



Basolateral amygdala opioids contribute to increased high-fat intake following intra-accumbens opioid administration, but not following 24-h food deprivation

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ABSTRACT

Previous research has demonstrated that administration of μ -opioid receptor agonists into the nucleus accumbens increases high-fat diet consumption in sated rats and has shown a role of basolateral amygdala (BLA) activity in mediating this response. The present experiments were conducted to examine the role of BLA opioid transmission in mediating high-fat feeding driven by either intra-accumbens opioid activation or 24-h home cage food deprivation. Injection of the μ -opioid agonist, D-Ala2-NMe-Phe4-Glyol5-enkephalin (DAMGO) into the nucleus accumbens (0.25 μ g/0.5 μ l/site) increased consumption of a high-fat diet, and this effect was attenuated by pre-treatment with the opioid antagonist, naltrexone (5 μ g/0.25 μ l/site) administered into the BLA. In contrast, intra-BLA naltrexone administration had no influence on the increase in high-fat intake following 24-h food deprivation. These findings suggest that BLA opioid transmission is an important mediator of palatability-driven feeding as modeled by intra-accumbens opioid activation, while BLA opioid transmission has no significant influence on the increase in high-fat feeding driven by short-term negative-energy balance.

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1. Introduction

Feeding behavior is mediated by an assortment of factors, including homeostatic mechanisms (Saper et al., 2002), learned associations (Petrovich et al., 2007), and the rewarding nature of the food (Berridge, 2009; Berthoud, 2004). The process by which the rewarding, or hedonic, characteristic of food drives feeding (Kelley et al., 2005) is vital to understanding the current obesity trend. A well-characterized animal model of this process involves opioid activation of the nucleus accumbens (Kelley et al., 2005). Intra-accumbens administration of μ -opioid receptor agonist D-Ala2-NMe-Phe4-Glyol5-enkephalin (DAMGO) produces exaggerated consumption, specifically of palatable foods such as a high-fat diet, and enhances operant responding for food reward (Bakshi and Kelley, 1993; Zhang and Kelley, 2002). Additionally, intra-accumbens μ -opioid receptor activation increases “liking” reactions displayed by rats in taste reactivity responses to intra-oral sucrose administration (Pecina and Berridge, 2005). These studies and others suggest that activation of the nucleus accumbens opioid system increases consumption by altering the hedonic impact (or palatable nature) of food (Kelley et al., 2005).

The potentiation of high-fat intake following intra-accumbens opioid activation is dependent on a distributed network of feeding-related regions located throughout cortical, limbic, and brainstem areas (Will et al., 2003). The basolateral amygdala (BLA), shown to be important for regulating emotion and motivation, is an integral part of this distributed opioid-driven feeding network (Will et al., 2004). The BLA is well positioned to communicate with brain regions that influence processes that drive feeding behavior, including emotional and sensory inputs from prefrontal and gustatory cortex (Shi and Cassell, 1998) and brainstem parabrachial nuclei (Fulwiler and Saper, 1984; Saper and Loewy, 1980), and critical outputs to the hypothalamus, ventral striatum, and motor output regions necessary to express feeding behavior (Kelley et al., 1982; Swanson, 1982; Alheid, 2003).

It has been demonstrated that activation of the BLA is required to observe the increased consumption of a high-fat diet following intra-accumbens opioid activation (Will et al., 2004), as temporary inactivation of the BLA with the GABA_A agonist muscimol prevented the robust increase in high-fat intake following intra-accumbens DAMGO, yet having no influence on baseline intake (Will et al., 2004). In contrast, intra-BLA muscimol had no influence on high-fat consumption following 24-h food deprivation, suggesting a specific role for BLA activity in mediating feeding driven by striatal opioid activation (Will et al., 2009). Together, these data point to an important BLA signaling pathway that specifically drives opioid-induced high-fat feeding beyond satiety, as opposed to driving feeding towards satiety through a short-term energy-deficit.

