Published in final edited form as:
Physiol Behav. 2011 July 25; 104(1): 87–97. doi:10.1016/j.physbeh.2011.04.041.

Feeding and reward: Perspectives from Three Rat Models of Binge Eating

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Abstract

Research has focused on understanding how overeating can affect brain reward mechanisms and subsequent behaviors, both preclinically and in clinical research settings. This work is partly driven by the need to uncover the etiology and possible treatments for the ongoing obesity epidemic. However, overeating, or non-homeostatic feeding behavior, can occur independent of obesity. Isolating the variable of overeating from the consequence of increased body weight is of great utility, as it is well known that increased body weight or obesity can impart its own deleterious effects on physiology, neural processes, and behavior. In this review, we present data from three selected animal models of normal-weight non-homeostatic feeding behavior that have been significantly influenced by Bart Hoebel's 40+-yr career studying motivation, feeding, reinforcement, and the neural mechanisms that participate in the regulation of these processes. First, a model of sugar bingeing is described (Avena/Hoebel), in which animals with repeated, intermittent access to a sugar solution develop behaviors and brain changes that are similar to the effects of some drugs of abuse, serving as the first animal model of food addiction. Second, another model is described (Boggiano) in which a history of dieting and stress can perpetuate further binge eating of palatable and non-palatable food. In addition, a model (Boggiano) is described that allows animals to be classified as having a binge-prone vs. binge-resistant phenotype. Lastly, a limited access model is described (Corwin) in which non-food deprived rats with sporadic limited access to a high-fat food develop binge-type behaviors. These models are considered within the context of their effects on brain reward systems, including dopamine, the opioids, cholinergic systems, serotonin, and GABA. Collectively, the data derived from the use of these models clearly show that behavioral and neuronal consequences of bingeing on a palatable food, even when at a normal body weight, are different from those that result from simply consuming the palatable food in a non-binge manner. These findings may be important in understanding how overeating can influence behavior and brain chemistry.

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Keywords

bulimia nervosa; binge eating disorder; dopamine; food addiction; opioids; palatable food

Introduction

Overeating has been increasingly studied in both preclinical and clinical research. This is partly driven by scientific interest in understanding the etiology of and developing treatments for the ongoing obesity epidemic. Many studies have used palatable diets to induce overeating and obesity in rats with outcomes relevant to the neurobiology of addiction being reported [1–4]. However, overeating, or non-homeostatic feeding behavior, can occur independent of obesity. It is well known that increased body weight or the state of obesity alone can impart deleterious effects on physiology, neural processes, and behavior. It is equally important to understand how these parameters are affected by the act of overeating.

In honor of the festschrift of Bart Hoebel, we will present data derived from three selected animal models of normal-weight non-homeostatic feeding behavior that have been significantly influenced by his 40+ yr career studying motivation, feeding, reinforcement, and the neural mechanisms that participate in the regulation of these processes. The common theme that joins these models together in this paper is that that they are focused on modeling binge eating behavior, a common aberrant eating behavior that is seen in eating disorders, obesity and in subclinical populations [5–7]. Binge episodes are characterized objectively by the consumption of more food in a brief period of time than would normally be consumed under similar conditions and within a similar period of time. In addition, bingeing is accompanied by a subjective sense of loss of control [8]. Bingeing is intermittent, and becomes problematic when it occurs frequently, i.e. several times a week for months or years. The lifetime prevalence of frequent binge eating in the United States is about 5% with a median age of onset of about 12.5 years [5, 6]. About 35% of those who regularly binge are overweight or obese, but the prevalence of bingeing increasing with BMI. Furthermore, the risk of weight regain after treatment is higher in bingeing than in non-bingeing subjects [5–7]. Among those who binge, about 76% of adults and 85% of adolescents experience psychiatric co-morbidities such as anxiety, mood, impulse control or substance use disorders [5, 6]. The ability to function in the home, work, school, personal or social environment is also impaired among those who binge. For instance, 78% of those with bulimia nervosa and 62.6% of those with binge eating disorder (BED) report role impairment [5, 6]. Suicide ideations and suicide attempts are frighteningly higher in adolescents who binge eat than in those who do not. Among adolescents without eating disorders, 11.2% experienced suicide ideation and 3% attempted suicide. However, among adolescents with bulimia nervosa, 53% and 35.1% reported suicide ideation and suicide attempts, respectively; among adolescents with BED, the respective percentages were 34.4% and 15.1% [6]. In short, bingeing is common and is associated with co-morbidities that complicate treatment. The use of animal models, such as those described in this review, will advance our understanding of this difficult form of disordered eating and lay the groundwork for the development of new intervention strategies.

The models described here meet the DSM-IV definition of an objective binge episode, i.e. the consumption of more energy in a discrete period of time than would normally be consumed under similar circumstances within a similar period of time [8]. The challenge in the development of these models was to distinguish normal eating from excessive eating during discrete bouts. The contributions of Bart Hoebel to the field of ingestive behavior

have been integral to the development of these models, and laid much of the groundwork for studies of feeding and reward that have resulted from their use.

