Published in final edited form as:

Neuroscience. 2014 March 7; 261: 144–152. doi:10.1016/j.neuroscience.2013.12.004.

Mu opioid receptor antagonism in the nucleus accumbens shell blocks consumption of a preferred sucrose solution in an anticipatory contrast paradigm

Yoshihiro Katsuura and Sharif A. Taha*

Department of Neurobiology and Anatomy, University of Utah, Salt Lake City, Utah

Abstract

Binge eating, a central feature of multiple eating disorders, is characterized by excessive consumption occurring during discrete, often brief, intervals. Highly palatable foods play an important role in these binge episodes – foods chosen during bingeing are typically higher in fat or sugar than those normally consumed. Multiple lines of evidence suggest a central role for signaling by endogenous opioids in promoting palatability-driven eating. This role extends to binge-like feeding studied in animal models, which is reduced by administration of opioid antagonists. However, the neural circuits and specific opioid receptors mediating these effects are not fully understood. In the present experiments, we tested the hypothesis that endogenous opioid signaling in the nucleus accumbens promotes consumption in a model of binge eating. We used an anticipatory contrast paradigm in which separate groups of rats were presented sequentially with 4% sucrose and then either 20% or 0% sucrose solutions. In rats presented with 4% and then 20% sucrose, daily training in this paradigm produced robust intake of 20% sucrose, preceded by learned hypophagia during access to 4% sucrose. We tested the effects of site-specific infusions of naltrexone (a nonspecific opioid receptor antagonist: 0, 1, 10, and 50 ug/side in the nucleus accumbens core and shell), naltrindole (a delta opioid receptor antagonist: 0, 0.5, 5, and 10 ug/side in the nucleus accumbens shell) and beta-funaltrexamine (a mu opioid receptor antagonist: 0 and 2.5 ug/side in the nucleus accumbens shell) on consumption in this contrast paradigm. Our results show that signaling through the mu opioid receptor in the nucleus accumbens shell is dynamically modulated during formation of learned food preferences, and promotes binge-like consumption of palatable foods based on these learned preferences.

Keywords

Anticipatory contrast; Mu opioid receptor; Binge eating; Palatability; Nucleus accumbens

Introduction

Binge eating is a behavioral abnormality characterized by excessive consumption occurring during brief periods, often accompanied by feelings of loss of control (American Psychological Association, 2000). It is a hallmark of several eating disorders including bulimia and binge eating disorder (Miller and Golden, 2010). Binge eating is also associated

© 2013 IBRO. Published by Elsevier Ltd. All rights reserved.

*Corresponding author: 36 South Wasatch Drive, Salt Lake City, UT 84112, s.taha@utah.edu, p. 801-585-6214.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

with obesity and may importantly contribute to excessive weight gain (Spitzer et al., 1992). Neural mechanisms underlying binges are poorly understood and undoubtedly multifactorial in their origins, with changes in neural signaling underlying stress, reward, and motivation likely contributing (Adam and Epel, 2007, Davis et al., 2009). Food selection during binges, however, suggests an important role for neural circuits that promote hedonically-driven feeding in binge eating. Foods eaten during binges are often higher in fat and sugar than those typically consumed and often include dessert and/or snack foods (Yanovski et al., 1992). Thus dissecting function in reward circuits promoting consumption of highly palatable foods may be particularly relevant to elucidating neural mechanisms underlying eating disorders as well as weight gain leading to obesity.

Opioid signaling in the nucleus accumbens (NAcc) has been strongly implicated in the control of food intake. Several lines of evidence suggest that mu opioid receptor (MOR) signaling in the NAcc selectively promotes hedonically-driven feeding. First, stimulation of MORs in the NAcc increases consumption of palatable sweet and fatty foods, and blockade of opioid signaling decreases intake of these foods (Kelley et al., 1996, Kelley et al., 2002). However, MOR stimulation or blockade has more modest effects on consumption of hedonically neutral substances, such as water or standard rat chow (Zhang and Kelley, 1997, 2002, Lenard et al., 2010). Second, infusion of the MOR-specific agonist [D-Ala2, N-MePhe4, Gly-ol]-enkephalin (DAMGO) into the NAcc increases positive taste reactivity displays in response to intraoral infusion of a sucrose solution and can increase licking bout duration in rats consuming sweet or fatty solutions; previous work has shown that these measures are correlated with the palatability of the tastant consumed (Pecina and Berridge, 2000, Taha et al., 2009, Katsuura et al., 2011). Conversely, infusion of the MOR antagonist beta-funaltrexamine (beta-FNA) decreases positive taste reactivity (Shin et al., 2010). Third, in rats that are offered a choice of food pellets identical in macronutrient content but differing in flavor, NAcc MOR stimulation selectively increases consumption of the preferred flavor (Woolley et al., 2006). Fourth, MOR stimulation in the NAcc increases consumption of non-caloric sweet (Zhang and Kelley, 2002) and fatty (Katsuura et al., 2011) substances, demonstrating that rewarding orosensory taste and texture cues are sufficient for DAMGO-induced hyperphagia.

