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Intermittent-access binge consumption of sweet high-fat liquid does not require opioid or dopamine receptors in the nucleus accumbens

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HIGHLIGHTS

- Rats were given intermittent binge access to sweet high-fat liquid.
- D1, D2, μ, δ and κ antagonists were injected in the nucleus accumbens core and shell.
- The drugs did not reduce consumption in binge or control animals.
- Accumbens dopamine and opioid systems likely do not directly regulate consumption.

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ABSTRACT

Binge eating disorders are characterized by episodes of intense consumption of high-calorie food. In recently developed animal models of binge eating, rats given intermittent access to such food escalate their consumption over time. Consumption of calorie-dense food is associated with neurochemical changes in the nucleus accumbens, including dopamine release and alterations in dopamine and opioid receptor expression. Therefore, we hypothesized that binge-like consumption on intermittent access schedules is dependent on opioid and/or dopamine neurotransmission in the accumbens. To test this hypothesis, we asked whether injection of dopamine and opioid receptor antagonists into the core and shell of the accumbens reduced consumption of a sweet high-fat liquid in rats with and without a history of intermittent binge access to the liquid. Although injection of a μ opioid agonist increased consumption, none of the antagonists (including μ opioid, δ opioid, κ opioid, D1 dopamine and D2 dopamine receptor antagonists, as well as the broad-spectrum opioid receptor antagonist naltrexone) reduced consumption, and this was the case whether or not the animals had a prior history of intermittent access. These results suggest that consumption of sweet, fatty food does not require opioid or dopamine receptor activation in the accumbens even under intermittent access conditions that resemble human binge episodes.

1. Introduction

Binge eating disorders are common in the American population. These disorders, which are associated with other medical problems such as depression and obesity, are characterized by intermittent binge episodes during which large amounts of highly palatable food (typically sweet, fat and calorie-dense) are consumed [1]. Because currently available pharmacotherapies are only minimally effective in preventing binges from occurring, there is a pressing need for new treatment options based on the neurobiological mechanisms of the disorder. Recent work in this area has focused on opioid antagonists, which reduce consumption of sweet and fatty foods in animals [2]. Indeed, the "gain of function" A118G allele of the μ opioid receptor gene is overrepresented in people with binge eating disorders vs obese controls [3], and several studies have tested the efficacy of opioid antagonists to reduce calorie-dense food consumption or binge eating in humans, with mixed success [4–6]. A more detailed understanding of the contributions of opioid receptors to caloric intake regulation, and particularly to binge consumption, may help to identify more specific and efficacious targets for therapeutic development.

Abbreviations: NAc, nucleus accumbens; COS, cream, oil, and sugar emulsion; B-FNA, β-funaltrexamine; nor-BNI, nor-binaltorphimine; DAMGO, [D-Ala2,N-MePhe4,Gly-ol]-enkephalin; CTAP, D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH2; M–W–F, Monday–Wednesday–Friday; IA, intermittent access group; CA, continuous access group; WA, water access group; ILI, inter-lick interval.

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Recently, several animal models of binge consumption have been developed [7]. In one subset of these models, rats are allowed intermittent access to a highly palatable food, such as sucrose solution [8–10], fat or high-fat food [11–14], or mixtures of sugar and fat [15–18]. Over 1–7 weeks, binge eating develops: animals increase consumption of the palatable food when it is available, such that their total consumption matches or exceeds that of animals given continuous access to the palatable food. A critical difference between animal and human bingeing is that humans decide themselves when to initiate a binge, whereas the interval between animals' binges is set by the experimenter. However, in both humans and animals, binges occur even in the absence of a biological need for nutrients (hunger), the food consumed during binges is almost always sweet and/or high-fat food, and a reduction in consumption of less palatable food occurs between binges. These parallels suggest that similar neural mechanisms in humans and animals regulate consumption both during and between binges [1,19–23].

Pharmacological studies of animal models point towards a role for endogenous opioids in promoting binge consumption. Somatic and behavioral signs of withdrawal can be precipitated in sucrose-bingeing rats by either withholding sucrose or giving an opioid receptor antagonist [24]. Moreover, opioid antagonist treatment reduces consumption of highly palatable food in rats previously exposed to an intermittent access or stress regimen that leads to binge eating [13,18,25–28]. These effects are more pronounced for high-fat than sweet food [27], and in some cases normal chow consumption is also not as strongly affected [13,18,25–27]. Because these studies used systemic injections of broad-spectrum opioid antagonists, which are likely to have blocked opioid receptors of all subtypes in many brain regions, an important next step is to determine which opioid receptors and brain areas are involved in promoting binge consumption.