The Sugar Addiction Model

Sugar bingeing results in addiction-like behaviors

There have been anecdotal accounts in which people claim to be "addicted" to certain foods, and this addiction manifests as excessive overeating, a feeling of distress when palatable food is not available, and craving of certain foods [9]. These food addictions tend to focus on highly palatable, energy dense foods, or for some people, refined carbohydrates. Much like a person addicted to drugs, those who feel they are addicted to certain foods find it difficult to stop overeating, which can ultimately result in body weight gain for some individuals.

Although the term "food addiction" is often used colloquially, its scientific definition is just now emerging, and evidence is accumulating to suggest that excessive intake of certain foods under specified conditions can, indeed, produce behaviors and changes in the brain that resemble an addiction-like state. Self-identified refined-food addicts use food to self-medicate; they eat when they feel tired, anxious, depressed or irritable in order to escape a negative mood state [9]. To establish guidelines for identifying such individuals, the Yale Food Addiction Scale, was developed. This instrument is the first psychometrically validated scale establishing criteria for dependence on food, based upon modifications of the DSM-IV criteria for substance dependence [10]. In addition to the establishment of clear identifying behavioral criteria, studies of the brain and genetics also support the idea that excessive consumption of palatable food has parallels with addiction. Scores on the Yale Food Addiction Scale correlate with greater activation of the anterior cingulate cortex, the medial orbitofrontal cortex and the amygdala, regions associated with motivation, in response to anticipation of palatable food [11]. Consumption of foods that are particularly palatable can activate these same brain regions [11, 12], which may underlie cognitive aspects of craving food. Further, PET scans reveal that obese subjects show a reduction in striatal D_2 receptor availability that is associated with the body weight of the subject [13] and is similar in magnitude to the reductions reported in drug-addicted subjects [14]. Further, these changes are more closely correlated with binge eating behavior than they are to body weight [15]. Subjects who binge eat have also been shown to have a "gain of function" of the mu-opioid receptor gene, which correlates with higher scores on a self-report measure of hedonic eating [16]. Several other papers have described overlaps that exist between addiction and overeating [17].

One may wonder how something as innocuous as a palatable food, which many people consume on a regular basis with no adverse effects on health or well-being, could be akin to a drug of abuse. In this section, we discuss an animal model that was developed in the Hoebel laboratory that demonstrates ways in which a palatable food can produce behaviors in rats that are like those seen with substances of abuse. This model, which was developed and refined in the final stage of Bart's career, is the end result of a 20+-year quest to understand whether or not food could become addictive. As stated in one of his early microdialysis papers in which effects of food intake on extracellular dopamine (DA) levels in the nucleus accumbens (NAc) were reported: "Eating may be addictive to the extent that it has effects like cocaine." ([18], pg. 1711). The sugar addiction model demonstrates the prescience of those words.

In this model, rats are maintained on daily 12-h food deprivation, followed by 12-h access to a 25% glucose or 10% sucrose solution and rodent chow [19, 20]. The model has been described in detail previously [20], and findings using this model are discussed in previous

reviews [19, 21]. In brief, after just a few days on this schedule, the rats begin to escalate their daily intake and binge on the sugar, as indicted by an increase in their intake of the sugar solution during the first hour of access. In addition to a binge at the onset of access, the daily feeding patterns change such that the rats take larger meals of sugar throughout the access period compared to control animals fed the sugar *ad libitum*. When administered the opioid-receptor antagonist naloxone, somatic signs of withdrawal, such as teeth chattering, forepaw tremor, and head shakes occur in rats that have been binge eating sugar [22]. Sugar-bingeing rats also exhibit anxiety-like behavior, as measured by a reduced amount of time spent on the exposed arm of the elevated plus-maze. Signs of opiate-like withdrawal also emerge spontaneously (i.e., without naloxone treatment), when all food is removed for 24 h [19, 22]. Sugar-bingeing rats also show signs of increased motivation to obtain sucrose; the rats lever pressed for 23% more sugar in a test after 2 wks of abstinence than they did before [23], while a control group with prior 0.5-h daily access to sugar followed by 2 wks of abstinence did not show the effect. This suggests a change in the motivational impact of sugar that persists throughout a prolonged period of abstinence, leading to enhanced intake. The results further suggest that relatively brief bouts of sugar intake are not sufficient to result in enhanced intake following abstinence, but rather, limited access in the form of prolonged daily binge-type eating, is needed to produce the effect.