MOR signaling in the NAcc thus plays an important role in palatability-driven consumption under normal conditions. Studies in rodent models of binge eating suggest this role extends to (and possibly plays an even larger role in) excessive, binge-like consumption. Opioid antagonists have been consistently reported to decrease consumption in a variety of rodent models that emphasize distinct aspects of binge eating. Thus, systemic administration of naltrexone decreases intake in rats offered limited, intermittent access to fat and/or sucrose (Rao et al., 2008, Corwin and Wojnicki, 2009, Wong et al., 2009); systemic administration of the nonspecific opioid antagonist naloxone potently and selectively decreases binge-like intake produced by cycles of food restriction, stress, and palatable food access (Boggiano et al., 2005); and systemic naltrexone (Taha et al., 2006), nalmefene (a mu and kappa opioid receptor antagonist; (Cottone et al., 2008) and GSK1521498 (a MOR inverse agonist; (Giuliano et al., 2012) decrease binge-like consumption in an anticipatory contrast paradigm, which has been proposed to model qualitative aspects of food restriction contributing to binge eating (Cottone et al., 2008).

Despite existing evidence of an important role for endogenous opioid signaling in promoting binge-like eating, little is known about the specific brain circuits which contribute to this behavior, as most previous studies of opioid antagonists in relevant animal models have made use of systemic drug administration. In the present study, we tested the effects of opioid antagonist infusion into the NAcc core and shell to assess the contribution of opioid signaling in these brain regions to consumption occurring in an anticipatory contrast

paradigm. The anticipatory contrast paradigm models binge-like consumption occurring during access to a preferred, highly palatable tastant. In addition, expectation of this tastant results in learned hypophagia for a less preferred alternative. Mechanisms underlying this learned hypophagia may be particularly relevant to understanding patterns of dietary selection in binge eaters that favor consumption of highly palatable foods over less palatable but perhaps healthier alternatives and thus serve to perpetuate binge eating (Waters et al., 2001, Cottone et al., 2008, Siega-Riz et al., 2008). Our results demonstrate that MOR signaling in the NAcc shell changes in concert with learned food preferences, and promotes binge-like intake of a preferred sucrose solution.

Experimental Procedures

Overview of Experimental procedures

All procedures used were approved by the University of Utah Medical School Institutional Animal Care and Use Committee. Male Long-Evans rats (300–400 g) were used in all experiments. Rats were individually housed on a 12:12 light:dark schedule with *ad lib* access to standard rat chow (8640 Teklad Rodent Diet, Harlan Laboratories, Indianapolis, IN) and tap water throughout the experimental period. After arrival at the facility, rats were habituated to gentle handling for one week. Rats were then surgically implanted with bilateral cannulae directed either at the NAcc core (28 rats) or shell (56 rats) and allowed 1 week of recovery. Thereafter, training in the anticipatory contrast paradigm was performed once daily, 5 times per week, with training continuing for 3 weeks. Though anticipatory contrast effects are apparent with much less training (Schroy et al., 2005), this extended training period was used because diet-dependent changes in opioid receptor expression in the NAcc and opioid signaling-dependent behaviors have been reported after 3–4 weeks access to palatable foods (Colantuoni et al., 2001, Colantuoni et al., 2002, Kelley et al., 2003). After training, the effects of opioid receptor antagonists in the NAcc core and/or shell were tested in the contrast paradigm.

Cannula implantation

Surgical anesthesia was induced and maintained with isoflurane (5% and ~2%, respectively). Cannulae were stereotactically implanted into the NAcc core (anterioposterior, AP 1.4 mm; mediolateral, ML $\pm$ 1.8; dorsoventral, DV – 5.5; coordinates relative to bregma) or shell (AP 1.4; ML $\pm$ 0.8, DV –5.5).

Anticipatory contrast paradigm

Training was performed daily in 8 identical operant chambers (Med Associates, Georgia, VT) equipped with a single photobeam lickometer. Sessions lasted one hour and were divided into two successive 30 minute blocks. Rats were randomly assigned to one of two behavioral groups: 4-0 or 4-20. During the first 30 minute block rats in both groups received free access to a 4% sucrose solution (w/v; 0.12 M). During the second 30 minute block, rats in the 4-0 group received free access to unsweetened water (0% sucrose), while those in the 4-20 group received access to a 20% sucrose solution (0.58 M). Sucrose solutions were manually switched between the first and second blocks. Lick counts (photobeam breaks) occurring during each block were recorded and stored on a PC (MedPC, Med Associates). 4-0 and 4-20 groups were run in parallel, with 4 rats in each group run simultaneously.

Our use of sucrose solutions differs from the paradigm proposed as a model of binge eating by Cottone et al. (2008), which used solid chow presentation followed by chow or chocolate pellet presentation. Use of successive sucrose solutions ensures that intake of even less preferred solutions (i.e., 4% sucrose in the 4-20 group) remains substantial, and that antagonist effects are not obscured by floor effects.

Drug infusion protocol

Drugs infused included the nonspecific opioid antagonist naltrexone (doses of 0, 1, 10, and 50 ug per infusion site), the delta opioid receptor (DOR) antagonist naltrindole (0, 0.5, 5, and 10 ug), and the MOR antagonist beta-FNA (0 and 2.5 ug). Doses were chosen based on previous studies (Bodnar et al., 1995, Kelley et al., 1996). In initial experiments, naltrexone was infused into the NAcc core or shell in separate groups of rats. Results from these experiments suggested that opioid signaling in the shell but not core contributed to consumption of a preferred sucrose solution. Thus, subsequent experiments focused only on the NAcc shell; the effects of naltrindole and beta-FNA infusion were tested after infusion only into the shell subregion.

