Published in final edited form as:
Physiol Behav. 2010 July 14; 100(5): 429–437. doi:10.1016/j.physbeh.2010.02.027.

Preference or fat? Revisiting opioid effects on food intake

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Abstract

It is well established that opioid signaling in the central nervous system constitutes a powerful stimulus for food intake. The role of opioids in determining food preference, however, is less well defined. Opioids have been proposed to promote intake of preferred foods, or, alternatively, to preferentially increase consumption of fat. In the present manuscript, I comprehensively review results from previous studies investigating this issue. Data from these studies suggests a mechanism for opioid action that may reconcile the previously proposed hypotheses: opioid effects on food intake do appear to be largely specific for fat consumption, but individual animals' sensitivity to this effect may be dependent on baseline food preferences. In addition, I highlight the possibility that the selectivity of endogenous opioid effects may importantly differ from that of exogenous agonists in the degree to which baseline preferences, rather than macronutrient intake, are altered.

Opioid signaling promotes food intake and alters food preferences

Signaling through central opioid receptors has potent effects on food intake. In sated animals, opioid administration can drive voracious feeding persisting for hours [1]. However, this hyperphagia is not indiscriminate. A fascinating aspect of opioid-induced consumption is its specificity, as opioid effects are typically most potent for highly palatable foods, particularly those that are sweet or fatty (or both) [2–4]. Studies of rodent models have shown that opioid agonists signaling at mu and kappa opioid receptors (MOR and KOR) increase consumption of reinforcing, energy-dense foods, but have little effect on consumption of less palatable alternatives [5–7]. Conversely, opioid antagonists suppress consumption of preferred foods but have smaller effects on nonpreferred foods [8]. Results reported by Cooper and Turkish [9] offer a particularly vivid illustration of the selectivity of opioid signaling effects. When offered a choice of a highly palatable food (cookies) or chow, rats consumed very little of the latter (<5% of total intake). Systemic administrations of the nonspecific opioid antagonist naltrexone (NTX) decreased cookie consumption but had quite the opposite effect on chow intake, significantly and dose-dependently increasing the total amount consumed. These data show that blockade of opioid signaling does more than to simply suppress consumption and provide evidence that opioids play a significant role in determining food preference when choosing between alternatives.

Several lines of evidence support the hypothesis that changes in food intake are mediated by opioid effects on tastant palatability signaled through orosensory cues. Among these is the observation that opioid effects are robust in sham feeding animals, in which post-ingestive cues are minimized [10–12]. Additional evidence comes from taste reactivity measures, facial displays correlated with the hedonic value of tastants [13]. Opioid antagonists decrease positive reactivity displays in response to sucrose [14], while morphine increases positive taste

reactivity displays to sucrose and decreases aversive responding to bitter quinine [14–16]. Together, these data show that orosensory cues are a sufficient substrate for opioid modulation of intake, consistent with a palatability-based mechanism of action. Psychophysical studies in human subjects provide additional support for this hypothesis, as opioid antagonists decrease subjective reports of taste reward without altering measures of taste quality [17,18]. Studies of the mechanisms and circuitry underlying opioid effects on consumption have been explored at length in several excellent reviews [19–23].

Role of opioids in macronutrients selection

Despite considerable progress in characterizing the mechanisms and neural pathways underlying opioid-induced food intake, the role of opioid signaling in determining macronutrient preference – an early area of study – remains unclear. Two principal arguments have been advanced: that opioid signaling increases consumption of preferred foods, independent of macronutrient content [2,24] or that opioid signaling preferentially increases consumption of fat [25,26] (More precisely, opioids have in the latter case been proposed to increase consumption of foods high in fat, as well as fat itself. For brevity, I use the term “fat” in this manuscript to refer to fats and fatty foods). Studies by Kanarek and colleagues were among the earliest to explore in detail the effects of opioids on macronutrient preference. In their experiments, rats were allowed to self-select daily fat, carbohydrate, and protein intake. Under these conditions, systemic morphine administration typically elevated consumption of fat, and in many cases also reduced carbohydrate intake, suggesting that opioid signaling increased preference for fat [25,27,28] (Generally, these manipulations had few effects on protein intake). However, fat is highly palatable for rodents, and often preferred over alternative calorie sources. Under conditions of baseline fat preference, the role of fat content is confounded with that of preference; dissociating these variables is necessary to assess a potential role for fat independent of preference. A number of investigators have addressed this issue by first characterizing animals’ baseline preference for a high vs. low fat food option, and subsequently testing opioid effects on rats with disparate carbohydrate or fat preferences [29–31]. Results from these experiments provide support for the notion that opioids alter consumption of preferred foods. Glass et al (1996) have reported, for instance, that naltrexone decreases intake specifically of preferred foods – carbohydrate in carbohydrate-preferring rats, and fats in fat-preferring animals.

In considering these hypotheses, it is important to note that opioid signaling clearly does increase consumption of non-fatty, highly reinforcing foods. Many studies have documented that opioid agonists potentiate sweet tastant intake and thus clearly show that opioid effects cannot be considered to apply exclusively to fat intake [2,5,32,33]. Rather, uncertainty over opioid effects on macronutrient consumption remains specifically in the context of food choice when food options differ substantially in the degree to which they are preferred and/or in their macronutrient content. Specifically, it is unclear whether opioid effects on intake in choice paradigms are primarily dictated by the degree to which food options are preferred, or how much fat they contain.

Previous studies addressing this issue have differed widely in their experimental approach, drugs (and doses) used, and conventions used to report data. This heterogeneity hinders efforts to compare studies and to draw general conclusions about the selectivity of opioid effects for fats vs. preferred foods. In this review, I have compiled and standardized data from rodent experiments in which opioid signaling was studied (using both agonists and antagonists) specifically in the context of food choice. This analysis is limited to investigations in which opioid effects were studied in experimental paradigms that allowed direct comparison of opioid effects on fat vs. carbohydrate preference. Typically these experiments took one of three formats – opioid effects were measured during a) free choice of simultaneously available

protein, carbohydrate, and fat macronutrients; b) free choice of simultaneously available high fat vs. low fat food options; or c) no-choice paradigms, in which only a single food option was made available, but in which opioid effects on both high and low fat food options were studied in successive experiments, enabling comparison of opioid effects on these foods under identical drug and dosing conditions.

Where available, published values were used in the results summarized in Tables 1 (opioid agonists) and 2 (antagonists). If exact values were not presented in the paper, consumption levels were estimated directly from graphs. Values are reported in kilocalories (kcal) of consumption, except where noted in table footnotes. Data was included only for doses that had statistically significant effects on intake as reported by the authors. Protein consumption was ignored in assembling these data as this was unchanged by drug treatment in the large majority of studies (but not in all; see [34,35]). The goal in assembling these data was not to undertake a quantitative meta-analysis of opioid effects, but rather to aggregate and standardize reporting of the experimental data to facilitate comparison across studies, and draw general conclusions about whether opioid signaling selectively elevates consumption of preferred foods, or instead, those high in fats.