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The present experiments aimed to examine the specific neurochemical nature of this BLA signaling that selectively contributes to the opioid-driven, but not energy-deficit driven feeding. BLA opioids are a likely candidate, considering that BLA opioids have been shown to influence reward-related behaviors associated with both drug (Marinelli et al., 2010) and natural rewards (Wassum et al., 2009; Petrovich and Gallagher, 2003). Therefore, the involvement of BLA opioid transmission was examined using the general nonselective opioid antagonist naltrexone. Rats were given ad libitum access to a high-fat diet following bilateral administration of naltrexone or vehicle into the BLA immediately prior to administration of DAMGO or vehicle into the nucleus accumbens. A second group of rats were given ad libitum access to a palatable diet immediately after bilateral administration of naltrexone or vehicle into the BLA following either 24-h home cage food deprivation or no deprivation. Automated feeding chambers simultaneously assessed general locomotor activity, number and duration of food hopper entries, and food consumption.

2. Methods

2.1. Subjects

18 adult male Sprague–Dawley rats (Harlan Sprague–Dawley, Inc., Indianapolis, IN) weighing 300–400 g, were housed in groups of two in Plexiglas cages in a climate-controlled colony room at a temperature of 22 °C. The rats were maintained on a 12-h light–dark cycle, and all experiments were conducted during the light phase (0700–1900) between the hours of 1200 and 1500. Unless otherwise noted, rats had free access to laboratory chow and drinking water before and throughout the experiment. Groups contained 8–10 rats. All experimental procedures were in accord with protocols approved by the University of Missouri Institutional Animal Care and Use Committee.

2.2. Surgery

Rats were anesthetized with a mixture of ketamine and xylazine (90 mg/kg and 9 mg/kg, respectively; Sigma, St. Louis, MO), and 2 sets of guide stainless steel cannulas (23 gauge, 10 mm) were stereotactically targeted bilaterally above the border of the nucleus accumbens core and lateral shell and above the BLA (Experiment 1). For Experiment 2, each rat was only implanted with bilateral cannulas targeted above the BLA. Therefore, each rat was implanted with four cannulas in Experiment 1 and two cannulas in Experiment 2. Guide cannulas were secured to the skull with stainless steel screws and light curable resin (Dental Supply of New England, Boston) using standard flat-skull techniques. After surgery, wire stylets were placed in the guide cannulas to prevent occlusion. Coordinates for the aimed sites are as follows: nucleus accumbens: AP, +1.4; ML, \pm 2.0; DV, –7.8 and BLA: AP, –2.8; ML, \pm 4.7; DV: –8.6. The coordinates for both regions were chosen to allow valid cross-study comparisons to an earlier study (Will et al., 2009). While the targeted region for the accumbens is near the border of the core and lateral shell, the injection volume used (0.5 μ l) likely allows diffusion beyond the core and lateral shell. Therefore, the region being studied is referred to more generally as the ‘nucleus accumbens’ throughout the paper.

2.3. Apparatus

Behavioral assessment of feeding took place in a room separate from the colony room in eight Plexiglas (30.5 cm \times 24.1 cm \times 21.0 cm) custom-built feeding chambers (Med Associates, St. Albans, VT). Rats had access to water ad libitum and approximately 35 g of palatable diet. Feeding chambers were equipped with four infrared locomotor activity beams located 6 cm apart across the length of the chamber and 4.3 cm above the floor. An automated weigh scale for the food

hopper monitored the consumption of food. An additional infrared beam spanning the entrance of the food hopper determined the number and duration of each head entry into the hopper area. The feeding hopper and water bottle were located on the same side (opposite corners) of one chamber wall, and a removable waste tray was located beneath the bar floor. The measurements included locomotor activity (number of horizontal beam breaks), duration of hopper entry (duration of beam break at the entrance of the hopper), hopper entries (number of beam breaks at the entrance to the hopper), and amount consumed (grams of diet consumed). Testing periods consisted of behavioral monitoring in the feeding chambers by a computer running Med-PC software (Med Associates Version IV, St. Albans, VT).