Naltrexone and naltrindole were infused 10 minutes prior to testing in the anticipatory contrast paradigm. Beta-FNA, which is an irreversible MOR antagonist but has early and transient activity as a kappa opioid receptor agonist (Portoghese et al., 1980), was infused 24 hours before testing, paralleling methods used in previous studies (Bodnar et al., 1995, Kelley et al., 1996, Ward et al., 2006). Naltrexone and naltrindole were prepared in physiological saline, and beta-FNA in 50% dimethyl sulfoxide in physiological saline. All drugs were infused bilaterally in a volume of 0.5 ul/hemisphere. Injectors protruded 2 mm beyond cannula tips. Drugs except for beta-FNA were administered in a randomized Latin-square design on alternate days, allowing a rest day in between infusions. Because beta-FNA is an irreversible antagonist, the control vehicle infusion was performed first, and beta-FNA infused after a rest day. Individual rats received multiple drug infusions but these were limited to a maximum of two drugs tested in a single animal. Thus, a maximum of 8 infusions (four concentrations of two drug tested) occurred in any single animal. Because of the long-lasting effects of beta-FNA, in animals that received this drug, it was the last antagonist tested. Group sizes for each drug tested were: naltrexone in NAcc core, $n = 28$ rats; naltrexone in NAcc shell, $n = 34$; naltrindole in NAcc shell, $n = 29$; beta-FNA in the NAcc shell, $n = 28$.

Statistical analysis and cannula localization

Drug effects on 4% sucrose consumption were compared in 4-0 and 4-20 groups using two-way repeated measures ANOVA (factors of drug and group). Where appropriate, Holm-Sidak post hoc tests were used. Drug effects on 20% sucrose were analyzed using one-way repeated measures ANOVA (levels of drug concentration). To further analyze beta-FNA effects, correlations between changes in licking caused by the drug (licks after beta-FNA – licks after vehicle) and baseline consumption (licks after vehicle) were analyzed using the Pearson Product Moment. To analyze cannula placements, rats were deeply anesthetized and infused with 0.5 ul of pontamine sky blue. Rats were then perfused, the brains removed, and sections prepared by standard methods. Dye infusion sites were localized under a light microscope and recorded on atlas figures adapted from (Paxinos and Watson, 1997). Infusions sites were localized by an observer blind to drug effects on behavior.

Results

Contrast paradigm

Training in the anticipatory contrast paradigm (Figure 1A) established a robust contrast effect (Figure 1B). Comparison of licking between the 4-0 and 4-20 groups revealed a significant group $\times$ block interaction ($F_{1,81} = 152.2$, $p < 0.001$) and post hoc testing showed that consumption of 4% sucrose by rats in the 4-0 group exceeded that of rats in the 4-20 group ($p < 0.001$). Main effects of group ($F_{1,81} = 31.0$) and block ($F_{1,81} = 37.8$) were also significant (both $p < 0.001$). Post hoc analysis showed that in the 4-0 group, licking was largely confined to the first block when 4% sucrose was presented; very little water was

consumed in the second block ($p < 0.001$, comparing licks in first and second block). In the 4-20 group, consumption of 4% sucrose in the first block was significantly lower than consumption of 20% sucrose occurring in the second block ($p < 0.001$).

Effects of naltrexone: NAcc shell

Blockade of opioid receptors in the NAcc shell by infusion of naltrexone differentially suppressed licking for 4% sucrose in the 4-0 and 4-20 groups (Figure 2A, significant group $\times$ drug interaction: $F_{3,96} = 5.1$, $p < 0.01$; also a significant main effect of group: $F_{1,32} = 10.3$, $p < 0.01$; but no main effect of drug: $F_{3,96} = 1.4$, $p = 0.24$). Posthoc tests indicated that within the 4-0 group, the 50 μ g dose of naltrexone significantly reduced licking for 4% sucrose compared to each of the other doses ($p < 0.05$). Within the 4-20 group, naltrexone did not have significant effects on 4% sucrose consumption. The number of 4% sucrose licks made by rats in the 4-0 and 4-20 groups differed after 0, 1, and 10 μ g doses of naltrexone ($p < 0.05$, posthoc tests) but not after the 50 μ g dose ($p > 0.05$).

In the 4-20 group, naltrexone significantly decreased consumption of 20% sucrose (significant effect of drug: $F_{3,45} = 6.6$, $p < 0.001$). Posthoc testing showed that the 50 μ g dose of naltrexone significantly decreased consumption of 20% sucrose relative to control saline infusion. Thus, naltrexone infusion in the NAcc shell suppressed licking in both groups, but only for the more preferred sucrose solution – 4% sucrose in the 4-0 group, and 20% sucrose in the 4-20 group.

Effects of naltrexone: NAcc core

Naltrexone infusion into the NAcc core also had differential effects on 4% sucrose intake in the 4-0 and 4-20 groups (Figure 3A; significant group $\times$ drug interaction: $F_{3,78} = 7.3$, $p < 0.001$; but no main effect of group: $F_{1,26} = 2.2$, $p = 0.15$; or drug: $F_{3,78} = 1.0$, $p = 0.40$). However, this interaction could be attributed solely to increased 4% sucrose licks in the 4-0 group after administration of 1 μ g naltrexone dose. Posthoc tests indicated that within the 4-0 group, licking was significantly increased only after the 1 μ g dose ($p < 0.05$, vs. 10 and 50 μ g doses). Consistent with this, posthoc comparison of licking between groups within different levels of drug showed that licking in the 4-0 and 4-20 groups differed only after the 1 μ g dose of naltrexone ($p < 0.05$).