Additionally, other studies suggest that sugar-bingeing rats show cross-sensitization with some drugs of abuse. They are hyperactive in response to a low, challenge dose of amphetamine that has little or no effect on naïve animals, whereas rats maintained on the sugar feeding schedule but administered saline are not hyperactive, nor are rats in control groups (e.g., rats allowed to binge on chow only, or with *ad libitum* access to sugar and chow, or *ad libitum* access to chow only) that were given the challenge dose of amphetamine [24]. Further, when rats are bingeing on sugar and then forced to abstain, they subsequently show greater intake of 9% alcohol compared to control groups that were previously maintained on *ad libitum* sucrose and chow, *ad libitum* chow or binge access to chow alone [25]. This suggests that intermittent excessive sugar intake may be a gateway to alcohol use. Together with the neurochemical findings described below, the results from this model suggest that bingeing on a sugar solution affects mesolimbic DA and opioid systems, with resultant neural adaptations that manifest as signs of dependency.

A clear strength of this model is that it is the first animal model in which a comprehensive set of criteria associated with addiction has been described when rats eat a palatable food. Thus, it can provide a useful tool with which to study brain mechanisms associated with repeated binge-like bouts, and perhaps assist with the development of pharmacotherapies aimed at suppressing binge eating of, or perhaps “addiction” to, palatable food [26]. Such therapies might prove to be particularly useful among clinical populations expressing comorbid substance use and binge eating disorders [5, 6]. Another strength of this model (and, indeed, the other models described in this review) is that, since the bingeing rats do not become overweight, the behavioral variable of binge-type eating can be isolated. This is important, as it is known that the effects of obesity can impart changes in the brain that influence reward [27]. Thus, by isolating the variable of binge-type eating from the consequence of increased body weight, the effects of palatable food bingeing on brain and behavior can be determined.

Other laboratories have reported complementary findings that suggest signs of addiction can emerge when using other intermittent sucrose access schedules. Intermittent sucrose access cross-sensitizes with cocaine [28] and facilitates sensitization to the DA agonist quinpirole [29]. Also, anxiety-like behavior has been reported in rats with limited access to a high-sucrose diet [30]. Other physiological and behavioral changes that suggest a negative state have been noted in rats that intermittently consume sugar. For instance, the removal of sugar

has been reported to decrease body temperature [31] and instigate signs of aggressive behavior [32].

The History of Dieting + Stress (HD+Stress) Model

A history of dieting + stress results in binge-eating

The HD+Stress model has been described in detail elsewhere [33, 34]. This model recapitulates several characteristics of clinical binge-eating [35, 36] and promotes bingeing by predisposing rats to a history of dieting (HD) and to stress. Therefore, it is appropriate for the study of bulimia nervosa, binge-purge anorexia nervosa, and BED, all of which are commonly anteceded by a HD and stress, and are characterized by binge-eating [8, 37–40].

Four groups of young female rats are compared: a pure control group (noHD+noStress), a HD only group (HD+noStress), a stress only group (noHD+Stress) and the experimental group that models binge-eating, the HD+Stress group. A HD is simulated by subjecting the rats to cycles of food restriction and refeeding. They are given 66% of controls' chow for 5 days followed by 2 days of *ad libitum* Oreo cookies (as the palatable food) with *ad libitum* chow, then 4 days with only *ad libitum* chow. Testing occurs on the 12th day of the cycle and by then the HD groups have recovered lost weight and weigh the same as noHD rats. Stress is administered with 3 sec of 0.6 mA foot shock just prior to the feeding test. Rats in the noStress condition spend equal time in the shock chamber without shock. During the feeding test, rats have *ad libitum* amounts of cookies and chow in their home cages. After the third restriction/refeeding and stress cycle, and after each cycle thereafter (up to 23 cycles have been reported [41]), the HD +Stress group distinguishes itself by eating statistically more food (from 30–100% more kcals of palatable food vs. the three other groups) within the first 4 h of the feeding test despite the fact that they were not in a state of food deprivation [33]. The rats binge on cookies, not chow, consistent with eating for reward as opposed to metabolic need [33, 42], and confirming that there is no lingering caloric deficit from restriction/refeeding. The most compelling proof that the binge-eating is not homeostatically driven occurs when the rats are stressed and tested while hungry (during the caloric restriction phase). HD rats both with and without stress consume more food by increasing their normal chow intake, but the HD+Stress group exceed this homeostatically driven overeating by also consuming significantly more palatable food [43]. The bingeing on palatable food vs. chow, and subsequent studies with opioidergic drugs (discussed below) suggest that the binge eating is reward-driven. Eating for reward and the triggering effects of stress (vs. hunger) are characteristic of clinical binge eating [44–48]. It is noteworthy to point out that all three of the control groups always eat more palatable food than chow under sated conditions, a normal effect driven by the high palatability of the cookies. However, the exaggerated intake demonstrated by the HD+Stress rats is not normal, and it is operationally considered bingeing in this model. Several other groups have modified the HD+Stress model, by altering the length of each component of the cycle, the type of binge food, the type of stress administered, and the species of rodent utilized [60, 62, 91, 92, 182].

