide was dissolved in isotonic saline shortly before administration and was injected in a volume of 5 μl. Isotonic saline served as a control solution.

Table 1
Composition of diets used in the study

Components	Diet, wt.%	
	High sucrose	High fat
Cornstarch	13.8	0
Sucrose	50.0	0
Shortening	0	43.9
Corn oil	5.0	7.8
Casein	21.2	32.9
DL-Methionine	0.3	0.4
Vitamin mix	1	1.5
Mineral mix	3.5	5.4
Fiber	5	7.5

Caloric value of high-sucrose diet: 3.89 kcal/g; and of high-fat diet: 6.03 kcal/g. Vitamin and mineral mixtures were American Institute of Nutrition vitamin mixture 76 and mineral mixture 76, respectively. Fiber was Celufil (US Biochemical, Cleveland, OH).

Table 2
Intake of high-fat and high-sucrose diets and cumulative intake of both diets (expressed in kcal and g) in rats fed ad libitum measured 1 h after injection of 0 (saline), 0.3, 1 and 3 nmol N/OFQ icv

Treatment	High-fat diet intake		High-sucrose diet intake		Total intake	
	kcal	g	kcal	g	kcal	g
0 nmol N/OFQ	4.4±0.7	0.7±0.1	0.7±0.2	0.2±0.1	5.1±0.8	0.9±0.1
0.1 nmol N/OFQ	6.8±1.1*	1.1±0.2*	1.5±0.6	0.4±0.1	8.3±1.2*	1.5±0.2*
0.3 nmol N/OFQ	6.8±0.9*	1.2±0.1*	3.1±0.8*	0.8±0.2*	9.9±1.3*	1.9±0.3*
1.0 nmol N/OFQ	7.2±1.1*	1.2±0.2*	3.3±0.9*	0.9±0.2*	10.5±1.6*	2.1±0.3*

Values are means±S.E.M.; n=39 (repeated measures).
* P<.05.

2.4. Feeding studies and data analysis

Animals (n=39) had constant access to both high-sucrose and high-fat powder diets for 2 weeks before the beginning of experimental trials; no pharmacological treatment was performed during this period. When a choice of these diets is offered, some animals prefer only one, whereas others exhibit equal preference toward both of them. Thus, a 7-day food preference was established for each animal, and rats were divided into the following groups: (1) fat-preferring (n=13)—62.1±2.5% total calories came from the high-fat diet (range: 47–71%); (2) sucrose-preferring (n=12)—34.4±0.9% calories came from the high-fat diet (16–36%); and (3) neutral (n=14)—the high-fat diet was the source of 45.1±0.8% of their daily calorie intake (37–46%). There was no significant difference in total 24-h calorie intake between these groups (fat preferrers: 116±3 kcal; sucrose preferrers: 121.4±7 kcal; and neutrals: 122.9±6.0 kcal; 24-h calorie intake based on the 7-day average).

On treatment days, animals were injected with 0.3, 1 and 3 nmol N/OFQ or isotonic saline icv; injections took place between 11:00 and 12:00 h. Each of the 39 rats received treatment, thus, the study was divided into four individual experimental sessions spaced 3–4 days apart. Immediately after the injection, preweighed diets were placed in jars. As N/OFQ affects feeding in animals fed ad libitum most