In the 4-20 group, naltrexone significantly decreased consumption of 20% sucrose (significant effect of drug: $F_{3,42} = 4.7$, $p < 0.01$). Posthoc testing indicated that licking for 20% sucrose was decreased after 10 μ g and 50 μ g naltrexone doses (vs. vehicle, $p < 0.05$).

Together, results from naltrexone infusion into the NAcc core and shell suggested that blockade of opioid signaling in the NAcc shell but not NAcc core selectively decreased consumption of a preferred sucrose solution. Thus in subsequent experiments drug effects were tested only in the NAcc shell. We focused in these experiments on DOR and MOR-specific antagonists, as signaling through these receptors in the NAcc has previously been shown to modulate food intake (Kelley et al., 2002, Katsuura and Taha, 2010).

Effects of naltrindole

Infusion of the DOR-specific antagonist naltrindole into the NAcc shell increased 4% licking (Figure 4A, main effect of drug, $F_{3,81} = 3.3$, $p < 0.05$), with no differential effect on 4-0 and 4-20 groups (no group $\times$ drug interaction, $F_{3,81} = 0.6$, $p = 0.61$; but a significant main effect of group $F_{1,27} = 15.9$, $p < 0.001$). Post hoc testing revealed a significant increase in 4% sucrose licks after the 5 μ g dose of naltrindole (vs. 0.5 μ g dose, $p < 0.05$).

In the 4-20 group, naltrindole infusion significantly increased 20% sucrose consumption (significant effect of drug $F_{3,45} = 3.3$, $p < 0.05$). Posthoc testing indicated that this was due to a significant elevation of licking after the 10 ug dose (vs. control, $p < 0.05$). Thus there was a significant effect of naltrindole in increasing 4% sucrose consumption in both groups, without apparent differences between 4-0 and 4-20 groups, as well as a significant effect of the drug in increasing 20% sucrose consumption.

Effects of beta-FNA

Finally, we examined the effects of infusion of the MOR-specific antagonist beta-FNA into the NAcc shell on 4% sucrose consumption in the two groups (Figure 5A). Beta-FNA significantly reduced 4% sucrose consumption (main effect of drug, $F_{1,25} = 5.7$, $p < 0.05$; and main effect of group $F_{1,25} = 7.6$, $p = 0.01$). There was a strong trend toward a differential effect of beta-FNA on the two groups though this did not reach significance (drug $\times$ group interaction, $F_{1,25} = 3.4$, $p = 0.08$). Planned comparison of drug effects on 4% sucrose consumption within each group, however, showed that the drug significantly reduced 4% sucrose consumption in the 4-0 group ($t = 2.6$, $p < 0.05$), but had no effect in the 4-20 group ($t = 0.4$, $p = 0.71$).

In the 4-20 group, beta-FNA significantly decreased 20% sucrose consumption ($t = 2.2$, $p < 0.05$). Thus, beta-FNA decreased intake of preferred sucrose solutions in the 4-0 and 4-20 groups. In the 4-0 group, 4% sucrose consumption was significantly decreased. However, in the 4-20 group, 20% but not 4% sucrose was significantly reduced by beta-FNA administration.

To determine if beta-FNA effects within the 4-0 and 4-20 groups varied as a function of individual rats' preference for each solution, we further investigated correlations between beta-FNA effects and individual animals' baseline consumption levels (licks following control vehicle injections: Figure 6A–B). In both groups, suppression of intake caused by beta-FNA was significantly correlated with baseline consumption, but only for the relatively more preferred sucrose solution: 4% sucrose in the 4-0 group ($p < 0.001$ for 4% sucrose; $p = 0.40$ for 0% sucrose [latter data not shown because of low consumption levels]; Pearson correlation) and 20% sucrose in the 4-20 group ($p < 0.001$ for 20% sucrose; $p = 0.39$ for 4% sucrose). Importantly, the significant correlation in the 4-20 group was not dependent on inclusion of an outlying data point (from a rat in which baseline licks were very high: 7871 licks, > 3 SDs from the mean). When this point was excluded, the correlation between baseline consumption and beta-FNA effects on 20% sucrose intake remained highly significant ($r = -0.95$, $p < 0.001$).

Histological analysis showed that injections sites were successfully targeted to the core or shell of the NAcc (Figure 7).

Discussion

We found that administration of the opioid antagonists naltrexone and beta-FNA into the NAcc shell significantly reduced sucrose consumption in both 4-0 and 4-20 groups. However, the suppressive effects of the antagonists were strongly selective, and dependent upon the relative value of sucrose solutions within each group. In the 4-0 group, both naltrexone and beta-FNA decreased 4% sucrose consumption. However, in the 4-20 group, both antagonists decreased 20% but not 4% sucrose consumption. Together, these results demonstrate that endogenous opioid signaling through the MOR promotes consumption of preferred tastants. Moreover, they show that this signaling is dynamic, and can be altered by learned preferences. In the specific case of the 4-20 group, our results suggest that two changes in opioid signaling through the MOR may contribute to consummatory behavior: 1)

loss or attenuation of MOR signaling promoting consumption of 4% sucrose, contributing to learned hypophagia; and 2) increased MOR signaling during 20% sucrose intake, contributing to high levels of consumption.