Although stress is an important binge trigger, rats need *not* be exposed to stress or palatable food during the initial HD cycles for subsequent binge-eating to occur [49]. While all three factors are necessary at later points for binge-eating to be expressed, the prior history of energy deprivation is the most critical factor in neuroadapting the rats to binge-eat [33]. A scientific explanation for a connection between dieting and reward was first provided by Bart Hoebel: food deprivation dramatically reduced extracellular DA levels in the NAc [50]. He also found that rats worked harder to self-stimulate electrically in the lateral hypothalamus when hungry [51] and reported that refeeding in once food deprived rats elevates DA levels in the NAc shell to amounts outlasting the feeding period [52]. This work helped solidify a neurobiological connection between feeding states and reward and

suggested a mechanism by which a HD might prime the brain to binge. A HD would produce anhedonia that is reversed by the increase of DA afforded by eating. Indeed, subsequent work from the Boggiano lab found that rats with a HD developed neurochemical and behavioral changes consistent with anhedonia despite normal energy balance. This was true regardless of experience with or without stress [53] and whether rats had intermittent, daily, or no exposure to palatable food during the HD [53, 54]. Translating to humans, "forbidden foods" (typically palatable foods) are often consumed during a binge [55, 56]. The accompanying surge in DA would render these foods much more reinforcing to individuals in a state of energy deprivation (i.e. during a low calorie diet), than in individuals who consume the same foods in a non-energy-deprived state.

In addition to the apparently strong influence that a HD has on subsequent binge eating, recent evidence also suggests that binge-eating may reduce stress. This additional positive value would render binge eating more difficult to extinguish. Bart Hoebel made the early prediction that "stress-induced release of DA may facilitate circuits in the NAc and other sites that process feeding stimuli and responses" ([57], pg. 182). Indeed, stress and specifically, corticosterone (CORT), has since been shown to augment DA release in the NAc [58, 59]. Of several metabolic hormones examined, studies conducted in the Boggiano lab as well as by others using the HD+Stress model revealed that elevations in plasma CORT distinguished the binge-eating rats from the control groups (including the noHD +Stress group). This was found even when using alternate stressors. For example, Cifani et al. used a more isomorphic stressor than foot shock, that of allowing rats to see and smell palatable food (a Nutella®/chow paste) but not allowing them to eat it for 15 minutes [41, 60–62]. This introduces the possibility of targeting the HPA axis to treat binge-eating; this will be discussed below in the neurochemistry section.

A surprising finding with the HD+Stress model was that if the HD+Stress rats are given a morsel of palatable food then left with nothing but plain rat chow after stress, they still binge. In fact, they consumed 160% more chow kcals than the control groups that were similarly primed with palatable food [43]. A similar action of palatable food to prime overeating of plain chow was observed in non-cycled rats if they were in a location with cues previously paired with palatable food intake (also Oreos) [63]. This increased consumption of even a less preferred food that can be triggered by eating palatable food [64–67], is attributed to higher cognitive processes in humans (e.g., self-defeating thoughts or rationalizations over weight-gain or failure to adhere to a diet) [56, 68–70]. Cognitive processes undoubtedly play a role in triggering binge eating in humans but the large chow intake displayed by the sated HD+Stress rats suggests that palatable food can activate a powerful reflexive drive to overeat, one that would be very difficult to control. Refined sugars and flours, saturated fats, and high sodium levels, are common ingredients of modern palatable foods [71–73] and may be acting like drug primers [9, 10, 72–75]. In the predisposed brain, just a small amount may lead to relapse. Hoebel has provided some of the most compelling animal data for the existence of "food addiction", as described in the previous section [18, 22, 76–78]. The power of palatable food to trigger binge-eating in this and other rat models ought to be considered when making decisions concerning the introduction of such foods in the management of eating disorders characterized by bingeing (however, see Murphy et al., 2010 [79], regarding addressing dietary rules in the treatment of binge eating).

A note on individual differences: clues from the Binge-Eating Prone vs. Resistant model

Among humans, not all with a HD or who encounter trauma or stress binge on food. Genetic and possibly early-life experiences are known to increase risk for binge-eating [80–83]. The same may be true for binge-type eating to be expressed in rats once subjected to a HD and stress. In the course of working with the HD+Stress model, it was noted that there were rats

that consistently ate below or above the group mean intake of palatable food within the HD +Stress group. Hence, if not for the dramatic binge-eating of some rats, the group mean intakes may not have differed from controls. Therefore, this within-rat consistency in palatable food intake has been systematically studied, which led to the development of a different animal model, the binge-eating prone and binge-eating resistant model (BEP/BER model) [84].

