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Research report

Central amygdala opioid transmission is necessary for increased high-fat intake following 24-h food deprivation, but not following intra-accumbens opioid administration

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HIGHLIGHTS

- CeA opioid blockade does not affect intra-Acb DAMGO-induced intake of a high-fat diet.
- CeA opioid blockade attenuates high-fat intake following 24-h food deprivation.
- CeA opioids mediate energy-deficit feeding, but not palatability-driven feeding of a high-fat diet.

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ABSTRACT

Previous research has demonstrated a dissociation of certain neural mediators that contribute to the increased consumption of a high-fat diet that follows intra-accumbens (Acb) administration of μ-opioid receptor agonists vs. 24-h food deprivation. These two models, both which induce rapid consumption of the diet, have been shown to involve a distributed corticolimbic circuitry, including the amygdala. Specifically, the central amygdala (CeA) has been shown to be involved in high-fat feeding within both opioid and food-deprivation driven models. The present experiments were conducted to examine the more specific role of CeA opioid transmission in mediating high-fat feeding driven by either intra-Acb administration of the μ-opioid agonist D-Ala2–NMe-Phe4–Glyol5-enkephalin (DAMGO) or 24-h home cage food deprivation. Injection of DAMGO into the Acb (0.25 μg/0.5 μl/side) increased consumption of the high-fat diet, but this feeding was unaffected by administration of opioid antagonist, naltrexone (5 μg/0.25 μl/side) administered into the CeA. In contrast, intra-CeA naltrexone administration attenuated high-fat intake driven by 24-h food deprivation, demonstrating a specific role for CeA opioid transmission in high-fat consumption. Intra-CeA naltrexone administration alone had no effect on baseline feeding levels within either feeding model. These findings suggest that CeA opioid transmission mediates consumption of a palatable high-fat diet driven by short-term negative-energy balance (24-h food deprivation), but not intra-Acb opioid receptor activation.

1. Introduction

Feeding behavior is facilitated by a variety of factors, including homeostatic mechanisms [1,2], learned associations [3,4], and the palatable nature of the food being consumed [5]. The integration of all these factors to generate feeding behavior requires the output of a complex neural circuitry, including mesocorticolimbic areas such as the striatum, hypothalamus, amygdala and prefrontal cortex (see [6] for review). Thorough investigation of these regions and their neurochemical mediators across different feeding models has produced the proposition that there are dissociable feeding pathways; including a homeostatic signaling pathway responding to energy balance that guides behavior toward seeking and consuming sustenance, while another pathway mediates information about palatability to guide intake of energy-rich foods beyond homeostatic needs [1,6,7]. Further dissociation of these two types of feeding behavior and the related neural circuitry is critical to understanding what role each plays in the maladaptive behaviors related to obesity.

The nucleus accumbens (Acb) is well known for its role in reward processing and translating "motivation to action" [8]. It also contains a critical site where the administration of μ-opioid agonists enhance the palatability of sucrose as measured by taste reactivity [9]. Intra-accumbens administration of the μ-opioid receptor agonist D-Ala2–NMe-Phe4–Glyol5-enkephalin (DAMGO)

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results in increased food consumption, an effect that is preferential in magnitude for specific diets such as sugar or those rich in fat [10,11]. Additionally, these particular experimental manipulations have implicated a role for the central amygdala (CeA) in feeding behaviors. Indeed, temporary inactivation of the CeA, but not the basolateral amygdala (BLA), blocks the increase in feeding observed following intra-Acb shell administration of the GABAA agonist muscimol, a pharmacological model that is analogous to the motivational state induced by energy deficit (moderate or severe food deprivation) [12]. In this experiment, intra-CeA inactivation produced by muscimol administration dose-dependently blocks increased chow intake following both intra-Acb muscimol administration and 24-h home cage food deprivation [12]. In addition, CeA muscimol inactivation blocks both baseline and intra-Acb DAMGO induced consumption of a high-fat diet [13,14]. However, previous experiments that investigated the involvement of CeA activity on palatable food consumption did not explore its role in mediating negative energy balance. Furthermore, considering these studies induced general inactivation (i.e., muscimol administration); it is unknown which specific neurochemical mediators are contributing to these different models of feeding.