Beta-FNA infusion decreased consumption of preferred 4% sucrose in the 4-0 group, but had no significant effect on intake of the same solution for the 4-20 group, for which it was nonpreferred. This dissociation of beta-FNA effects provides evidence that MOR signaling promoting food intake is importantly controlled by learned food preferences, and further suggests that decreased MOR signaling can contribute to development of a learned hypophagia. This finding is consistent with previous studies that have shown that opioid signaling plays an important role in selectively promoting intake of preferred foods. In much of this work, food preference has been dictated by differences in the orosensory properties of food options such as taste intensity, macronutrient content, or flavor (Giraud et al., 1993, Glass et al., 1996, Weldon et al., 1996, Zhang et al., 1998, Woolley et al., 2006) for which innate preferences may be present (e.g., for sweet foods over less-sweet alternatives). Our results extend these findings by showing that MOR signaling in the NAcc shell is regulated not only by innate preference, but also by the learned relative value of food options.

Learned hypophagia in the 4-20 group during 4% sucrose access was followed by binge-like consumption of 20% sucrose. Infusion of beta-FNA into the NAcc shell suppressed 20% sucrose intake, reducing intake by approximately 42% relatively to that measured after vehicle infusion. In the 4-0 group, beta-FNA caused a decrease of similar magnitude of 4% sucrose consumption, reducing it by approximately 35%. Together, these findings show that blockade of MOR signaling in the NAcc shell reduced consumption of the preferred sucrose solution in each group, and the magnitude of this reduction was proportional to preference for each solution, as measured by baseline intake (Figure 6). These findings are consistent with a large body of evidence supporting a role for opioid signaling in regulating food preference (Kelley et al., 2002, Gosnell and Levine, 2009, Olszewski et al., 2011), and demonstrate a specific role for MOR signaling in the NAcc shell in selectively increasing intake of preferred foods. Notably, opioid signaling in the NAcc does not appear to regulate intake of all preferred tastants: sugar-conditioned flavor preferences are not significantly decreased by infusion of naltrexone into either the NAcc core or shell (Bernal et al., 2010).

It is notable that beta-FNA infusion was quite selective in its effects on sucrose consumption in the 4-20 group –20% sucrose consumption was substantially decreased (a 42% reduction comparing intake after beta-FNA relative to vehicle), but the effects of the drug on 4% sucrose consumption were small (a 10% reduction). MOR signaling promoting consumption thus acted preferentially to increase consumption of the 20% sucrose solution in this group of animals. This learning-dependent selectivity in MOR signaling may serve to increase feeding efficiency in foraging animals, ensuring that animals consume the most palatable food when choosing between alternatives. Given that palatability cues such as sweetness are typically reliable predictors of caloric content, MOR signaling would thus serve to promote intake of the most energy-dense food available.

Similar learning-dependent changes in opioid signaling may be maladaptive in humans living in environments characterized by food surplus, rather than scarcity. In developed nations, highly palatable foods are easily and cheaply available; the reinforcing value of less-energy dense, possibly healthier alternatives may be diminished by proximity to and anticipation of highly palatable alternatives, resulting in overconsumption of the latter and underconsumption of the former. This selectivity in food choice has been proposed to be particularly relevant to mechanisms underlying binge eating (Cottone 2008). Increased consumption of highly palatable, energy dense foods may increase the likelihood of binge episodes for vulnerable individuals, given that sensory cues associated with these foods can

serve as triggers initiating binge eating episodes (Rogers and Hill, 1989, Waters et al., 2001). Because binge eating is associated with obesity (Spitzer et al., 1992) these mechanisms may also contribute to difficulty in maintaining low-energy diets used for weight control management.

The core and shell regions of the nucleus accumbens have distinct anatomical connections underlying different functional roles in behavior and learning (Zahm, 1999). Our results suggest that these differences extend to regulation of learned food preferences by opioid signaling, as only opioid antagonist infusions in the NAcc shell resulted in a selective reduction of preferred sucrose solution consumption. This is consistent with evidence demonstrating that the NAcc shell, rather than the NAcc core, is more closely associated with mediating the primary reinforcing properties of rewards (e.g., (Rodd-Henricks et al., 2002, Sellings and Clarke, 2003). Consistent with this, MOR stimulation in a small portion of the NAcc shell potently increases positive taste reactivity displays (Pecina and Berridge, 2000, 2005). Exposure to a diet-induced binge protocol selectively increases MOR-binding in the NAcc shell, with no change apparent in the NAcc core (Colantuoni et al., 2001). Anatomically, the NAcc shell has direct projections to the lateral hypothalamus, which plays a key role in control of food intake (Heimer et al., 1991, Zahm and Brog, 1992), and intact neural signaling in the hypothalamus is required for hyperphagia induced by NAcc infusion of DAMGO (Will et al., 2003).