Details on this model are described elsewhere [84] but in summary, it was observed that while female rats eat homogenous amounts of chow, when palatable food is available (e.g., Oreo cookies) approximately one-third consistently eat significantly more palatable food kcals (BEPs) than the lowest palatable food-eating third (BERs) in the first 4 to 24 hrs of palatable food access, over and above their regular intake of chow [84]. Like other models described here, the palatable food is given intermittently vs. daily (2–3x a week for 24 h). Interestingly, when foot-shocked, both groups decrease total intake but the decrease for BEPs is due to reduced chow intake while for BERs it is due to reductions in the consumption of palatable food [84]. Also under sated conditions, more BEPs than BERs cross incrementing levels of foot shock for M&Ms® with BEPs also tolerating higher levels of shock than BERs to retrieve M&Ms® [85]. The binge-eating of BEPs generalizes not only to other fat/sweet foods [85–87] but also to non-sweet fats (e.g., Crisco®) and non-fat sweets (e.g., Froot Loops®). Moreover, when BEP and BER rats are placed on a traditional diet-induced obesity regimen where only high-fat pellets are available on a daily basis [88], half of the BEPs and half of the BERs become obese while the other half of the BEPs and BERs resist obesity [84]. Hence this model may be useful to explore the mechanisms underlying various clinical conditions, e.g., BED (modeled by obese-prone BEPs), non-BED obesity (modeled by obese-prone BERs), bulimia nervosa (modeled by obese-resistant BERs) and normal weight not eating disordered healthy individuals (modeled by obese-resistant BERs).

In addition to inherent differences in proclivity to consume palatable food, individual differences in eating behavior may also arise from early-life environmental experiences. Despite the robustness of the HD+Stress model to alterations in experimental manipulations by us and others [33, 43, 53, 60–62, 89–92], we have not always been able to obtain binge-eating in the rats. Sometimes others, also, could not obtain the effect with foot shock or if they did, the binge-eating was attenuated [91, 92]. While frustrating, the problem actually presents a fortuitous opportunity to investigate predispositional factors. Interestingly, Hancock et al. found, when using the HD+Stress model, that *only* rats deprived of maternal licking and grooming as pups later binged following a HD and stress [92]. This only occurred during adolescence and not later in adulthood but is consistent with the typical human age of onset for bingeing-related disorders [8]. Similarly, rat pups that experience maternal separation show exaggerated chow intake during the refeeding phase of restriction/refeeding cycles in adolescence. These rats also have elevated CORT levels vs. non early-stressed cohorts [93, 94]. We have since learned that commercial rodent colonies, even within vendor companies, do not control for differences in number of pups nurtured per mother or other husbandry factors. Even stress from shipping can have different latent effects on animals. These are factors that have been known to influence outcomes of otherwise exquisitely controlled experimental protocols [95–100]. Considering this, we cannot rule out the possibility that early-life experiences might also be driving the differences in palatable food intake in the BEP/BER model. In sum, early-life stressors and possibly any dietary differences resulting from those stressors need to be considered when using rodent models of binge eating. This is relevant to the strong etiological link between childhood trauma and early life stressors on binge-eating in humans [101–104].

The Limited Access Model

Sporadic limited access to palatable food results in binge-type eating

The limited access model has been described in detail elsewhere [105]. Unlike the HD +Stress and sugar overeating models described above, the limited access model does not make use of previous or current food deprivation to stimulate binge-type eating. Rats in this model are never food deprived, as they have continuous access to chow and water at all times. This has allowed for the study of binge-type consumption that is independent of neuronal alterations that may be introduced by the use of food deprivation. To stimulate binge-type eating, the rats are given sporadic (generally 3 times per week), time-limited (generally 1–2 h) access to palatable food, in addition to the continuously available chow. The limited access model has relevance to eating in the absence of hunger, as described for BED [8, 106], as well as to the “forbidden foods” hypothesis of human bingeing in which those foods to which people restrict their access are the foods upon which they binge [55, 56].

Two groups of rats are used in this model, one that has brief, time-limited access to the palatable food every day (daily access control group), and one that has brief time-limited access to the palatable food a few times (usually 3 days) a week (sporadic access binge group). The palatable food typically is a bowl of pure vegetable shortening, which is a hydrogenated solid fat that is commonly used in baked goods. When shortening is provided for 1–2 hours every day, consumption does not change very much across time and intakes are generally around 2 g (~18 kcal). However, when the shortening is provided sporadically, intakes during the limited access period escalate across a period of several weeks to ~4–6 g (~36–54 kcal), and become significantly greater than those of the rats with daily access. Bingeing is operationally defined in this model when intake of the palatable food in the sporadic access group exceeds that of the daily access group. Indeed, after about 4 weeks, the sporadic group consumes as much or more palatable food in 1–2 h as rats with continuous access to the palatable food consume in 24 h [107, 108]. The escalation of palatable food intake occurs in the sporadic group even though they always have access to chow; only access to the palatable food is restricted. The rats with time-limited daily access to palatable food are included as controls for the palatability of the palatable food, as well as for learning about the limited period of time during which the palatable food is available. The daily group is, therefore, considered the “normal” controls, against which bingeing in the sporadic group is compared. The phenomenon has been reported in males and females, different strains, and across several age groups [107, 109, 110].

Although shortening has generally been used in this model, other palatable food also have been tested including sucrose solutions, various concentrations of fat presented as solid emulsions, high-fat diets, and fat/sucrose mixtures [111–118]. Shortening works well as the palatable food for these studies, as rats readily consume it [119] and differences between groups can be assessed. In addition, although intakes approach the ceiling of the rat’s stomach capacity (as calculated according to Bull and Pitts [120]) they do not quite attain maximal stomach fill. This allows for the assessment of both reductions and stimulations of intake using pharmacological probes (e.g., [121]).