Effects of opioid agonists on diet choice

Table 1 summarizes opioid agonist effects on diet choice. In most experiments, rats either self-selected macronutrient intake through consumption of freely available fat, carbohydrate, and protein rations, or chose between high and low fat food options. (For details of experimental paradigms, see table legend and footnotes). For each experiment, the carbohydrate and fat composition of pre-drug and post-drug intake, as well as the macronutrient composition of the drug-induced change in consumption, are summarized. The last column provides the most salient measure, of the percentage of the drug–induced increase in consumption that could be attributed to fat. Thus, for instance, in the first study summarized (Barnes et al, 2006, experiment 1a; for this and other studies, individual experiments are identified by the designation indicated in the first column for ease of reference), [D-Ala2, N-MePhe4, Gly-ol]-enkephalin (DAMGO) infusion (0.025 μg) into the 3rd ventricle caused a 5 kcal decrease in carbohydrate intake, and a 6 kcal increase in fat intake. 100%, then, of the increased consumption could be attributed to fat.

In a substantial majority of studies, opioid agonists increased intake through preferential increases in fat consumption. Indeed, in many studies, increased consumption occurred exclusively through fat intake. In seventeen of the forty experiments included in Table 1, 100% of increased consumption occurred via fat intake for all drug doses. Adopting a less stringent criterion for preferential fat effects, in 34/40 (85%) experiments >50% of agonist-induced increases in consumption could be attributed to fat intake for all drug doses. These preferential effects on fat intake occurred under conditions which spanned experimental conditions, including different baseline macronutrient preferences, infusion sites and the drug tested. Notably, in many experiments agonist administration decreased carbohydrate intake, while simultaneously increasing fat intake (e.g., experiments 1a, 5a–b, 6, 7a–b).

In addition to this overall pattern, examination of the data suggests two additional trends. The first of these is the apparent dose-dependent selectivity of opioid effects. In thirteen experiments in which multiple drug concentrations were used, the effect of the drug was dependent on the dose tested. (In seven other experiments [1a–b, 7a–b, 15c, 17a–b] multiple drug doses were used and all increased consumption entirely through fat intake). In a majority of these studies, the highest dose used resulted in greater selectivity for fat consumption than the lowest dose (11 of 13 studies; Experiments 3a–c, 4a–e, 14b, 15a–b). Some of these dose-dependent differences were quite small (e.g., 91% vs. 95% of increase due to fat after 3 and

10 mg/kg morphine in experiment 3c), but many were substantial (e.g., 28% vs. 59% of increase due to fat after 3 and 10 mg/kg morphine in experiment 3a). The two exceptions to this pattern occurred in the only study in which multiple doses of KOR-specific agonists were tested (14a and 14d). Because this was the only study in which dose-response effects were studied for KOR agonists, it is difficult to know if KOR and MOR agonists (for which 11/11 studies showed greatest selectivity for the low dose) differ in this dose-dependence.

The second trend is that baseline preference played a role in determining drug effects. In six sets of experiments (1a–b, 3a–c, 4a–e, 13a–b, 15b–c, 16a–b) baseline macronutrient preference was identified (animals were classified as carbohydrate or fat preferring), or baseline preference was manipulated by using fat sources of varying palatability. In these experiments, opioid effects on fat intake were generally less robust under conditions in which fat was less preferred. For instance, in experiments by Glass et al (1999: Experiments 3a–c), the fat component of a high fat chow was derived from corn oil, lard, or vegetable shortening. Groups of rats received a choice of one of these high fat chows paired with a high carbohydrate diet. Comparing relative intake of the high fat chow across groups, corn oil was the least preferred (comprising 37% of baseline intake) and shortening the most (99%). The effects of low dose (3 mg/kg) morphine administration varied as a function of preference for the fat source, selectively increasing fat intake when the source was lard or shortening but not corn oil (92%, 91%, and 28% of increased intake due to fat, respectively).

This result suggests that preference plays some role in determining opioid effects on fat intake, at least for a single concentration of morphine. Interestingly, however, higher doses of morphine preferentially increased fat consumption for all fat sources, both preferred (lard and shortening) and nonpreferred (corn oil). Thus there was a dose dependent increase in the degree to morphine potentiated fat intake, even when the fat source was nonpreferred corn oil (59, 99, and 95% of increased consumption due to fat for corn oil, lard, and shortening, respectively, for high dose of 10 mg/kg).

This result was not anomalous. Similar results were obtained by Gosnell et al (1990: Experiments 4a–e), where rats were divided into groups reflecting baseline macronutrient preference. The effects of systemic morphine administration were correlated with baseline preference, with strong fat selective increases in consumption apparent for groups with highest baseline fat preference (Experiments 4b and 4e). However, for each group – including those in which rats showed baseline preferences for carbohydrate (4a and 4c) – the degree to which morphine selectively increased fat consumption was determined not just by preference, but by dose. Larger opioid doses more selectively increased fat intake in all groups. A similar pattern of results was obtained by Ookuma et al (1998; Experiments 13a–b) and Zhang et al (1998; Experiments 15b–c). In the remaining two studies in which different baseline fat preferences were present (1a–b and 16a–b), fat comprised 100% of agonist-induced increased intake, regardless of animals' baseline fat or carbohydrate preference.

These data suggest that baseline preferences can play a (perhaps modest) role in determining opioid agonist effects: in some but not all cases, lower baseline preference for fat resulted in an attenuated response to agonist effects in preferentially promoting fat intake. While supporting a modulatory role for baseline preference, these data provide little support for the hypothesis that opioid agonists increase consumption of preferred foods. Rather, they suggest that the predominant effect of opioid agonists is to increase fat intake, but sensitivity to this effect may be related to preference, a possibility previously suggested by Kelley et al [30]. Consistent with this model, data summarized in Table 1 shows that rats with strong baseline preferences for fat showed a strong, preferential increase in fat intake with low doses of opioid agonists, while higher drug doses were required to produce similarly selective effects in rats with baseline preferences for carbohydrates.

Do these trends offer some insight into the conditions under which opioid agonists did not preferentially increase fat intake? In six experiments, fat comprised ≤50% of agonist-induced intake for at least one of the drug doses used (experiments 2, 3a, 4a, 4c, 4d, and 13b). In three of these six experiments, this effect occurred for just one dose of two or more tested (experiments 3a, 4a, and 4d). In these cases, morphine preferentially increased preferred carbohydrate intake after the lower dose – but nonpreferred fat after the higher dose. Thus, for example, in Experiment 4a, 2 mg/kg morphine administration in carbohydrate-preferring rats increased food intake principally through carbohydrate intake rather than fat (83% of increased intake due to carbohydrate consumption). A higher dose of 10 mg/kg, however, resulted in a reversal of these proportions, with 86% of increased food intake due to fat. In each of these three experiments, fat was not the animals' preferred macronutrient (4a, 4d), or a less preferred fat source was used (3a). The results observed in these three cases fit the pattern of a quantitative (reduced sensitivity to opioid effects) but not qualitative (agonists still preferentially increase fat consumption) change in opioid agonist effects produced by baseline preference.