Given these data, it is somewhat surprising that MOR stimulation in both the NAcc shell and NAcc core increase palatable food intake; indeed, substantially stronger hyperphagia is seen after stimulation in the core (Zhang and Kelley, 2000, Katsuura et al., 2011). Other results are also consistent with more widespread involvement of both core and shell in mediating food reward. Access to a highly palatable diet (chocolate Ensure) alters expression of preproenkephalin broadly across the NAcc, encompassing both the core and shell subregions (Kelley et al., 2003). Also, a recent study has shown that chronic suppression of MOR signaling in either core or shell suppresses intake of palatable foods (Lenard et al., 2010). Notably, NAcc core injections selectively attenuated high fat food intake, while shell injections decreased consumption of a sweet solution (chocolate Ensure). Overall, these data suggest a shared role for NAcc subregions in control of palatable food intake, but with distinct roles for the core and shell in controlling specific aspects of intake, such as learned food preferences or macronutrient intake. Our results suggest that that opioid-dependent control of learned food preference is specifically controlled by neural circuits involving the NAcc shell.

Conclusions

Our results demonstrate that MOR signaling in the NAcc shell promotes consumption of a preferred sucrose solution. Through use of an anticipatory contrast paradigm, we demonstrate that this preference and MOR signaling promoting consumption can be dissociated from the sensory properties of the solution. Further, we show that anticipation of a preferred solution reduces MOR signaling-dependent consumption of a less-preferred sucrose solution. These results may have relevance to opioid-dependent mechanisms contributing both to food preference and to binge eating.

Acknowledgments

This work was supported by grants from the March of Dimes and NIH grant R01MH094870 (S.A.T.). We thank Annie Schwager and Shashank Tandon for their critical comments on this work.

Abbreviations

NAcc	nucleus accumbens
Beta-FNA	beta-funaltrexamine
MOR	mu opioid receptor
DOR	delta opioid receptor
DAMGO	[D-Ala2, N-MePhe4, Gly-ol]-enkephalin

References

- Adam TC, Epel ES. Stress, eating and the reward system. *Physiol Behav.* 2007; 91:449–458. [PubMed: 17543357]
- American Psychological Association. Diagnostic and statistical manual of mental disorders. 4. Washington, DC: 2000. text rev
- Bernal SY, Touzani K, Gerges M, Abayev Y, Sclafani A, Bodnar RJ. Opioid receptor antagonism in the nucleus accumbens fails to block the expression of sugar-conditioned flavor preferences in rats. *Pharmacol Biochem Behav.* 2010; 95:56–62. [PubMed: 20006967]
- Bodnar RJ, Glass MJ, Ragnauth A, Cooper ML. General, mu and kappa opioid antagonists in the nucleus accumbens alter food intake under deprivation, glucoprivic and palatable conditions. *Brain Res.* 1995; 700:205–212. [PubMed: 8624711]
- Boggiano MM, Chandler PC, Viana JB, Oswald KD, Maldonado CR, Wauford PK. Combined dieting and stress evoke exaggerated responses to opioids in binge-eating rats. *Behav Neurosci.* 2005; 119:1207–1214. [PubMed: 16300427]
- Colantuoni C, Rada P, McCarthy J, Patten C, Avena NM, Chadeayne A, Hoebel BG. Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. *Obes Res.* 2002; 10:478–488. [PubMed: 12055324]
- Colantuoni C, Schwenker J, McCarthy J, Rada P, Ladenheim B, Cadet JL, Schwartz GJ, Moran TH, Hoebel BG. Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. *Neuroreport.* 2001; 12:3549–3552. [PubMed: 11733709]
- Corwin RL, Wojnicki FH. Baclofen, raclopride, and naltrexone differentially affect intake of fat and sucrose under limited access conditions. *Behav Pharmacol.* 2009; 20:537–548. [PubMed: 19724193]
- Cottone P, Sabino V, Steardo L, Zorrilla EP. Opioid-dependent anticipatory negative contrast and binge-like eating in rats with limited access to highly preferred food. *Neuropsychopharm.* 2008; 33:524–535.
- Davis CA, Levitan RD, Reid C, Carter JC, Kaplan AS, Patte KA, King N, Curtis C, Kennedy JL. Dopamine for “wanting” and opioids for “liking”: a comparison of obese adults with and without binge eating. *Obesity (Silver Spring).* 2009; 17:1220–1225. [PubMed: 19282821]
- Giraud SQ, Grace MK, Welch CC, Billington CJ, Levine AS. Naloxone’s anorectic effect is dependent upon the relative palatability of food. *Pharmacol Biochem Behav.* 1993; 46:917–921. [PubMed: 8309972]
- Giuliano C, Robbins TW, Nathan PJ, Bullmore ET, Everitt BJ. Inhibition of Opioid Transmission at the mu-Opioid Receptor Prevents Both Food Seeking and Binge-Like Eating. *Neuropsychopharm.* 2012; 37:2643–2652.
- Glass MJ, Grace M, Cleary JP, Billington CJ, Levine AS. Potency of naloxone’s anorectic effect in rats is dependent on diet preference. *Am J Physiol.* 1996; 271:R217–221. [PubMed: 8760223]
- Gosnell BA, Levine AS. Reward systems and food intake: role of opioids. *Int J Obes (Lond).* 2009; 33(Suppl 2):S54–58. [PubMed: 19528981]
- Heimer L, Zahm DS, Churchill L, Kalivas PW, Wohltmann C. Specificity in the projection patterns of accumbal core and shell in the rat. *Neurosci.* 1991; 41:89–125.