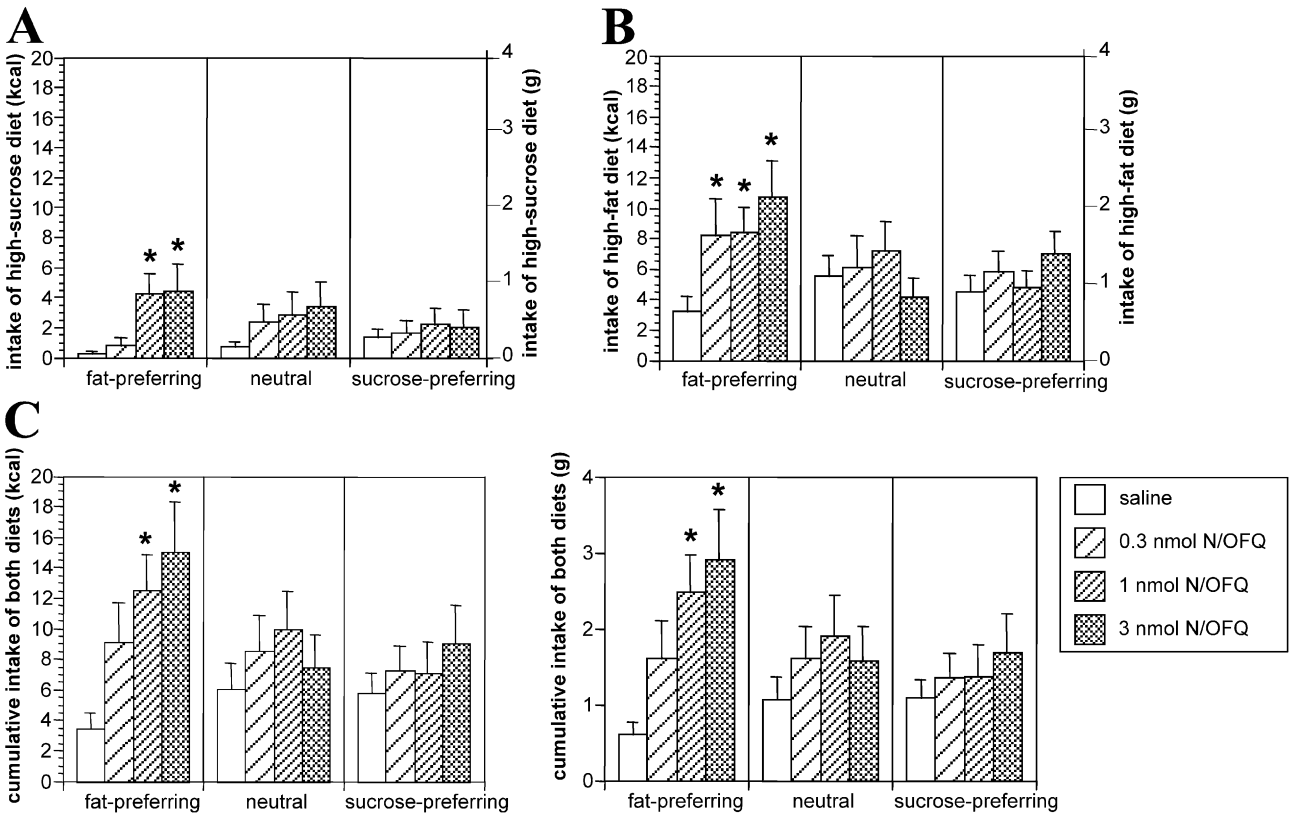

Fig. 1. One-hour feeding response, expressed in kilocalories and grams of ad libitum fed fat-preferring, sucrose-preferring and "neutral" rats injected with saline, 0.3, 1 and 3 nmol N/OFQ icv. Graphs depict intakes of (A) the high-sucrose diet, (B) the high-fat diet and (C) both diets (cumulative). *Significantly different from controls (P<.05); n=12–14/group (repeated measures).

potently during the first 60 min after treatment (Pomonis et al., 1996), the amount of consumed food was measured 1 h postinjection.

The following parameters were assessed: intakes of the high-fat and high-sucrose diets, as well as total food intake. Results were analyzed for all rats regardless of their diet preference and separately for each of the three preference-based groups. Food intake data are expressed in grams and kilocalories. All statistical analyses were carried out using StatView 5.0 (SAS Institute, Cary, NC) statistical software. Data are presented as group mean values (±S.E.M.). As each animal received each treatment, a one-factor ANOVA with repeated measures was used, followed by Fisher's least significance test. A P value <.05 between group mean values was considered statistically significant.

3. Results

Analysis of feeding data for all animals regardless of their diet preference (Table 2) revealed that all three doses of N/OFQ (0.3, 1 and 3 nmol) used in our study were effective in increasing total food consumption (P=.0347, P=.0017 and P=.0004, respectively), as well as the intake of the high-fat diet (P=.0412, P=.0328 and P=.0127, respectively). High-sucrose diet intake was elevated in rats treated with 1 and 3 nmol N/OFQ (P=.0046 and P=.0020, respectively).

A different pattern of feeding response was observed when animals were divided into three groups based on their diet preference (Fig. 1). No dose of intracerebroventricularly administered N/OFQ had an effect on food intake in "neutral" and sucrose-preferring rats: N/OFQ did not alter intakes of the high-sucrose or high-fat diet, nor did it affect the cumulative intake of both diets.

In contrast to sucrose-preferring and neutral animals, fat-preferring rats injected with N/OFQ exhibited a hyperphagic response. In this group, 1 and 3 nmol N/OFQ stimulated the cumulative intake of the high-sucrose diet (P=.0125 and P=.0088, respectively), and all three doses of the peptide were effective in increasing the intake of high-fat diet (0.3 nmol, P=.0448; 1 nmol, P=.0378; and 3 nmol, P=.0039).