For the remaining three experiments, a speculative possibility is that administration of higher drug doses would have also yielded preferential effects on fat intake. Two of these studies (experiments 2 and 13b) tested the effect of only a single dose of agonist. The third (experiment 4c) tested two doses, both of which produced mainly increases in carbohydrate intake (2 and 10 mg/kg morphine, causing 17 and 20% of increased intake due to fat respectively).

On balance, then, these data are most consistent with the notion that opioid agonists preferentially increase fat intake, supported by two main lines of evidence: 1) in most studies, a clear-cut preferential effect of opioids agonists in increasing fat intake was apparent, as all or nearly all of drug-induced intake could be attributed to fat consumption; and 2) baseline preferences modulated the sensitivity of individual animals' response to opioids, but did not qualitatively change opioid effects.

Effects of opioid antagonists on diet choice

Opioid antagonist effects (Table 2) were more variable than those produced by agonists in the degree to which drug-induced changes in intake (in this case, decreases in consumption) were expressed through changes in fat intake. In contrast to agonist effects, antagonist-induced changes could rarely be attributed entirely to changes in fat consumption (only 6 of 37 studies for antagonists, compared to 17 of 40 for agonists, 16% vs. 43%). Nonetheless, the prevailing trend in the data was similar to that present for opioid agonists in Table 1. In a majority of studies, preferential effects of opioid antagonists on fat intake were apparent – more than 50% of antagonist-induced decreased intake could be accounted for by changes in fat consumption (29 of 37 studies; 78%; 1a–b, 2, 3a–b, 4, 5, 6, 7a, 8, 9a, 9c–d, 10, 11, 12, 13a–b, 13d, 14, 15, 16a, 16c, 17a–b, 18a, 19, 20a–b).

As was the case with agonists, the degree to which antagonists preferentially altered fat consumption appeared to be dose-dependent. Antagonist doses were, however, inversely correlated with preferential effects on fat - the greatest selectivity for effects on fat consumption occurred after administration of the lowest antagonist dose. In many cases, a low dose of antagonist preferentially decreased fat consumption, but higher doses decreased intake less specifically. This was true of 11 of 16 experiments in which multiple doses were used and effects on macronutrient intake varied as a function of dose (greatest fat selectivity with lowest dose:1b, 3a, 8, 9c–d, 11, 12, 13b, 13d, 14, 16a). In another five studies, the greatest selectivity of antagonists' effects on fat consumption did not occur with the lowest dose (9a, 9b, 13c, 16b, 18a). However, in two of the latter studies (9a and 9b), low doses tested in experiment 9a were on average much more selective in their effects on fat intake than high doses tested in experiment 9b, using the same paradigm and the same rats (but different injection schedules).

Including these two studies, then, 13 of 16 experiments showed a pattern of relative selectivity for fat-specific effects when antagonists were administered at low doses.

This pattern of results suggests that the dose of antagonist employed can be a critical determinant of the degree to which fat-specific effects are detected. Low doses of antagonists are more likely to specifically reduce consumption of high fat food options, but the effects of high doses may be largely non-specific, a possibility noted by previous investigators [24]. Even at relatively modest concentrations, opioid antagonists can be aversive [36], likely resulting in decreased intake of all food options.

Manipulations of baseline preference had mixed effects on the impact of opioid antagonists. In three experiments, rats were divided by baseline preference into fat and carbohydrate preferring groups: experiments 7a–b, 17a–b, and 20a–b. Of these three, strong effects of baseline preference on antagonist effects were apparent in one study (7a–b); in the other two cases, naltrexone administration almost exclusively reduced fat intake. In experiments 7a–b, the kappa antagonist norbinaltorphimine (nor-BNI) selectively reduced fat consumption in fat-preferring Osborne-Mendel rats (7a) but reduced intake in carbohydrate-preferring S5Bl/P rats almost exclusively through decreases in carbohydrate intake (7b; only 13% of decrease due to changes in fat intake). It is likely that floor effects contributed to this result, as the latter group of rats consumed very little fat to begin with (only 8% of baseline intake was fat), and thus decreases in intake of necessity were predominantly due to changes in carbohydrate intake. This is a general concern in studies utilizing antagonists, where the overall effect of the drug is to reduce consumption. When strong baseline preferences are present, selective effects of antagonists in reducing consumption of the nonpreferred food option are unlikely to be detected.

In two other series of studies (experiments 17a–b and 20a–b), preference was manipulated by altering the carbohydrate source (either highly preferred sucrose or less preferred starch) and NTX was infused either into the CeA (17a–b) or the PVN (20a–b). Interesting, this manipulation had different effects in these two sites. NTX administration in the CeA (17a) preferentially decreased fat intake when the carbohydrate source was starch, conditions under which a strong baseline preference for fat existed. When sucrose instead comprised the carbohydrate option, naltrexone preferentially decreased carbohydrate intake. When infused into the PVN at similar doses, baseline preference had little apparent impact on NTX effects, as the drug decreased intake in both experiments (sucrose- and starch-derived carbohydrates) occurred preferentially through decreases in the carbohydrate source. However, this latter finding is somewhat at odds with later results obtained by the same laboratory (Naleid 2007; Experiment 19a–b), demonstrating that NTX infusion in the PVN at identical doses (100 nmol) preferentially reduced fat intake for both carbohydrate and fat preferring rats.

Summarizing antagonist data, there is evidence supporting two conclusions: 1) in a majority of experiments, blockade of endogenous opioid signaling preferentially reduced fat intake; and 2) low doses of antagonists more specifically reduced fat intake than higher doses. The role of baseline preference in determining opioid antagonist effects remains unclear, however, with some evidence for strong preferential effects on fat intake in a few experiments (regardless of preference), and in other cases suppression of preferred intake regardless of macronutrient content.

Conclusions and caveats

Comparing data from Tables 1 and 2 suggests an overarching similarity between opioid agonist and antagonist effects. For both agonists and antagonists, fat-selective effects predominate across studies, providing the main evidence in favor of a preferential effect of these

manipulations on fat intake. The apparent dose dependence of these effects, in which the drug concentration was directly correlated with specificity for agonists and inversely for antagonists, provides additional support. Finally, baseline preference may determine sensitivity to drug effects, without apparent changes in the degree to which these are specific for fat intake.