It is important to use a palatable food in this model that is readily consumed, but that does not promote such large intakes that group differences cannot be discerned. If the daily and sporadic groups both consume large amounts, then binge intake cannot be distinguished from that which is induced simply by the palatability of the palatable food, as has been reported in some studies. For instance, rats consumed large amounts (5–9 g) of solid fat emulsions during the limited access period in one study, and intakes did not differ between daily and sporadic groups [116]. A lack of difference between daily and sporadic groups has

also been reported when high-fat chow, sugar/fat mixtures, and certain sugar solutions have been used as the palatable food [111–115, 117, 118]. Interestingly, behavioral and pharmacological differences between sporadic and daily access groups have been reported, even when intake during the limited access period did not differ between the groups (e.g. [115, 116, 121, 122]). However, even in these cases, intakes were relatively large. If intakes are quantity-limited (clamped) during an initial 5-week period of shortening exposure (rats are only allowed to consume 2 g), then subsequent bingeing is attenuated when intake no longer is clamped [108]. Thus, mere exposure to the palatable food, and being allowed to sample it, is not sufficient; the rats must be allowed to 'gorge' when first introduced to the palatable food for the binge behavior to later be fully expressed.

Rats with sporadic brief access to palatable food do not gain more weight, and do not accumulate significantly more body fat, than chow controls [107, 109]. This is because of reductions in chow intake that occur. An overeat/undereat, or 'sawtooth' pattern of daily energy intake develops in the rats with sporadic access to palatable food because they overeat on days that palatable food is provided and undereat when palatable food is not provided [107, 109, 112–115, 123]. The net result is that total cumulative energy intake (chow + shortening) and body weight do not differ between sporadic access rats and chow controls (e.g. [107, 109, 112, 113, 115]. Since the binge rats overeat on binge days, and undereat on non-binge days, studies have been conducted to determine if the bingeing develops because of the self-imposed periodic energy restriction that occurs on the days prior to palatable food access. This does not appear to be the case; bingeing still develops, even when undereating does not occur on the previous day [124]. The maintenance of energy intake and body weight at control levels is similar to human conditions such as bulimia nervosa in which bingeing occurs, but body weight remains within the normal range because of compensatory behavior such as undereating [8]. Indeed, the failure to accumulate excess body weight is a common feature of the models described in this review and is typical of human binge eating; only about 35% of people who binge have a BMI ≥30 [5].

In addition to consuming more shortening during the limited access period, sporadic binge rats also work harder for shortening in operant sessions. Progressive ratio breakpoint escalates over time in the rats with sporadic access to shortening [125], and is significantly greater than that of the daily rats [122]. Progressive ratio responding for sucrose after a period of food deprivation also increased to a greater extent in rats with sporadic access to sweetened vegetable shortening relative to rats with daily access [115]. Progressive ratio responding is considered a behavioral measure of motivation [126] suggesting that reward-related circuitry may be differentially engaged in rats with sporadic and daily brief bouts of palatable food consumption.

What is it about sporadic bouts of palatable food intake that might produce such alterations? Clearly, rats learn to binge, but the neurocircuitry involved in that learning process has only begun to be characterized. One possibility is that some form of cue-induced potentiation of eating may take place. Rats in the sugar addiction and HD+Stress models learn to consume the palatable food when food deprived. Thus, part of what may drive binge-type consumption in those models is neurocircuitry required for learning associations between environmental cues and palatable food while in a state of energy deprivation, as described by Holland and colleagues [127]. Recent data from the Boggiano lab indicate that such learning can also occur even in the absence of food deprivation [63]. Therefore, it is quite possible that cue-induced potentiation of eating is operating in the limited access model, as well, even though the rats are never food deprived.

While cue-induced potentiation of feeding may be common to all three models, it is entirely possible that different mechanisms also are involved. The sugar addiction model provides

sugar every day to mildly food deprived rats several hours into the dark cycle. Thus, the presentation of sugar is highly predictable in that model. In contrast, presentation of the palatable food is sporadic, and less predictable, in the HD+Stress and Limited Access models. We propose that unpredictable consumption of palatable food contributes to bingeing. Human research supports this idea. Binges are not always planned [8] and binge-to-binge intakes can vary widely for any given individual [128]. In addition, environments that encourage unpredictable meal patterns appear to promote bingeing. For instance, when adolescent females frequently eat dinner with the family, the likelihood of bingeing is lower than when adolescent females rarely eat dinner with the family [129]. At least one successful therapeutic intervention targets the unpredictable nature of eating episodes and palatable food consumption by establishing regular eating as part of the treatment strategy [79].