4. Discussion

Studies published to date have consistently shown that centrally administered N/OFQ induces food intake (Pomonis et al., 1996; Stratford et al., 1997; Leventhal et al., 1998; Polidori et al., 2000). However, the few feeding-related behavioral models used so far have not been sufficient to clarify whether the role of N/OFQ in food intake regulation resembles that of "classical" opioid peptides.

The current study confirms that intracerebroventricular N/OFQ evokes a moderate increase in feeding. Analysis of data for all animals regardless of their diet preference showed that 0.3 nmol N/OFQ significantly increased total food consumption. Noteworthy, the dose of N/OFQ necessary to induce feeding in our experiment was lower than in previous studies, in which 1 and 3 nmol N/OFQ were typically established as minimum effective doses (Pomonis et al., 1996; Polidori et al., 2000). This discrepancy may be attributed to differences in the consistency (powder) and palatability of the diets used in the current project versus foods supplied in the earlier experiments (pellets; neutral flavor) (Pomonis et al., 1996; Stratford et al., 1997; Leventhal et al., 1998; Polidori et al., 2000). However, it is also possible that, simply, a large number of animals (larger than in other studies) and a repeated-measures paradigm allowed us to achieve significance with relatively low doses of the peptide.

Probably, the most extensively studied and established function that opioids play in the control of consummatory behavior is their involvement in "reward"-driven feeding. Numerous injection studies have shown that stimulation of the opioid receptors leads to an increase in the consumption of preferred/palatable diets (Levine and Billington, 1997). It also affects selection of ingestants that differ in macronutrient composition (Welch et al., 1994). Opioids and opiates are particularly effective in increasing the intake of foods high in fat. Consequently, morphine-injected rats, given a choice between a high-carbohydrate and high-fat diets, increase intakes of both, although morphine has a greater effect on the consumption of the high-fat diet (Gosnell et al., 1990). In the present study, we established that 0.3 nmol N/OFQ increased the intake of the high-fat diet, whereas the dose of 1 nmol was necessary to stimulate the consumption of the high-sucrose diet. Thus, the initial analysis of diet selection in animals that had not been divided based on their diet preference could suggest that N/OFQ, indeed, influences feeding in a manner very similar to opioid peptides, having a more potent effect on the consumption of the high-fat diet.

Gosnell et al. (1990) showed a strong relationship between baseline preference toward diets differing in their macronutrient composition and drug-induced diet selection. They observed that morphine increased the intake of a high-fat diet in fat-preferring rats and increased ingestion of a high-carbohydrate diet in carbohydrate-preferring animals when both diets were presented at the same time. Thus, opioids are thought to stimulate the intake of a preferred diet rather than to increase the intake of a specific macronutrient (Gosnell et al., 1990).

The results of the present study, taking into account initial diet preferences, indicate that N/OFQ does not affect the intake of (thus, preference toward) palatable diets differing in a macronutrient content in a similar way to opioids. In contrast to feeding effects established for opioid peptides, N/OFQ did not increase the intake of a more preferred, high-sucrose diet in sucrose-preferring animals. In fat-preferring rats, N/OFQ increased the intake of both diets to a similar degree. A lower dose of the peptide (0.3 nmol) was sufficient to stimulate the intake of the high-fat diet in those

rats, whereas a 1-nmol dose of N/OFQ was necessary to increase the ingestion of high-sucrose diet or affect the cumulative intake of both diets. These data suggest that the N/OFQ system is unlikely to be involved in the mediation of "rewarding" aspects of feeding, thus, the role of N/OFQ in the regulation of food intake appears to differ from that played by opioid peptides.

This outcome is somewhat surprising, as initial studies have suggested that the N/OFQ and opioid systems may share a certain degree of interaction in feeding control. This notion was based on several findings, such as that N/OFQ and opioids evoke similar orexigenic (Pomonis et al., 1996; Leventhal et al., 1998) and antiaversive effects (Olszewski et al., 2000b) and that N/OFQ-induced feeding can be blocked by opioid receptor antagonists (Pomonis et al., 1996; Leventhal et al., 1998). Importantly, N/OFQ does not bind to opioid receptors, nor can the ORL1-R be activated by opioid receptor ligands (Sim et al., 1996), which excludes a possibility that feeding effects observed following the injection of N/OFQ and opioid ligands are due to their action via the same receptor. Our data indicate the lack of involvement of N/OFQ in the "rewarding" aspect of ingestive behavior, and they are corroborated by the preliminary results reported by Polidori et al. (2000) who observed that intracerebroventricular N/OFQ, in contrast to opioids, does not increase the intake of the highly palatable sucrose solution available 30 min/day to rats that have ad libitum access to food and water (Polidori et al., 2000). In addition, intracerebroventricularly administered N/OFQ has been found to reduce the intake of ethanol in alcohol-preferring rats—an effect opposite to that evoked by opioid receptor agonists (Ciccocioppo et al., 1999). Thus, N/OFQ's action on consummatory behavior appears to have an extremely wide range, from opioid-like to anti-opioid effects.