The evidence for an effect of baseline preference on sensitivity to opioid effects is more compelling for agonists than antagonists. In part, this is due simply to the smaller number of studies making use of antagonists. However, it is quite possible that antagonist effects may differ fundamentally from agonist effects in their effects on preferred foods (independent of fat). Endogenous opioid signaling is highly plastic, and can be altered by learned food preferences [37] as well as anticipation of food [38]. In a recent study, we trained two groups of rats with daily intervals of sucrose access [37]. One group received successive presentation of 4% sucrose in two 15 minute intervals, while the other received 4% sucrose followed by a much sweeter and more preferred 20% sucrose solution. Comparing 4% sucrose consumption across these rats, the latter group's intake was substantially lower (though still robust), as might be expected. When these groups were injected with NTX, intake of the 4% solution was strongly decreased in the first group (4-4) but not the second group (4–20), where instead consumption of the twenty percent sucrose solution was suppressed. Thus, endogenous opioid signaling quite clearly can reflect relative preference for an identical calorie source, at least under certain conditions, and this may account for some of the results included in Table 2 (e.g., experiment 7a–b).

Several caveats attend to my conclusions. The first of these is that I do not attempt a rigorous statistical analysis of the assembled data, nor, as might be better still, a quantitative meta-analysis, which is beyond the scope of this review. Nonetheless, the standardized presentation of experimental results provides a platform for comparing results across disparate studies. Because opioid effects are quite robust (particularly for agonists), comparison of these results provides a useful starting point for identifying prevailing trends in the data.

An additional potential concern is that baseline preference effects were considered only in studies which either grouped rats by baseline preference, or explicitly manipulated preference. The measures of baseline preference included in Tables 1 and 2 (first three columns) are averages, calculated from all rats included in each experimental condition. A considerable amount of information is lost in this representation, as correlating individual rats' baseline diet preferences with opioid effects offers the most direct and powerful method of analyzing the importance of baseline preference on opioid effects. Unfortunately, individual animals' raw data for these studies is not available, so conclusions about the role of baseline preference are necessarily drawn from a small group of studies.

Several investigators have carried out correlational analyses of baseline preference on opioid-induced intake, and all found that these measures were significantly correlated [29,30,39]. This might appear to argue against a preferential effect on fats, but this correlation alone does not disprove a macronutrient effect. If, as I conclude, baseline preference alters sensitivity to opioid effects, these correlations are expected. A prediction of this hypothesis is that there should be a dose-dependent upward shift in these correlations – i.e., in the case of agonist administration, preferential increases in fat intake should occur for all rats with higher drug doses, though the magnitude of this effect may be a function of baseline preference.

Finally it is noteworthy that with respect to food intake, the effects of stimulating different opioid receptors (i.e., mu and kappa receptors) in different brain regions (PVN and NAcc) had similar effects. Signaling through both receptors at both sites (as well as systemically) increased intake predominantly through increases in fat consumption [30,31,40]. This is surprising, given that neural processing events in the PVN and NAcc are typically thought of as participating in

distinct aspects of neural function, contributing to homeostatic and hedonic processing, respectively [1,41,42]. In addition, signaling through kappa and mu receptors typically has divergent, often have opposing effects. Mu signaling in the ventral tegmental area, for instance, is highly reinforcing, while kappa signaling in that brain region is aversive [43]. Opioid signaling in distributed brain regions acting at distinct receptors may thus affect very different aspects of neural processing relevant to control of food intake (e.g., homeostatic and hedonic processing, and possibly other types as well) that ultimately converge to elevate palatable food intake [22].

Acknowledgments

I gratefully acknowledge Dr. Richard Bodnar and Dr. Rebecca Corwin for valuable comments on this paper. This work was supported by the Office of the Vice-President for Research at the University of Utah; NARSAD; the March of Dimes; and by the National Institute of Mental Health.

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Table 1

Opioid agonists

From left to right, columns indicate the experiment number (**Expt,** included for ease of referencing specific experimental conditions in the text); the citation for each experiment (**Reference**); the motivational state under which the animals were tested (**Drive**); the test diet (**Diet**); animals' baseline macronutrient preference (**BL pref**); notes regarding experimental conditions (**Notes**; further explanation of select experiments is included in table footnotes); the drug used (**Drug**), the doses tested (**Dose**); the site at which the drug was infused (**Site**); pre-drug, baseline macronutrient intake (**Pre**, in kcal consumed), broken down into carbohydrate/low fat intake (**C**), fat/high fat intake (**F**), and the percent of total consumption due to fat (**% F**); post-drug intake (**Post**); and the drug-induced change in intake (**Change**), broken down into macronutrient components (**C** and **F**), the total *increase* in consumption caused by drug administration (**Total**), and the percent of that drug-induced *increase* (ignoring any decreases in intake of individual macronutrient) that could be attributed to increased fat consumption (**% F**). From top to bottom, experiments are arranged by the pharmacology of the drug tested and the site of administration, and include, respectively, MOR and KOR-specific drugs, and systemic/ICV infusion and site-specific CNS infusions. Abbreviations used in each column are summarized below, again moving from left to right. Drive: **AL**, ad lib fed; **6 h res**, restricted to 6 hours consumption daily, **20 h dep**, 20 hour food deprivation. Diet: **HF v LF**, free choice of high fat (HF) and low fat (LF) diet options presented simultaneously; **Macro**, free choice of protein, carbohydrate and fat macronutrient options presented simultaneously; **HF or LF**; high fat and low fat diet intakes assessed in separate experiments. BL pref: **C**, carbohydrate preferring; **F**, fat preferring; **C=F**, fat and carbohydrate equally preferred; C **(S5)**, carbohydrate preferring S5B/Pl rat strain; **F (OM)**, fat preferring Osborne-Mendel rat strain. Drug: **DAMGO**, [D-Ala2, N-MePhe4, Glyol]-enkephalin; **Mor**, morphine; **Butor**, butorphanol; **Ketocyc**, ketocyclazocine; **Dyn A**, dynorphin A. Site: **3rd v**, third ventricle; **Sys**, systemic administration; **LV**, lateral ventricle; **NAcc**, nucleus accumbens; **PVN**, paraventricular nucleus. Horizontal lines separate different experimental conditions. Note that for experiments designated **HF or LF**, animals were not given a choice of macronutrients, but opioid effects on these different diet options were compared in separate experiments. Thus figures presented in the table for these experiments (pre, post and change) represent comparison across groups of animals of the relative magnitude of opioid effects on these diets.