Endogenous opioid transmission within the CeA has also been implicated in feeding behavior and is a likely candidate for mediating feeding behaviors [12,15]. Indeed, a bi-directional μ-opioid–opioid connection between the CeA and the Acb has been demonstrated [16]. For example, DAMGO administration into CeA increases feeding, but prior naltrexone administration into the Acb blocks this increase in food consumption and vice versa [16]. However, these experiments did not explore the role of CeA opioid transmission in baseline consumption of a palatable high-fat diet or following intra-Acb DAMGO administration. Glass and colleagues have shown that intra-CeA naltrexone administration reduces consumption of a "preferred" diet following 24-h food deprivation [17]. The authors suggest that the CeA may be an interface between forebrain affective systems and the hypothalamic feeding circuitry where the CeA may mediate hypothalamic activity by pairing sensory processes to the animal's current metabolic state [17]. It is possible that this integration of sensory information about the food with the homeostatic signaling could produce an increase in the incentive value of the food, and subsequently food consumption.

The present experiments aim to extend these findings and examine how the CeA may mediate opioid-driven and energy-deficit driven feeding behaviors associated with a high-fat diet. The involvement of CeA opioid transmission was examined via intra-CeA administration of naltrexone. One group of animals was given ad libitum access to a high-fat diet following bilateral administration of naltrexone or vehicle into the CeA following 24-h home cage chow deprivation or no deprivation. A second group of animals was given ad libitum access to a high-fat diet following bilateral administration of naltrexone into the CeA immediately prior to administration of DAMGO or saline into the Acb. Feeding behavior was monitored with automated feeding chambers assessing general locomotor activity, frequency and duration of food hopper entries, and food consumption.

2. Materials and methods

2.1. Subjects

Eighteen 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 1100 and 1300. Unless otherwise noted, rats had free access to laboratory chow and drinking water before and throughout the experiment. Experiment 1 had a total of 8 animals, while Experiment 2 had a total of 10 animals. 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). Stainless steel guide cannulas (23 ga, 10 mm) were sterotaxically targeted bilaterally above the CeA (Experiment 1). For Experiment 2, each rat was implanted with 2 sets of bilateral cannulae targeted above the Acb and the CeA (Experiment 2). Therefore, each rat was implanted with two cannulae in Experiment 1 and four cannulae in Experiment 2. Coordinates for the targeted injection sites (2.5 mm below the bottom of the 10 mm guide cannula) were as follows: Acb: AP,+1.4; ML, ±2.0; DV, −7.8 and CeA: AP, −2.0; ML, ±4.0; DV: −8.3. The coordinates for both regions were chosen to allow comparisons to earlier studies [12–14]. 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.

2.3. Apparatus

Behavioral assessment of feeding took place in a room separate from the colony room in eight Plexiglas (30.5 cm × 24.1 cm × 21.0 cm) automated feeding chambers (Med Associates, St. Albans, VT) running Med-PC software (Med Associates Version IV, St. Albans, VT). Rats had access to water ad libitum and approximately 35 g of palatable high-fat 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 food hopper continuously monitored the weight (consumption) of high-fat diet. 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).

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. A dose of 5 μg was chosen for naltrexone based on previous studies that demonstrated this dose to be effective in ethanol self-administration [18] and both chow and palatable diet consumption [16,17,19,20]. Rats were gently handheld and infusions were delivered with a microdrive pump (Harvard Apparatus, South Natick, MA), through polyethylene tubing (PE-10). Thirty-three-gauge 12.5-mm injectors were used, extending 2.5 mm beyond the end of the 10 mm guide cannulas. The rate of injection was 0.32 μl/min for the Acb and 0.16 μl/min for the CeA, with the total duration of infusion being 93 s, resulting in 0.5-μl and 0.25-μl volumes, respectively. One additional minute was allowed for diffusion. The current volume (0.25 μl) used for CeA infusions