2.4. Drug microinjection

D-Ala2, NMe-Phe4, Glyol5-enkephalin (DAMGO; Research Biochemicals, Natick, MA) and naltrexone (Sigma, St. Louis, MO) were both dissolved in sterile 0.9% saline. The vehicle control was always sterile 0.9% saline. Infusions were delivered with a microdrive pump (Harvard Apparatus, South Natick, MA), connected by means of polyethylene tubing (PE-10), while rats were gently handheld. Thirty-three-gauge 12.5-mm injectors were used, extending 2.5 mm beyond the end of the guide cannulas. The rate of injection was 0.32 μ l/min for the nucleus accumbens and 0.16 μ l/min for the BLA, with the total duration of infusion being 93 s, resulting in 0.5- μ l and 0.25- μ l volumes, respectively. One additional minute was allowed for diffusion.

2.5. Behavioral assessment of feeding

All behavioral testing began 1-week post-surgery and occurred in the Med Associates monitors described. Rats were placed in these monitors for 2 h daily until stable food consumption across 3 days was obtained, usually occurring within 6 days. Animals were given 2 days of sham injections over the last 2 days of the baseline period to ensure acclimation to the treatment procedure. On the first day of this acclimation procedure, a 10-mm injector was inserted and left in place for 2 min, with no volume injected. The following day, a 12.5-mm injector was inserted, and saline was administered for 93 s. In Experiment 1, naltrexone (5 μ g/0.25 μ l/side bilaterally) or saline was infused into BLA, followed immediately by DAMGO (0.25 μ g/0.5 μ l/side bilaterally) or saline into the nucleus accumbens, thus resulting in four possible treatment combinations. In Experiment 2, naltrexone (5 μ g/0.25 μ l/side bilaterally) or saline was administered into the BLA after either a 24-h period of home cage chow deprivation or ad libitum access. The test session began immediately after the last injection. There were at least 2 days between treatment sessions that were scheduled in a counter-balanced order.

2.6. Specialized diet

The specialized sweetened high-fat diet was obtained from Teklad, Inc., Madison, WI. The diet contained 278.3 g/kg vitamin free casein, 4.2 g/kg DL-methionine, 100.0 g/kg sucrose, 441.2 g/kg shortening, 77.7 g/kg safflower oil, 26.3 g/kg cellulose, 53.3 g/kg mineral mix, 15.2 g/kg vitamin mix and 3.8 g/kg choline chloride. All components are expressed as weight (g). Based on energy, the diet is 6.2 kcal/g.

2.7. Histology

After behavioral testing was completed, subjects were overdosed with sodium pentobarbital and perfused transcardially with heparinized saline (200 ml), followed immediately by 500 ml of a 10% buffered formalin solution. The brains were then removed and placed in 10% formalin–20% sucrose for 1 week. Frozen serial sections

(40 μ m) were collected through the entire extent of the injection site, mounted on gelatinized slides, and counter-stained with cresyl violet. Cannula placement profiles were then analyzed for accuracy and data from rats with misplaced cannula were not included in the analyses. The placement of all BLA cannula and nucleus accumbens cannula are represented in histological schematic drawings (Fig. 1).

2.8. Statistical analysis

For Experiment 1 ($n = 10$), all feeding measures (food consumption, locomotor activity, hopper entries, duration of hopper entry) for the total 2 h session and across the various treatment conditions were analyzed using a two-factor within-subjects analysis of variance (ANOVA: nucleus accumbens treatment \times BLA treatment), with the levels for each factor being either vehicle or drug. For Experiment 2 ($n = 8$), these same measures were also analyzed using a two-factor within-subjects analysis of variance (ANOVA: Food deprivation state \times BLA treatment), with the levels for each factor being either non-deprived or deprived and vehicle or naltrexone. Preplanned contrasts of means were conducted across treatments, between drug and vehicle and between each brain region (Experiment 1) or drug or vehicle and deprivation state (Experiment 2).