										Pre (kcal)			Post (kcal)			Change (kcal)			
	Expt	**Reference**	**Drive**	**Diet**	**BL pref**	**Notes**	**Drug**	**Dose**	**Site**	**C**	**F**	**% F**	**C**	**F**	**% F**	**C**	**F**	**Total ↑**	**% F**
MOR	1a	Barnes et al. 2006	AL	HF v LF	C (S5)		DAMGO	0.025 μg	3rd v	5.0	0.0	**0**	0.0	6.0	**100**	−5.0	6.0	6.0	**100**
								0.25	3rd v	5.0	0.0	**0**	0.0	11.0	**100**	−5.0	11.0	11.0	**100**
								2.5	3rd v	5.0	0.0	**0**	0.0	9.0	**100**	−5.0	9.0	9.0	**100**
	1b				F (OM)		DAMGO	0.25 μg	3rd v	0.0	6.0	**100**	0.0	14.0	**100**	0.0	8.0	8.0	**100**
								2.5	3rd v	0.0	6.0	**100**	0.0	30.0	**100**	0.0	24.0	24.0	**100**
	2	Bhakthavatsalam et al. 1986	AL	macro			Mor	2.5 mg/kg	Sys	4.0	1.0	**20**	6.0	2.5	**29**	2.0	1.5	3.5	**43**
	3a	Glass et al. 1999[1]	AL	HF v LF		F=corn oil	Mor	3 mg/kg	Sys	2.2	1.3	**37**	6.3	2.9	**32**	4.1	1.6	5.7	**28**
								10	Sys	2.2	1.3	**37**	6.2	7.1	**53**	4.0	5.8	9.8	**59**
	3b					F=lard	Mor	1	Sys	0.0	2.8	**99**	0.8	9.6	**92**	0.8	6.8	7.6	**90**
								3	Sys	0.0	2.8	**99**	1.0	14.0	**93**	1.0	11.2	12.2	**92**
								10	Sys	0.0	2.8	**99**	0.3	21.6	**99**	0.3	18.8	19.1	**99**
	3c					F=shortening	Mor	3	Sys	1.8	2.6	**59**	2.8	12.2	**81**	1.0	9.6	10.6	**91**
								10	Sys	1.8	2.6	**59**	2.7	19.5	**88**	0.9	16.9	17.8	**95**
	4a	Gosnell et al. 1990	AL	macro	C		Mor	2 mg/kg	sys	0.0	1.0	**100**	5.0	2.0	**29**	5.0	1.0	6.0	**17**

									Pre (kcal)			Post (kcal)			Change (kcal)			
Expt	**Reference**	**Drive**	**Diet**	**BL pref**	**Notes**	**Drug**	**Dose**	**Site**	**C**	**F**	**% F**	**C**	**F**	**% F**	**C**	**F**	**Total ↑**	**% F**
							10	sys	0.0	1.0	**100**	0.5	4.0	**89**	0.5	3.0	3.5	**86**
4b				F		Mor	2	sys	0.0	3.0	**100**	1.0	7.5	**88**	1.0	4.5	5.5	**82**
							10	sys	0.0	3.0	**100**	0.5	8.5	**94**	0.5	5.5	6.0	**92**
4c			HF v LF	C		Mor	2	Sys	2.0	2.0	**50**	7.0	3.0	**30**	5.0	1.0	6.0	**17**
							10	Sys	2.0	2.0	**50**	10.0	4.0	**29**	8.0	2.0	10.0	**20**
4d				C=F		Mor	2	Sys	1.5	6.0	**80**	8.0	6.0	**43**	6.5	0.0	6.5	**0**
							10	Sys	1.5	6.0	**80**	5.0	10.0	**67**	3.5	4.0	7.5	**53**
4e				F		Mor	2	Sys	1.0	4.0	**80**	3.0	10.0	**77**	2.0	6.0	8.0	**75**
							10	Sys	1.0	4.0	**80**	2.0	16.0	**89**	1.0	12.0	13.0	**92**
5a	Gosnell et al. 1993[2]	AL	HF v LF		group 1	Chronic mor	2.8 mg/kg/h	Sys	70.0	40.0	**36**	20.0	65.0	**76**	−50.0	25.0	25.0	**100**
5b					group 2	Chronic mor	2.8	Sys	70.0	40.0	**36**	30.0	75.0	**71**	−40.0	35.0	35.0	**100**
6	Marks-Kaufman et al. 1980	6 h res	macro			Mor	30 mg/kg	Sys	25.0	25.0	**50**	5.0	40.0	**89**	−20.0	15.0	15.0	**100**
7a	Marks-Kaufman 1982[3]	6 h res	macro			Mor	1 mg/kg	Sys	40.0	35.0	**47**	25.0	63.0	**72**	−15.0	28.0	28.0	**100**
							10	Sys	40.0	35.0	**47**	20.0	66.0	**77**	−20.0	31.0	31.0	**100**
							20	Sys	40.0	35.0	**47**	20.0	61.0	**75**	−20.0	26.0	26.0	**100**
7b					Isocaloric fat	Mor	10	Sys	47.0	15.0	**24**	35.0	20.0	**36**	−12.0	5.0	5.0	**100**
							20	Sys	47.0	15.0	**24**	30.0	25.0	**45**	−17.0	10.0	10.0	**100**
8	Marks-Kaufman et al. 1990[4]	6 h res	macro			Chronic mor	10 mg/kg/d	Sys	20.0	20.0	**50**	10.0	30.0	**75**	−10.0	10.0	10.0	**100**
9	Ottaviani et al. 1984[5]	6 h res	macro			Chronic mor	10 mg/kg/d	Sys	11.0	21.0	**66**	13.0	30.0	**70**	2.0	9.0	11.0	**82**
10a	Shor-Posner et al. 1986[6]	6 h res	macro		Light phase	Mor	2 mg/kg	Sys	28.3	65.6	**70**	11.0	59.5	**84**	−17.3	−6.1	-	
10b					Dark phase	Mor	2	Sys	13.2	46.4	**78**	3.7	66.5	**95**	−9.5	20.1	20.1	**100**
10c		AL	macro		Light phase	Mor	2	Sys	2.5	2.0	**44**	5.0	5.0	**50**	2.5	3.0	5.5	**55**
10d					Dark phase	Mor	2	Sys	4.0	8.0	**67**	7.0	12.0	**63**	3.0	4.0	7.0	**57**
11a	Welch et al. 1994[7]	AL	HF v LF			Mor	5 mg/kg	Sys	75%	25%	**25**	32%	68%	**68**	−43%	43%	43%	**100**