In the limited access model, bingeing develops in non-food deprived rats that only get the binge food on three days per week, i.e. sporadically. Most of these studies have provided the binge food on Mon, Weds, and Fri each week. Thus, sometimes there is only one day between binges and sometimes two. This access schedule introduces a certain level of uncertainty regarding when opportunities to binge will occur. We also have tested more sporadic schedules with similar results [36]. In addition, the rats with sporadic access to palatable food are housed in the same room as the rats that have daily access. Therefore, the sporadic rats are exposed to cues associated with palatable food every day, but only get to actually eat the palatable food sporadically. As a result, the cue-food associations are also associated with uncertainty. Fiorillo et al.[130] reported differential firing of DA neurons in the ventral tegmental area (VTA) as a function of uncertainty in a protocol in which cues predicted the delivery of a liquid food reward. Thus, dopaminergic signaling in VTA projection sites (NAc, prefrontal cortex) may differ in rats with sporadic (uncertain/unpredictable) and rats with daily (certain/predictable) access to palatable food. Indeed, pharmacological data collected using the Limited Access model are consistent with this scenario (see below).

Selected Neurotransmitter Systems Implicated in Binge Eating: Results and Clinical Implications

Bart Hoebel was a pioneer in the study of overlaps that exist in the neurocircuitry regulating food and drug intake. In this section, we highlight findings inspired by Bart's work derived from the models described herein, that provide insight into neuronal alterations that occur as a function of binge eating.

Dopamine

The involvement of DA and its receptors in bingeing has been reviewed elsewhere [131, 132], and the work of Bart Hoebel has had a profound impact on this area of research. Drugs of abuse can alter DA receptors and DA release in mesolimbic regions of the brain [133, 134]. Similar changes have been noted using the sugar addiction model (see [19, 21] for review). Specifically, autoradiography reveals increased D1 receptor binding in the NAc and decreased D2 receptor binding in the striatum relative to chow-fed rats [76]. Others have reported a decrease in D2 receptor binding in the NAc of rats with intermittent access to sucrose and chow compared with rats fed restricted chow only [135]. Rats with intermittent sugar and chow access also have decreased D2 receptor mRNA in the NAc, and increased D3 receptor mRNA in the NAc and caudate-putamen compared with chow-fed controls [78]. However, one of the strongest neurochemical similarities between sugar bingeing and drugs of abuse is the effect on extracellular DA. The repeated increase in extracellular DA within the NAc shell is a hallmark effect of drugs that are abused [136], whereas normally during feeding, the DA response fades out after repeated exposure to food as it loses its novelty

[137]. When rats are bingeing on sugar, the DA response is more like that of a drug of abuse than a food, with DA being released upon each binge [77]. Control rats fed sugar or chow *ad libitum*, rats with intermittent access to just chow, or rats that taste sugar only two times, develop a blunted DA response that is typical of a food that loses its novelty. Thus, bingeing on sugar produces a neurological response that is quite different from that of consuming sugar without bingeing, even if total sugar intake is similar in both conditions. These results are supported by findings using other models of sugar overeating in which alterations in accumbens DA turnover and DA transporter have been reported [138, 139].

In the limited access model, pharmacological probes for D1 and D2 receptors have been tested. Peripheral administration of the D1-like antagonist SCH23390 reduced intake of both fat and sugar in binge and control rats, but these results were often also accompanied by reductions in chow intake [121]. Therefore, the effects of D1 blockade may have been due to generalized suppression of behavior. Peripheral administration of the D2-like antagonist raclopride, on the other hand, had effects that were not explained by generalized behavioral suppression. Raclopride reduced consumption of sugar solutions in rats with either daily or sporadic access, but had differential effects on consumption of fatty palatable food. Specifically, intake of fatty palatable food was generally reduced by raclopride at relatively high doses in rats with daily limited access but was either unaffected or increased by raclopride at lower doses in rats with sporadic limited access [121]. These results implicate D2 receptors in the consumption of fatty food, but also indicate differential D2 signaling in binge rats and controls. Since lower doses stimulated intake in the binge (sporadic) rats and higher doses reduced intake in the controls, these results further suggest differential pre- and post-synaptic D2 signaling under binge and control conditions. These findings are consistent with reports in humans and in rats implicating altered DA signaling in the consumption of fatty foods [3] and in binge eating [15, 131].

In addition to the NAc, VTA dopamine neurons project to regions of the prefrontal cortex involved in decision making and executive function (anterior cingulate), as well as attention (medial agranular or Fr2; [140]; see [141] for review). Human imaging studies suggest the involvement of the anterior cingulate in people who binge [142–146], and the involvement of the medial agranular regions in chewing [147]. Hence, studies have recently been initiated using the Limited Access model in which direct infusions of DA receptor antagonists have been administered into these brain areas. Results, thus far, are consistent with the results obtained with peripheral injections, i.e. a low dose of the D2 antagonist eticlopride increased consumption of fat in the binge rats but not in controls [148]. Taken together, these results indicate that reduced D2 receptor actions in cortical regions do not cause bingeing, but can exacerbate bingeing once it is established. In short, the results suggest that binge experience can disrupt DA signaling, making it difficult to stop once a binge has been initiated.