3. Results

3.1. Experiment 1 – Influence of intra-BLA naltrexone on the increased high-fat feeding behavior following intra-accumbens DAMGO

An ANOVA conducted on the food consumption data for Experiment 1 revealed a significant main effect of intra-accumbens DAMGO treatment ($F(1,9) = 164.7$, $p < 0.0001$), intra-BLA naltrexone treatment ($F(1,9) = 41.58$, $p < 0.0001$), and a significant nucleus accumbens \times BLA treatment interaction ($F(1,9) = 16.78$, $p < 0.005$). As displayed in Fig. 2, post-hoc comparisons revealed that naltrexone administration into the BLA had no effect on baseline consumption by itself ($p = 0.48$). Intra-BLA naltrexone treatment

significantly reduced the increased food consumption driven by DAMGO administration into the accumbens ($p < 0.0001$), yet remained significantly elevated compared to baseline levels ($p < 0.0001$). An ANOVA conducted on the total duration of all hopper entries across the entire feeding session revealed a significant main effect of intra-accumbens DAMGO treatment ($F(1,9) = 77.67$, $p < 0.0001$), intra-BLA naltrexone treatment ($F(1,9) = 16.75$, $p < 0.005$), and a significant nucleus accumbens \times BLA treatment interaction ($F(1,9) = 17.24$, $p < 0.005$). Post-hoc comparisons revealed that naltrexone had no effect compared to saline treatment ($p = 0.89$). Naltrexone treatment significantly reduced the increased DAMGO-driven hopper entry duration driven by food deprivation ($p < 0.0005$), yet remained significantly elevated compared to baseline levels ($p < 0.005$) (Fig. 3).

An ANOVA conducted on the number of hopper entries across the entire feeding session revealed a significant main effect of intra-accumbens DAMGO treatment ($F(1,9) = 34.23$, $p < 0.001$), but there was no effect of intra-BLA naltrexone treatment ($F(1,9) = 1.74$, ns). Post-hoc comparisons revealed that intra-accumbens DAMGO increased the total number of hopper entries compared to saline treatment ($p < 0.005$) and while intra-BLA naltrexone reduced the total number of hopper entries elicited by DAMGO, this did not quite reach significance ($p = 0.08$) (see Table 1). The trend for naltrexone to decrease hopper entries was not related to general activity, as an ANOVA conducted on locomotor activity revealed no effect of these drug treatments across the feeding session for intra-accumbens DAMGO treatment ($F(1,9) = 2.28$, ns), intra-BLA naltrexone treatment ($F(1,9) = 0.23$, ns), or nucleus accumbens \times BLA treatment interaction ($F(1,9) = 1.1$, ns) (Table 2).

3.2. Experiment 2 – Influence of intra-BLA naltrexone on high-fat feeding following 24-h food deprivation

24-h food deprivation led to a significant increase in palatable diet consumption, as an ANOVA conducted across the entire session revealed a significant main effect of deprivation state ($F(1,7) = 58.47$, $p < 0.001$), a