										Pre (kcal)			Post (kcal)			Change (kcal)			
	Expt	**Reference**	**Drive**	**Diet**	**BL pref**	**Notes**	**Drug**	**Dose**	**Site**	**C**	**F**	**% F**	**C**	**F**	**% F**	**C**	**F**	**Total ↑**	**% F**
	11b			macro			Mor	5	Sys	40%	30%	**43**	25%	50%	**67**	−15%	20%	20%	**100**
KOR	12a	Ookuma et al. 1997	AL	HF v LF			U50	215 nmol	LV	2.5	0.5	**17**	3.0	11.0	**79**	0.5	10.5	11.0	**95**
	12b		20 h dep	HF v LF			U50	215	LV	9.0	21.0	**70**	13.0	32.0	**71**	4.0	11.0	15.0	**73**
	13a	Ookuma et al. 1998	AL	HF v LF	F (OM)		U50	22 nmol	3rd v	2.0	3.0	**60**	5.0	12.0	**71**	3.0	9.0	12.0	**75**
	13b				C (S5)		U50	22	3rd v	1.0	1.0	**50**	7.5	7.5	**50**	6.5	6.5	13.0	**50**
	14a	Romsos et al. 1987[8]	AL	HF v LF			Butor	0.5 mg/kg	Sys	0.5	0.5	**50**	2.0	8.0	**80**	1.5	7.5	9.0	**83**
								1	Sys	0.5	0.5	**50**	3.0	3.0	**50**	2.5	2.5	5.0	**50**
								10	Sys	0.5	0.5	**50**	7.5	12.5	**63**	7.0	12.0	19.0	**63**
	14b			HF or LF			Butor	1 mg/kg	Sys	6.0	2.0	**25**	14.0	14.0	**50**	8.0	12.0	20.0	**60**
								10	Sys	6.0	2.0	**25**	19.0	29.0	**60**	13.0	27.0	40.0	**68**
	14c						Chronic butor	10 mg/kg/d	Sys	6.0	4.0	**40**	17.0	31.0	**65**	11.0	27.0	38.0	**71**
	14d						Ketocyc	1 mg/kg	Sys	6.0	1.0	**14**	6.0	12.0	**67**	0.0	11.0	11.0	**100**
								10	Sys	6.0	1.0	**14**	7.0	14.0	**67**	1.0	13.0	14.0	**93**
Site-specific infusions																			
MOR	15a	Zhang et al. 1998	AL	HF or LF			DAMGO	0.25 µg	NAcc	15.0	30.0	**67**	35.0	100.0	**74**	20.0	70.0	90.0	**78**
								2.5	NAcc	15.0	30.0	**67**	35.0	125.0	**78**	20.0	95.0	115.0	**83**
	15b			HF vs LF	C		DAMGO	0.25 µg	NAcc	20.0	20.0	**50**	25.0	45.0	**64**	5.0	25.0	30.0	**83**
								2.5	NAcc	20.0	20.0	**50**	20.0	70.0	**78**	0.0	50.0	50.0	**100**
	15c				F		DAMGO	0.25 µg	NAcc	15.0	40.0	**73**	10.0	70.0	**88**	−5.0	30.0	30.0	**100**
								2.5	NAcc	15.0	40.0	**73**	5.0	150.0	**97**	−10.0	110.0	110.0	**100**
	15d		24 h dep	HF vs LF			DAMGO	0.25 µg	NAcc	28.0	33.0	**54**	23.0	70.0	**75**	−5.0	37.0	37.0	**100**
	16	Leibowitz 1999	6 h res	macro			DAMGO	3 nmol	PVN	5.0	2.0	**29**	3.5	10.0	**74**	−1.5	8.0	8.0	**100**
	17a	Naleid et al. 2007[9]	AL	HF vs LF	F		DAMGO	0.25 nmol	PVN	17.0	40.0	**70**	11.0	56.0	**84**	−6.0	16.0	16.0	**100**
								2.5	PVN	17.0	40.0	**70**	9.0	72.0	**89**	−8.0	32.0	32.0	**100**
	17b				C		DAMGO	0.25 nmol	PVN	41.0	17.0	**29**	39.0	20.0	**34**	−2.0	3.0	3.0	**100**

	Expt	Reference	Drive	Diet	BL pref	Notes	Drug	Dose	Site	Pre (kcal)			Post (kcal)			Change (kcal)			
										C	F	% F	C	F	% F	C	F	Total ↑	% F
								2.5	PVN	41.0	17.0	**29**	33.0	25.0	**43**	−8.0	8.0	8.0	**100**
KOR	18	Leibowitz 1999	6 h res	macro			Dyn A	3 nmol	PVN	5.0	2.0	**29**	2.0	7.0	**78**	−3.0	5.0	5.0	**100**

[1]High fat vs. low fat intake was measured using three different fat sources: corn oil, lard, or vegetable shortening.

[2]Rats were divided into three groups in this experiment: a control group never administered drug; a group administered saline continuously for one week through minipump infusion, followed by a second week of continuous morphine infusion (Group 1 in Notes column); and a group in which drugs were administered in the opposite order - morphine first followed by saline (Group 2). For this experiment, baseline macronutrient preference was calculated from the control (never injected) group's intake averaged over the first week. Drug effects were calculated from macronutrient intake on first post-drug day only.

[3]Two experiments were performed in which rat self-selected macronutrients after morphine injection. In the first experiment the fat component was 7.8 kcal/g; in the second, it was 3.8 kcal/g, isocaloric to the protein and carbohydrate rations. In both experiments, morphine doses (0, 1, 10, 20 mg/kg) were administered in two rounds of injection. Only data from the second round is included here, as the first round had no significant effects on intake.

[4]Morphine was injected daily for 10 days. Baseline intake for this experiment was calculated from the average intake over the five days preceding injection. Drug effects were calculated from last 5 days of morphine injection, the interval over which drug effects differed significantly from control values.

[5]Morphine was injected daily for 22 days. Drug effects on macronutrient intake were calculated from the mean intake over the 5 days of injection, the interval over which there was a statistically significant difference from vehicle injected control rats. Baseline macronutrient preference was calculated from mean intake of control animals during this period.

[6]Morphine effects on diet preference were assessed either during light or dark phase, as indicated in the Notes column.

[7]The authors measured baseline preference by averaging macronutrient intake over 3 days preceding drug treatments, and expressed these preferences as the percent of total caloric intake. To be consistent with baseline measures, drug effects on macronutrient intake (reported in kcal) were converted to percent of total intake in the test session. Thus, all measures for this experiment are reported in Table 1 as percentages of total consumption.

[8]In one experiment (14c), butorphanol was chronically administered (once/day for four days). Data shown are those following only the first day of injection.

[9]The authors provided measures of total intake (kcal) as well as intake difference (fat kcal – sucrose kcal). Raw measures of macronutrient intake were derived algebraically from these values.

Table 2

Opioid antagonists

For table conventions, see explanations in Table 1 legend. Abbreviations unique to Table 2 are summarized below, moving from left to right across columns. Drive: **2DG**, food intake was motivated by 2-deoxyglucose administration; **NPY**, Neuropeptide Y. Drug: **b-FNA**, beta-funaltrexamine; **Nlz**, naloxonazine; **NTI**, naltrindole; **nor-BNI**, nor-binaltorphamine; **NTX**, naltrexone; **NLX**, naloxone. Site: **ACe**, central nucleus of the amygdala. Drug effects on macronutrient intake are arranged identically to Table 1 with the exception of the final two columns. The **Total ↓** column indicates the total *decrease* in intake caused by antagonist administration, and the **% F** column indicates the percentage of that decrease that can be attributed to declines in fat intake.