The nucleus accumbens (NAc) may be an important locus where opioid receptors of the μ subtype may contribute to binge eating. Binding studies demonstrate greater numbers of μ opioid receptors in the NAc shell of rats given prolonged intermittent access to glucose [29], and similar limited access schedules for sucrose or a sweet/fat liquid (Ensure®) causes reduced expression of the opioid peptide enkephalin in the NAc [30,31]. Injection of opioid agonists (especially μ-specific) into the core or shell of the NAc is potently orexigenic [32–37], and increases consumption of high-calorie food more than less palatable food [38,39]. However, opioid receptor antagonist effects are less clear. Injection of the broad-spectrum antagonist naltrexone into the NAc typically results in reduction of sweet or fatty food intake only at very high doses [38,40–42], and the δ receptor antagonist naltrindole actually increases sucrose consumption [42]. Moreover, although some studies show that injection of μ receptor-specific antagonists reduces consumption [41–44], another found no effect [45].

Notably, in rodent binge eating models, consumption escalates over weeks of intermittent access, and this escalation only occurs with extremely calorie-dense food [16]. One attractive hypothesis, then, is that this escalation is due to plasticity in the NAc opioid system, such that binge consumption comes to depend on activation of NAc opioid receptors by endogenous opioids. This hypothesis predicts that opioid antagonist injection in the NAc should block binge-like consumption whereas it should be less effective in reducing non-binge consumption. To test this hypothesis, we subjected rats to 5 weeks of intermittent access to an emulsion consisting of cream, corn oil and sugar (COS), a procedure that produces a binge-like escalation of consumption [16], and asked whether these animals' binge consumption of COS was more affected by injection of opioid receptor antagonists in the NAc than that of control animals that were given intermittent access to water alone (but not COS).

One additional prediction of our hypothesis is that if μ opioid receptor numbers are increased in bingeing animals [29], then activation of NAc μ receptors should cause a greater increase in consumption in animals with a history of binge access than in those with a history of intermittent access to water alone. We tested this prediction by injecting the μ agonist DAMGO into animals previously given intermittent access to COS or water. We also injected DAMGO into a group of animals given 5 weeks of continuous access to COS. These animals become obese [16]; thus, comparing the effects of DAMGO in intermittent and continuous access groups allows us to assess whether the NAc opioid consumption-promoting effects are similarly escalated in models of bingeing and obesity, which would suggest a similar neural mechanism.

In addition to a potential role for NAc opioid receptors in binge consumption, several lines of evidence suggest that NAc dopamine receptors may be involved as well. For instance, bingeing rats exhibit increased dopamine D1 receptor binding [29], reduced D2 and increased D3 receptor expression [31], and increased expression of the dopamine transporter [46] in the NAc. In addition, microdialysis studies show that sucrose binges are invariably accompanied by an increase in dopamine levels in the NAc, whereas animals given continuous access to sucrose, or insufficient sucrose access to develop binging, show no or much smaller increases [8,10,47]. Although the dopamine response to palatable food habituates with repeated episodes of consumption [48], binge-associated dopamine release does not [8,10,47]. Moreover, locomotor sensitization to psychostimulants – a NAc dopamine-dependent process – is enhanced in animals binging on sucrose [49–51], and amphetamine-sensitized animals show more locomotion in response to a brief taste of sucrose, and consume more freely-available sucrose, than controls [52]. Finally, abnormalities in dopamine turnover, dopamine transporters and dopamine receptors have been observed in humans with binge eating disorders [53].

The foregoing studies suggest that NAc dopamine may contribute to binge consumption. Food consumption is typically not strongly affected by disruption of NAc dopamine [54–60], but the effects of NAc dopamine manipulations on binge consumption have not been tested. Therefore, in this study we assessed the effects of NAc injection not only of opioid receptor ligands, but of dopamine receptor antagonists on binge intake of COS.

2. Materials and methods

2.1. Animals

Male Long–Evans rats ($n = 233$, Harlan) weighing 275–300 g were housed in a room with a 12 h light cycle. Experiments were conducted during the light phase. Animals were handled daily for at least one week before experiments; chow intake and body weight were measured daily. Prior to the start of the experiment, three groups of rats were matched by average amount of chow consumed and average body weight. All animal procedures were consistent with the U.S. National Institutes of Health Guide for the Care and Use of Laboratory Animals, and were approved by the Institutional Animal Care and Use Committee of the Albert Einstein College of Medicine.

2.2. Behavior

2.2.1. Operant chambers

Behavioral experiments were run in standard Med Associates operant chambers (30 × 25 cm). The chambers were illuminated with one 28 V white house light, and white noise (65 dB) was played through a dedicated speaker. Operant chambers were equipped