- Katsuura Y, Heckmann JA, Taha SA. Mu opioid receptor stimulation in the nucleus accumbens elevates fatty tastant intake by increasing palatability and suppressing satiety signals. *Am J Physiol Regul Integr Comp Physiol*. 2011; 301:R244–254. [PubMed: 21543633]
- Katsuura Y, Taha SA. Modulation of feeding and locomotion through mu and delta opioid receptor signaling in the nucleus accumbens. *Neuropeptides*. 2010; 44:225–232. [PubMed: 20044138]
- Kelley AE, Bakshi VP, Haber SN, Steininger TL, Will MJ, Zhang M. Opioid modulation of taste hedonics within the ventral striatum. *Physiol Behav*. 2002; 76:365–377. [PubMed: 12117573]
- Kelley AE, Bless EP, Swanson CJ. Investigation of the effects of opiate antagonists infused into the nucleus accumbens on feeding and sucrose drinking in rats. *J Pharmacol Exp Ther*. 1996; 278:1499–1507. [PubMed: 8819538]
- Kelley AE, Will MJ, Steininger TL, Zhang M, Haber SN. Restricted daily consumption of a highly palatable food (chocolate Ensure(R)) alters striatal enkephalin gene expression. *Eur J Neurosci*. 2003; 18:2592–2598. [PubMed: 14622160]
- Lenard NR, Zheng H, Berthoud HR. Chronic suppression of mu-opioid receptor signaling in the nucleus accumbens attenuates development of diet-induced obesity in rats. *Int J Obes (Lond)*. 2010; 34:1001–1010. [PubMed: 20065959]
- Miller CA, Golden NH. An introduction to eating disorders: clinical presentation, epidemiology, and prognosis. *Nutr Clin Pract*. 2010; 25:110–115. [PubMed: 20413691]
- Olszewski PK, Alsio J, Schioth HB, Levine AS. Opioids as facilitators of feeding: can any food be rewarding? *Physiol Behav*. 2011; 104:105–110. [PubMed: 21536057]
- Paxinos, G.; Watson, C. The rat brain in stereotaxic coordinates. New York: Academic Press; 1997.
- Pecina S, Berridge KC. Opioid site in nucleus accumbens shell mediates eating and hedonic ‘liking’ for food: map based on microinjection Fos plumes. *Brain Res*. 2000; 863:71–86. [PubMed: 10773195]
- Pecina S, Berridge KC. Hedonic hot spot in nucleus accumbens shell: where do mu-opioids cause increased hedonic impact of sweetness? *J Neurosci*. 2005; 25:11777–11786. [PubMed: 16354936]
- Portoghese PS, Larson DL, Sayre LM, Fries DS, Takemori AE. A novel opioid receptor site directed alkylating agent with irreversible narcotic antagonistic and reversible agonistic activities. *J Med Chem*. 1980; 23:233–234. [PubMed: 6245210]
- Rao RE, Wojnicki FH, Coupland J, Ghosh S, Corwin RL. Baclofen, raclopride, and naltrexone differentially reduce solid fat emulsion intake under limited access conditions. *Pharmacol Biochem Behav*. 2008; 89:581–590. [PubMed: 18353432]
- Rodd-Henricks ZA, McKinzie DL, Li TK, Murphy JM, McBride WJ. Cocaine is self-administered into the shell but not the core of the nucleus accumbens of Wistar rats. *J Pharmacol Exp Ther*. 2002; 303:1216–1226. [PubMed: 12438546]
- Rogers PJ, Hill AJ. Breakdown of dietary restraint following mere exposure to food stimuli: interrelationships between restraint, hunger, salivation, and food intake. *Addict Behav*. 1989; 14:387–397. [PubMed: 2782122]
- Schroy PL, Wheeler RA, Davidson C, Scalera G, Twining RC, Grigson PS. Role of gustatory thalamus in anticipation and comparison of rewards over time in rats. *Am J Physiol Regul Integr Comp Physiol*. 2005; 288:R966–980. [PubMed: 15591157]
- Sellings LH, Clarke PB. Segregation of amphetamine reward and locomotor stimulation between nucleus accumbens medial shell and core. *J Neurosci*. 2003; 23:6295–6303. [PubMed: 12867514]
- Shin AC, Pistell PJ, Phifer CB, Berthoud HR. Reversible suppression of food reward behavior by chronic mu-opioid receptor antagonism in the nucleus accumbens. *Neurosci*. 2010; 170:580–588.
- Siega-Riz AM, Haugen M, Meltzer HM, Von Holle A, Hamer R, Torgersen L, Knopf-Berg C, Reichborn-Kjennerud T, Bulik CM. Nutrient and food group intakes of women with and without bulimia nervosa and binge eating disorder during pregnancy. *The American journal of clinical nutrition*. 2008; 87:1346–1355. [PubMed: 18469258]
- Spitzer RL, Devlin M, Walsh BT, Hasin D, Wing R, Marcus M, Stunkard A, Wadden T, Yanovski S, Agras S, Mitchell J, Nonas C. Binge eating disorder: A multisite field trial of the diagnostic criteria. *International Journal of Eating Disorders*. 1992; 11:191–203.
- Taha SA, Katsuura Y, Noorvash D, Seroussi A, Fields HL. Convergent, not serial, striatal and pallidal circuits regulate opioid-induced food intake. *Neurosci*. 2009; 161:718–733.