										Pre (kcal)			Post (kcal)			Change (kcal)			
	Expts	**Reference**	**Drive**	**Diet**	**BL pref**	**Notes**	**Drug**	**Dose**	**Site**	**C**	**F**	**% F**	**C**	**F**	**% F**	**C**	**F**	**Total ↓**	**% F**
MOR	1a	Koch et al. 1994	24 h dep	macro			β-FNA	20 µg	ICV	15.0	22.0	**59**	9.0	12.0	**57**	−6.0	−10.0	−16.0	**63**
	1b		2DG	macro			β-FNA	1 µg	ICV	8.0	10.0	**56**	9.0	5.0	**36**	1.0	−5.0	−5.0	**100**
								5	ICV	8.0	10.0	**56**	8.0	3.0	**27**	0.0	−7.0	−7.0	**100**
								20	ICV	8.0	10.0	**56**	5.0	5.0	**50**	−3.0	−5.0	−8.0	**63**
	2	South et al. 2007[1]	AL	HF v LF		Mice	Chronic β-FNA	15 mg/kg/day	Sys	2.0	10.0	**83**	3.0	4.0	**57**	1.0	−6.0	−6.0	**100**
	3a	Koch and Bodnar 1994	24 h dep	macro			Nlz	10 µg	ICV	6.0	34.0	**85**	12.0	34.0	**74**	6.0	0.0	0.0	-
								50	ICV	10.0	37.0	**79**	6.0	15.0	**71**	−4.0	−22.0	−26.0	**85**
								100	ICV	13.0	22.0	**63**	1.0	9.0	**90**	−12.0	−13.0	−25.0	**52**
	3b		2DG	macro			Nlz	40 µg	ICV	6.0	12.0	**67**	9.0	8.0	**47**	3.0	−4.0	−4.0	**100**
DOR	4	Koch and Bodnar 1994	2DG	macro			NTI	20 µg	ICV	6.0	10.0	**63**	11.0	7.0	**39**	5.0	−3.0	−3.0	**100**
KOR	5	Koch and Bodnar 1994	2DG	macro			nor-BNI	5 µg	ICV	8.0	10.0	**56**	9.0	8.0	**47**	1.0	−2.0	−2.0	**100**
								20	ICV	8.0	10.0	**56**	8.0	5.0	**38**	0.0	−5.0	−5.0	**100**
	6	Ookuma et al. 1997	20 h dep	HF v LF			nor-BNI	10 µg	LV	14.0	21.0	**60**	18.0	15.0	**45**	4.0	−6.0	−6.0	**100**
								20	LV	14.0	21.0	**60**	17.0	9.0	**35**	3.0	−12.0	−12.0	**100**
	7a	Ookuma et al. 1998	20 h dep	HF v LF	F (OM)		nor-BNI	20 µg	3rd v	12.5	10.0	**44**	12.5	4.0	**24**	0.0	−6.0	−6.0	**100**
	7b				C (S5)		nor-BNI	20 µg	3rd v	24.0	2.0	**8**	17.0	1.0	**6**	−7.0	−1.0	−8.0	**13**
Nonspecific	8	Corwin et al. 2009[2]	AL	HF or LF			NTX	0.1 mg/kg	Sys	13.0	54.0	**81**	10.0	36.0	**78**	−3.0	−18.0	−21.0	**86**
								0.3	Sys	13.0	54.0	**81**	7.5	32.0	**81**	−5.5	−22.0	−27.5	**80**
								1	Sys	13.0	54.0	**81**	7.0	32.0	**82**	−6.0	−22.0	−28.0	**79**
								3.2	Sys	13.0	54.0	**81**	6.0	22.0	**79**	−7.0	−32.0	−39.0	**82**
	9a	Glass et al. 1996[3]	24 h dep	HF v LF		1st series	NLX	0.01 mg/kg	Sys	5.1	42.7	**89**	4.9	33.5	**87**	−0.2	−9.2	−9.4	**98**
								0.03	Sys	5.1	42.7	**89**	4.5	32.3	**88**	−0.6	−10.4	−11.0	**95**

									Pre (kcal)			Post (kcal)			Change (kcal)			
Expts	**Reference**	**Drive**	**Diet**	**BL pref**	**Notes**	**Drug**	**Dose**	**Site**	**C**	**F**	**% F**	**C**	**F**	**% F**	**C**	**F**	**Total ↓**	**% F**
							0.1	Sys	5.1	42.7	**89**	4.9	24.1	**83**	−0.2	−18.6	−18.8	**99**
9b					2nd series		0.3 mg/kg	Sys	14.2	21.9	**61**	6.6	18.9	**74**	−7.6	−3.0	−10.6	**28**
							1	Sys	14.2	21.9	**61**	9.2	14.2	**61**	−5.0	−7.7	−12.7	**61**
							3	Sys	14.2	21.9	**61**	4.2	13.7	**77**	−10.0	−8.2	−18.2	**45**
9c		NPY	HF v LF		1st series	NLX	0.1 mg/kg	Sys	11.5	15.7	**58**	8.9	9.2	**51**	−2.6	−6.5	−9.1	**71**
							0.3	Sys	11.5	15.7	**58**	6.5	7.4	**53**	−5.0	−8.3	−13.3	**62**
9d					2nd series		1 mg/kg	Sys	7.4	9.6	**56**	3.3	2.8	**46**	−4.1	−6.8	−10.9	**62**
							3	Sys	7.4	9.6	**56**	2.6	2.6	**50**	−4.8	−7.0	−11.8	**59**
10	Gosnell et al. 1992[4]	AL	HF v LF			Chronic NTX	210 µg/kg/h	Sys	55.0	63.0	**53**	21.0	25.0	**54**	−34.0	−38.0	−72.0	**53**
11	Hagan et al. 1997[5]	24 h dep	HF or LF			NLX	0.1 mg/kg	Sys	22.0	33.0	**60**	29.0	13.0	**31**	7.0	−20.0	−20.0	**100**
							1	Sys	22.0	33.0	**60**	19.0	12.0	**39**	−3.0	−21.0	−24.0	**88**
12	Kirkham et al. 1987[6]	AL	HF or LF			NTX	1 mg/kg	Sys	18.0	22.0	**55**	17.0	18.5	**52**	−1.0	−3.5	−4.5	**78**
							10	Sys	18.0	22.0	**55**	16.0	18.0	**53**	−2.0	−4.0	−6.0	**67**
13a	Koch and Bodnar 1994	24 h dep	macro			NTX	50 µg	ICV	10.0	38.0	**79**	8.0	18.0	**69**	−2.0	−20.0	−22.0	**91**
13b		2DG	macro			NTX	5 µg	ICV	7.0	12.0	**63**	11.0	5.0	**31**	4.0	−7.0	−7.0	**100**
							20	ICV	7.0	12.0	**63**	4.0	4.0	**50**	−3.0	−8.0	−11.0	**73**
13c		24 h dep	macro			NTX	0.5 mg/kg	Sys	15.0	30.0	**67**	6.0	22.0	**79**	−9.0	−8.0	−17.0	**47**
							5	Sys	15.0	30.0	**67**	6.0	15.0	**71**	−9.0	−15.0	−24.0	**63**
13d		2DG	macro			NTX	0.1 mg/kg	Sys	8.0	12.0	**60**	8.0	6.0	**43**	0.0	−6.0	−6.0	**100**
							0.5	Sys	8.0	12.0	**60**	3.0	4.0	**57**	−5.0	−8.0	−13.0	**62**
							5	Sys	8.0	12.0	**60**	1.0	3.0	**75**	−7.0	−9.0	−16.0	**56**
14	Marks−Kaufman et al. 1981[7]	6 h res	macro			NLX	0.1 mg/kg	Sys	25.0	22.0	**47**	27.0	18.0	**40**	2.0	−4.0	−4.0	**100**
							1	Sys	25.0	22.0	**47**	20.0	16.0	**44**	−5.0	−6.0	−11.0	**55**
							10	Sys	25.0	22.0	**47**	23.0	15.0	**39**	−2.0	−7.0	−9.0	**78**
15	Marks-Kaufman et al. 1985	8 h res	macro			NTX	5 mg/kg	Sys	12.0	37.0	**76**	5.0	23.0	**82**	−7.0	−14.0	−21.0	**67**
16a	Romsos et al. 1987	20 h dep	HF or LF			NLX	0.1 mg/kg	Sys	25.0	32.0	**56**	22.0	22.0	**50**	−3.0	−10.0	−13.0	**77**