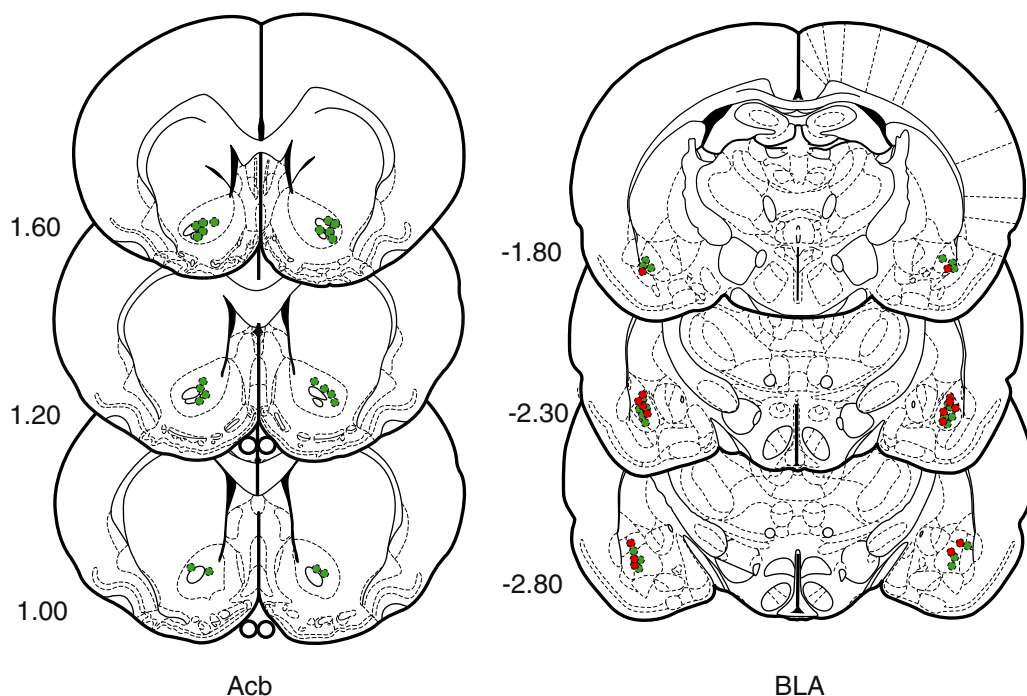


Fig. 1. Histological analysis and placement for DAMGO injections into the nucleus accumbens and naltrexone injections into the BLA for Experiment 1 (green) and Experiment 2 (red). Drawings and coordinates are based on the atlas of Paxinos and Watson (1998).

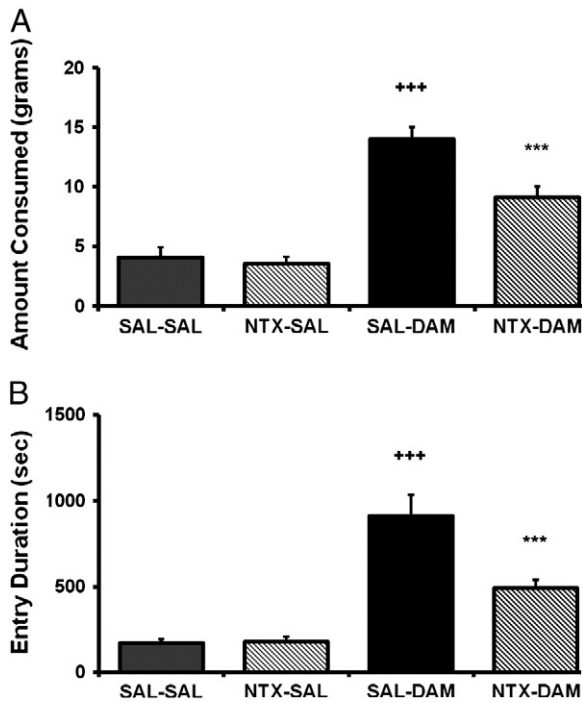


Fig. 2. (A) Amount of food intake and (B) hopper entry duration (duration of beam break at entry of hopper) after intra-accumbens DAMGO administration (DAM, 0.25 μ g/0.5 μ l) or saline (SAL) immediately after either naltrexone (NTX; 5 μ g/0.25 μ l per side) or saline (SAL) administration into the BLA. The x axis labels refer to treatment for the two regions (i.e., nucleus accumbens treatment-BLA treatment). Values represent group means (\pm S.E.M.). Plus sign represents SAL-SAL versus SAL-DAM. Asterisk represents SAL-DAM versus NTX-DAM. Level of significance in all noted comparisons, $p < 0.0005$.

non-significant trend for an effect of BLA treatment ($F(1,7) = 5.123$, $p = 0.06$), but no interaction ($F(1,7) = 0.005$, $p = 0.94$). In contrast to the DAMGO-driven food consumption observed in Experiment 1, post-hoc contrasts revealed that intra-BLA naltrexone did not significantly reduce the increased food consumption driven by food restriction ($p = 0.092$). This treatment also still produced a marked consumption increase compared to non-deprived control treatment ($p < 0.005$). There was a trend for naltrexone to reduce intake by itself in the non-deprived condition, but this was not significant ($p = 0.11$). An ANOVA conducted on the combined duration of all hopper entries across entire feeding session revealed no main effect of deprivation state ($F(1,7) = 4.84$, ns) or intra-BLA naltrexone treatment ($F(1,7) = 2.89$, ns). As shown in Table 1, there was no main effect of deprivation state ($F(1,7) = 0.89$, ns) or intra-BLA naltrexone treatment ($F(1,7) = 4.95$, ns) on the number of food hopper entries. Finally, an ANOVA conducted on the activity levels revealed no effect of deprivation state ($F(1,7) = 0.04$, ns) or intra-BLA naltrexone treatment ($F(1,7) = 1.50$, ns) (Table 2).