- Taha SA, Norsted E, Lee LS, Lang PD, Lee BS, Woolley JD, Fields HL. Endogenous opioids encode relative taste preference. *Eur J Neurosci.* 2006; 24:1220–1226. [PubMed: 16925586]
- Ward HG, Nicklous DM, Aloyo VJ, Simansky KJ. Mu-opioid receptor cellular function in the nucleus accumbens is essential for hedonically driven eating. *Eur J Neurosci.* 2006; 23:1605–1613. [PubMed: 16553624]
- Waters A, Hill A, Waller G. Internal and external antecedents of binge eating episodes in a group of women with bulimia nervosa. *Int J Eat Disord.* 2001; 29:17–22. [PubMed: 11135328]
- Weldon DT, O'Hare E, Cleary J, Billington CJ, Levine AS. Effect of naloxone on intake of cornstarch, sucrose, and polycose diets in restricted and nonrestricted rats. *Am J Physiol.* 1996; 270:R1183–1188. [PubMed: 8764280]
- Will MJ, Franzblau EB, Kelley AE. Nucleus accumbens mu-opioids regulate intake of a high-fat diet via activation of a distributed brain network. *J Neurosci.* 2003; 23:2882–2888. [PubMed: 12684475]
- Wong KJ, Wojnicki FH, Corwin RL. Baclofen, raclopride, and naltrexone differentially affect intake of fat/sucrose mixtures under limited access conditions. *Pharmacol Biochem Behav.* 2009; 92:528–536. [PubMed: 19217918]
- Woolley JD, Lee BS, Fields HL. Nucleus accumbens opioids regulate flavor-based preferences in food consumption. *Neurosci.* 2006; 143:309–317.
- Yanovski SZ, Leet M, Yanovski JA, Flood M, Gold PW, Kissileff HR, Walsh BT. Food selection and intake of obese women with binge-eating disorder. *The American journal of clinical nutrition.* 1992; 56:975–980. [PubMed: 1442665]
- Zahm DS. Functional-anatomical implications of the nucleus accumbens core and shell subterritories. *Ann N Y Acad Sci.* 1999; 877:113–128. [PubMed: 10415646]
- Zahm DS, Brog JS. On the significance of subterritories in the “accumbens” part of the rat ventral striatum. *Neurosci.* 1992; 50:751–767.
- Zhang M, Gosnell BA, Kelley AE. Intake of high-fat food is selectively enhanced by mu opioid receptor stimulation within the nucleus accumbens. *J Pharmacol Exp Ther.* 1998; 285:908–914. [PubMed: 9580643]
- Zhang M, Kelley AE. Opiate agonists microinjected into the nucleus accumbens enhance sucrose drinking in rats. *Psychopharm.* 1997; 132:350–360.
- Zhang M, Kelley AE. Enhanced intake of high-fat food following striatal mu-opioid stimulation: microinjection mapping and fos expression. *Neurosci.* 2000; 99:267–277.
- Zhang M, Kelley AE. Intake of saccharin, salt, and ethanol solutions is increased by infusion of a mu opioid agonist into the nucleus accumbens. *Psychopharm.* 2002; 159:415–423.

Highlights

- Anticipatory contrast models food choice and excessive consumption occurring in binge eaters.
- Opioid antagonists in the nucleus accumbens shell reduce intake of preferred sucrose solutions.
- Opioid signaling may contribute to patterns of food choice that increase the risk of binge eating.

Figure 1.

(A) Anticipatory contrast paradigm. (B) After training in the anticipatory contrast paradigm, rats in the 4-0 group (black bars) consumed significantly more 4% sucrose in block 1 than rats in the 4-20 group (gray bars). Data shown includes all rats in the 4-0 group (n=42) and the 4-20 group (n=41) and reflects performance in the final training session prior to drug infusion.

Figure 2.

Infusion of the nonspecific opioid antagonist naltrexone into the NAcc shell selectively decreased intake of the preferred sucrose solution in 4-0 and 4-20 groups. (A) Naltrexone infusion in the NAcc shell decreased licks devoted to 4% sucrose by rats in the 4-0 (black bars) group during block 1, but did not significantly change 4% sucrose consumption by rats in the 4-20 groups (gray bars). (B) Naltrexone infusion decreased 20% sucrose consumption in the 4-20 group during block 2.

Figure 3.

Naltrexone infusion into the NAcc core. (A) Naltrexone infusion increased 4% sucrose intake in 4-0 group after the 1 ug dose only. In the 4-20 group, 4% sucrose was decreased after the 1 ug dose. (B) 20% sucrose consumption was significantly decreased by NAcc core naltrexone. Conventions in Figures 3–5 are identical to those in Figure 2.

Figure 4. Naltrindole infusion into the NAcc shell (A) Naltrindole infusion increased 4% sucrose consumption for both 4-0 and 4-20 groups. (B) 20% sucrose consumption in block 2 was significantly increased by naltrindole infusion.

Figure 5. Beta-FNA infusion into the NAcc shell. (A) Beta-FNA significantly decreased 4% sucrose consumption in the 4-0 but not the 4-20 group. (B) Beta-FNA significantly decreased 20% consumption in the 4-20 group.

Figure 6.

Beta-FNA suppression of sucrose intake was correlated with baseline intake. (A) In the 4-0 group, the effects of beta-FNA were inversely correlated with baseline 4% sucrose intake (licks after control vehicle infusion). Y-axis shows the change in consumption after beta-FNA relative to baseline intake; the x-axis shows baseline intake (B) beta-FNA effects in the 4-20 group were negatively correlated with baseline intake of 20% but not 4% sucrose.

Figure 7.
Cannula placements were localized to the NAcc core (blue) or shell (black).