Unfortunately, data on functional interactions between N/OFQ and opioids obtained in feeding studies are too limited to provide us with a complete explanation of this phenomenon. However, some light can be shed on this issue using a wealth of information achieved in experiments on the similarly ambiguous role of N/OFQ in pain perception. Identification of N/OFQ, homologous to opioids, which are known for their antinociceptive effects, sparked interest in N/OFQ's involvement in nociception. Surprisingly, intracerebroventricular N/OFQ caused an increase in pain sensitivity (Zhu et al., 1997). Results of subsequent studies created more confusion, as intracerebroventricular N/OFQ was found to provoke hyperalgesia (Suaudeau et al., 1998), analgesia (Yamamoto et al., 1997), hyperalgesia followed by analgesia or no effect at all (Vanderah et al., 1998). An astonishing range of discrepancies in the outcome of those studies has been attributed to differences in pain tests, animal species or strains, drug doses and control groups/conditions used in the experiments. Although the consensus about the precise function of N/OFQ in the modulation of nociception has not been reached, there is a general agreement that intracerebroventricular N/OFQ does not affect pain sensitivity in a similar manner to opioids. In fact, it has been shown that intracerebroventricular N/OFQ reverses the analgesic actions of morphine, which suggests that N/OFQ may act as an "antiopioid" under some conditions (Mogil et al., 1996). These results are in concert with conclusions of anatomical analyses: Distribution of N/OFQ-ORL1 within the central pathways exhibits only a moderate level of resemblance to that of opioid receptors and their endogenous ligands (Schulz et al., 1996). These findings indicate that N/OFQ's action on pain sensitivity, to a large degree, does not correlate with that of (and does not depend on) opioid peptides. It should be emphasized that the range of discrepancy in N/OFQ's feeding effects resembles that seen in nociception studies. Thus, a similar conclusion can be drawn as to the possible interaction between the N/OFQ and opioid systems in food intake regulation: N/OFQ affects ingestive behavior independently of opioids under many conditions. Under those conditions where the N/OFQ–opioid crosstalk appears to take place, N/OFQ may positively (e.g. in aversion or chow intake) or negatively (intake of a preferred ingestant, ethanol) interact with opioid peptides. This issue needs to be further elucidated by employing methods (e.g. selective opioid receptor ligands instead of naltrexone/naloxone or specific site injections) that would take into account the complexity of the N/OFQ and opioid systems.

In the current study, it is particularly striking that intracerebroventricular N/OFQ did not have any effect on the intake of either of the two diets or the cumulative intake of both diets in sucrose-preferring and "neutral" rats. Hyperphagic action of N/OFQ could be observed only in animals that exhibited strong preference toward the high-fat diet. N/OFQ administration resulted in a similar increase in the consumption of both diet types in these rats. Phenomena of contrasting effects of an orexigenic peptide on food ingestion in animals that differ in macronutrient preference have been rarely reported, thus, mechanisms underlying these processes are not understood. We would like to propose a possible N/OFQ–leptin interaction as one of the potential avenues for the future research. Preferential intake of a high-fat versus high-carbohydrate diet over a period of several weeks may lead to a greater deposition of subcutaneous and visceral fat without causing weight gain (Smith et al., 1998). The size of the fat mass correlates well with the release of adipocyte-secreted hormone, leptin. Leptin is a peripheral signal that, through binding to its receptors located in several feeding-related central sites, regulates food intake and energy expenditure to maintain proper energy reserves. Exogenously administered leptin inhibits food consumption (Billington and Levine, 1996; Van Heek et al., 1996; Levine and Billington, 1997). The fact that N/OFQ stimulates feeding in fat-preferring rats exposed for a relatively long time to a high-fat diet (thus, rats presumably characterized by a high-fat depot) allows us to formulate a hypothesis that N/OFQ and leptin, peptides that produce opposing consummatory responses, may interact in the regulation of food intake. In addition, the

colocalization of receptors for leptin and N/OFQ in some feeding-related brain sites (Neal et al., 1999) suggests a possibility that these two peptides may constitute a counterbalancing system in food intake control.

In conclusion, the results of our studies indicate that intracerebroventricular N/OFQ induces hyperphagia only in rats that exhibit preference toward a high-fat diet. This peptide is not particularly effective in increasing the intake of a preferred diet. Thus, orexigenic actions of N/OFQ do not appear to parallel those of opioid peptides.

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