4. Discussion

The present experiments investigated the potential role of BLA opioid transmission in mediating feeding of a high-fat diet driven by either intra-accumbens opioid activation or 24-h food deprivation. Consistent with previous research (Zhang and Kelley, 2002; Will et al., 2003; Will et al., 2004; Kelley et al., 2005; Will et al., 2009), intra-accumbens DAMGO administration significantly increased consumption of the high-fat diet. Prior administration of intra-BLA naltrexone significantly reduced the intra-accumbens DAMGO-driven consumption of the high-fat diet. In regard to other measured feeding behaviors, intra-BLA naltrexone also significantly reduced the DAMGO-driven food hopper entries and hopper entry durations. These approach behaviors were not associated with changes in general locomotor activity levels as

intra-accumbens DAMGO administration led to similar locomotor activity levels, regardless of the BLA treatment.

In the second experiment, this same intra-BLA naltrexone treatment was without influence on the increased high-fat intake produced by 24-h home cage food deprivation. There was a trend for intra-BLA naltrexone treatment to reduce intake, yet this was observed for both non-deprived and deprived conditions to a similar degree. It is known that general inactivation of the adjacent central nucleus of the amygdala robustly reduces baseline feeding (Will et al., 2009), so the possibility of diffusion to this site may explain this trend. Together, these findings suggest that BLA opioid transmission is a key signaling event that specifically mediates opioid-driven feeding of a high-fat intake driven by ventral striatal opioid activation. In contrast, BLA opioid transmission does not appear to be involved in the increased feeding of a high-fat diet following short-term food deprivation.

Previous evidence suggesting a role for BLA neurons in mediating opiate reward processes include its role in altering sensory properties (Fontanini et al., 2009), learned reward associations (Schoenbaum et al., 1998; Tye and Janak, 2007) and taste reactivity and consumption behaviors (Berridge, 1996; Will et al., 2009). Moreover, BLA opioids in particular have been shown to influence reward-related behaviors associated with both drug (Marinelli et al., 2010) and natural rewards (Wassum et al., 2009; Petrovich and Gallagher, 2003). The anatomical connectivity of the BLA includes the major output pathway of the BLA to the accumbens (Kelley et al., 1982) and the ventral tegmental area, therefore having potential to alter the mesolimbic dopaminergic pathway known to regulate opiate reward (Koob, 1992). The BLA also projects to the lateral hypothalamus both directly and indirectly through the central nucleus of the amygdala (Petrovich et al., 2001) and receives inputs from gustatory cortex, brainstem and thalamic nuclei (Shi and Cassell, 1998; Fulwiler and Saper, 1984; Saper and Loewy, 1980). However, while the connectivity is well known, there is little evidence as to what influence blocking opioid transmission in the BLA would have on these pathways.

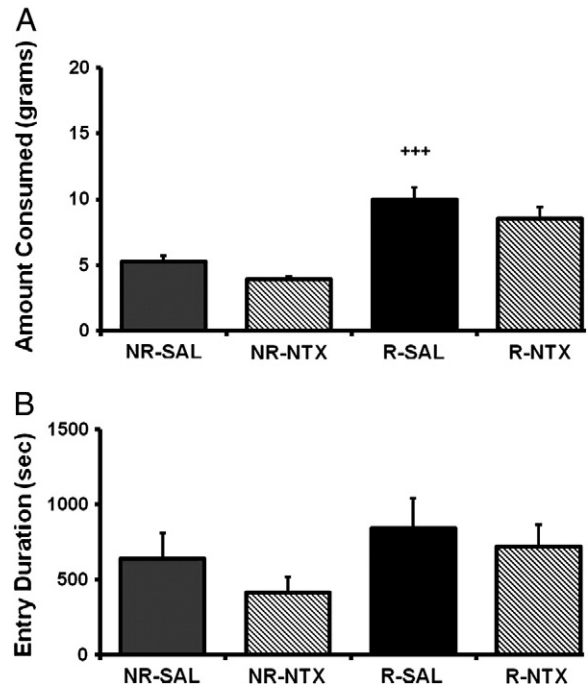


Fig. 3. (A) Amount of food intake and (B) hopper entry duration (duration of beam break at entry of hopper) after 24-h food deprivation (R) or no deprivation (NR) after either naltrexone (NTX; 5 μ g/0.25 μ l per side) or saline (SAL) administration into the BLA. The x axis labels refer to deprivation state and intra-BLA treatment (i.e., deprivation state-BLA treatment). Values represent group means (\pm S.E.M.). Plus sign represents NR/SAL versus R/SAL. Level of significance noted, $p < 0.001$.