										Pre (kcal)			Post (kcal)			Change (kcal)			
	Expts	Reference	Drive	Diet	BL pref	Notes	Drug	Dose	Site	C	F	% F	C	F	% F	C	F	Total ↓	% F
								1	Sys	25.0	32.0	**56**	17.0	14.0	**45**	−8.0	−18.0	−26.0	**69**
								10	Sys	25.0	32.0	**56**	10.0	10.0	**50**	−15.0	−22.0	−37.0	**59**
	16b		AL	HF or LF			NLX	1 mg/kg	Sys	18.0	16.0	**47**	13.0	13.0	**50**	−5.0	−3.0	−8.0	**38**
								10	Sys	18.0	16.0	**47**	11.0	10.0	**48**	−7.0	−6.0	−13.0	**46**
	16c		20 h dep	HF v LF			NLX	10 mg/kg	Sys	12.0	14.0	**54**	16.0	4.0	**20**	4.0	−10.0	−10.0	**100**
	16d		AL	HF v LF			NLX	10 mg/kg	Sys	16.0	8.0	**33**	12.0	4.0	**25**	−4.0	−4.0	−8.0	**50**
	17a	Zhang et al. 1998	24 h dep	HF v LF	C		NTX	5 mg/kg	Sys	32.0	20.0	**38**	32.0	13.0	**29**	0.0	−7.0	−7.0	**100**
	17b				F		NTX	5 mg/kg	Sys	20.0	40.0	**67**	25.0	30.0	**55**	5.0	−10.0	−10.0	**100**
	Site specific injections																		
Nonspecific	18a	Glass et al. 2000	24 h dep	HF v LF		C=starch	NTX	30 nmol	ACe	8.8	35.0	**80**	6.2	19.0	**75**	−2.6	−16.0	−18.6	**86**
								100	ACe	8.8	35.0	**80**	6.9	16.9	**71**	−1.9	−18.1	−20.0	**91**
	18b					C=sucrose	NTX	100	ACe	20.3	12.0	**37**	14.6	9.1	**38**	−5.7	−2.9	−8.6	**34**
	19	Zhang et al. 1998	24 h dep	HF v LF			NTX	20 μg	Nac c	30.0	33.0	**52**	25.0	19.0	**43**	−5.0	−14.0	−19.0	**74**
	20a	Naleid et al. 2007[8]	AL	HF v LF	F		NTX	100 nmol	PVN	19.0	59.0	**76**	16.5	42.5	**72**	−2.5	−16.5	−19.0	**87**
	20b				C		NTX	100 nmol	PVN	33.5	40.5	**55**	35.50	26.5	**43**	2.0	−14.0	−14.0	**100**
	21a	Glass et al. 2000	24 h dep	HF v LF		C=starch	NTX	100 nmol	PVN	11.3	16.0	**59**	6.4	11.8	**65**	−4.9	−4.2	−9.1	**46**
	21b					C=sucrose	NTX	10 nmol	PVN	23.6	11.2	**32**	18.6	7.9	**30**	−5.0	−3.3	−8.3	**40**
							NTX	30	PVN	23.6	11.2	**32**	12.7	7.6	**37**	−10.9	−3.6	−14.5	**25**
							NTX	100	PVN	23.6	11.2	**32**	8.4	6.7	**44**	−15.2	−4.5	−19.7	**23**

[1] β-FNA was injected once per day for four days. Drug effects for only first day following injection are reported. The baseline preference values reported are the average of 3 pre-drug saline injections that took place over 4 days. These experiments used mice rather than rats.

[2] Sucrose (3.2, 10%, or 32%) or fat intake (vegetable shortening) was measured when available on a daily (1 h) or intermittent (every other day) basis. Values reported in Table 2 were taken only from intermittent fat and intermittent 32% sucrose experiments. Total caloric intake as well as sensitivity to naltrexone effects was maximal with these macronutrients presentations, allowing comparison of naltrexone effects across macronutrients. Intake measures reported in the manuscript (grams of fat and mLs of sucrose) were converted to kcal for inclusion in the table.

[3] For both 24 h deprivation and NPY (Drive column) experiments, naloxone was administered in two separate schedules. In each case randomized presentation of low doses was subsequently followed by presentation of higher doses.

[4] Drugs were continuously infused via osmotic minipumps. Control saline was infused for one full week, followed by naltrexone. Baseline preference was calculated from mean intake over the first week (during saline infusion). Intake on the first day only following naltrexone administration is reported.

[5]The high fat food used in this experiment was Almond M&Ms (30% of calories derived from fat). The low fat (high carbohydrate) food was Froot Loops Cereal (3% of calories derived from fat).

[6]Values are given in grams of consumption rather than kcal, as caloric density of HF and LF options were not reported.

[7]Results reported were taken at the 4 hour time point (intake was measured over a total of 6 hours), the last time point for which statistically significant drug effects occurred.

[8]The authors provided measures of total intake (kcal) as well as intake difference (fat kcal – sucrose kcal). Raw measures of macronutrient intake were derived algebraically from these values.