Table 1
Food hopper entries.

Pre-treatment	Saline	NTX	Saline	NTX
Post-treatment	Saline	Saline	DAMGO	DAMGO
Experiment 1	70.3 ± 12.2	67.5 ± 17.9	210.5 ± 37.5*	145.1 ± 17.8
Pre-treatment	Non-restricted	Restricted	Non-restricted	Restricted
Post-treatment	Saline	Saline	NTX	NTX
Experiment 2	118.1 ± 20.6	137.9 ± 25.1	92.5 ± 15.0	93.5 ± 11.6

Note. Values represent group means plus or minus the standard error of the mean for a 2-h measure of food hopper entries (no. of beam breaks at entry of hopper). For Experiment 1, a superscript asterisk (* $p < 0.005$) represents DAMGO/SAL vs. SAL/SAL (each pairing represents the order of administration). For Experiment 2, there were no significant differences.

The influence of intra-BLA naltrexone on DAMGO-induced consumption produced the same effect as that found previously using intra-BLA muscimol administration (Will et al., 2009). However, while both drugs reduced the increased consumption, the magnitude of the effect produced by naltrexone in the present study was less. Whether this was due to the distinctive nature of the receptors targeted by each drug or a dose–response function is unknown, but a more extensive dose–response study would address this issue. It is likely that muscimol, commonly used pharmacological tool to “inactivate” a region of interest (Herry et al., 2008), led to more generalized inhibition of the BLA, including output pathways that were unaltered by intra-BLA naltrexone administration.

Future studies examining the role of opioid transmission in the central nucleus of the amygdala would be of interest, as prior research has shown activation of the central nucleus is required for intra-accumbens DAMGO-driven feeding of a high-fat diet (Will et al., 2009). While general inactivation of the central nucleus of the amygdala with muscimol blocks increased chow intake following a 24-h food deprivation (Minano et al., 1992; Baldo et al., 2005), the involvement of the central nucleus of the amygdala on high-fat feeding following food deprivation has not been explored. Administration of DAMGO and naltrexone into the central nucleus of the amygdala have been shown to increase or decrease chow feeding, respectively, in a study demonstrating a bi-directional μ -opioid–opioid connection between the central amygdala and the accumbens (Kim et al., 2004). It would be of interest to explore this defined network to potentially distinguish what the present results show to be dissociable systems underlying palatable feeding driven by opioids versus food deprivation.

In summary, the present experiments provide the novel finding that opioid transmission in the BLA is involved in mediating intra-accumbens opioid-driven feeding behavior associated with a high-fat diet. In contrast, feeding behavior driven by a short-term energy-deficit is not dependent on BLA opioid transmission, suggesting a specific role of BLA opioids in mediating palatability-driven feeding. This is especially intriguing when considering that one of the major

Table 2
Activity.

Pre-treatment	Saline	NTX	Saline	NTX
Post-treatment	Saline	Saline	DAMGO	DAMGO
Experiment 1	1556 ± 194.9	1356 ± 241.8	2028 ± 484	2524 ± 594.6
Pre-treatment	Non-Restricted	Restricted	Non-Restricted	Restricted
Post-treatment	Saline	Saline	NTX	NTX
Experiment 2	869 ± 118.9	910 ± 124.2	789 ± 121.7	785 ± 66.7

Note. Values represent group means (+/–S.E.M.) for a 2-h measure of general activity (beam breaks). In both experiments, there were no differences in activity.

underlying causes of the current obesity epidemic is overconsumption of palatable tasty food in a non-deprived state. Therefore, furthering our understanding of the feeding networks that drive consumption of highly palatable (i.e. densely caloric) diets based on their rewarding nature, rather than energy need, is of considerable importance.

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