Opioid Receptors

In addition to the effects on DA, opioid systems are also affected by bingeing in a manner that is consistent with the effects of some drugs of abuse. Data generated from the sugar addiction model has shown that sugar bingeing decreases enkephalin mRNA in the nucleus accumbens [78], and mu-opioid receptor binding is significantly enhanced in the NAc shell, cingulate, hippocampus and locus coeruleus, compared with chow-fed controls [76]. Also, the fact that sugar-bingeing rats are sensitive to the effects of the opioid antagonist naloxone, which can precipitate signs of withdrawal [22], suggests that repeated bouts of excessive sugar intake can alter brain opioid systems.

Results from the HD+Stress and Limited Access models also lend support for the role of opioids in binge eating behavior. HD+Stress-induced binge-eating is abolished by naloxone, a mixed kappa/mu-receptor antagonist. Although it is short-acting, there is no compensatory

binge-eating at 24 hrs; therefore, opioid-receptor signaling may be necessary for binge-eating to occur [89]. One mechanism by which a HD appears to prime the brain to binge is via sensitization of opioid-receptors [149]. Sensitization may occur from a decrease in opioid receptors because the binge-eating rats exhibit an exaggerated anorectic response to mu/kappa-receptor blockade with naloxone [89]. Receptor-downregulation would yield a more complete naloxone blockade as occurs in opiate addiction [150–152]. Consistent with opioid-receptor sensitivity, the opioid-receptor agonist butorphanol achieves a more potent hyperphagia in the binge-eating rats relative to the control groups despite their already increased levels of intake [89]. Given the amplification of DA release by opioid-receptors in mesolimbic neurons [153] and their confluent roles in wanting and liking [132] respectively, it is not surprising that HD-induced changes in opioid-receptors should play a role in binge-eating. Importantly, the findings extend Hoebel's pioneering reports on the inverse relation between food deprivation and reward by warning that even prior food deprivation can induce long-lasting changes in reward-related circuitry.

While a HD may prime the brain to binge via sensitization of opioid receptors, a HD may not be necessary for such sensitization to sugar to occur. In the Limited Access model, the opioid antagonist naltrexone reduced intake of solid 100% fat (shortening), solid emulsions made with different concentrations of shortening (32%, 56%), and fat sucrose mixtures when the sucrose concentration was low in rats with daily limited access as well as rats with sporadic limited access to the palatable food [116, 121]. Thus, naltrexone was effective at reducing consumption of fatty food regardless of access condition. In contrast, binge and control rats consuming sucrose were differentially sensitive to the intake-reducing effects of naltrexone. Specifically, naltrexone reduced intake of 3.2% and 10% sucrose solutions in rats with sporadic limited access, but not in rats with daily limited access [118]. This is consistent with other reports indicating the involvement of opioid receptors in binge-type consumption of sugary food in rats [76, 78, 89] as well as in humans [154]. Thus, while blockade of opioid receptors effectively reduces consumption of fatty substances under non-binge as well as binge-type conditions, opioids may have a unique role in the binge-type consumption of foods that are rich in sugar.

Taken together, the above results suggest that binge-eating may be mediated by opioid-receptor supersensitivity (possibly as a result of repeated endogenous opioid release due to palatable food intake, which releases endogenous opioids [155–160]. This is analogous to opiate addiction where opiates, not palatable food, flood the brain with endogenous opioid stimulation resulting in compensatory receptor downregulation [150–152]. It is noteworthy that addicts in withdrawal are known to overeat sugar perhaps as a substitute for the actions of opiates on the brain. Their drive for sugar is such that it can lead to obesity and glucose dysregulation [161–163]. Hence, targeting anti-craving treatments used in opiate addiction may prove beneficial in treating binge-eating (e.g., with buprenorphin [164], buprenorphin/naloxone [165], D-phenylalanine/L-amino-acids/naloxone [163]). The identification of gene markers that are common between opiate addiction and binge eating (rather than obesity) may also accelerate treatment progress. Support for this idea has been provided by clinical studies in which decreased insula mu-receptor binding in bulimia nervosa patients [166] and a greater frequency of the mu-receptor A118G variant (implicated in reward and addiction) among obese BED vs. obese non-BED subjects were reported [17].

Acetylcholine (ACh)

A rise in extracellular ACh has been associated with the onset of satiety [167]. In the sugar addiction model, sugar bingeing rats develop a delay in the rise of ACh, which may be one reason why the size of the binge meal increases over time [77]. Accumbens cholinergic neurons also appear to have a role in aversive behaviors. Behavioral signs of drug withdrawal are often accompanied by alterations in DA/ACh balance in the NAc; DA

decreases while ACh increases. This imbalance has been shown during withdrawal from several drugs of abuse, including morphine, nicotine and alcohol [168–170]. Rats bingeing on sugar also show this neurochemical imbalance in DA/ACh during withdrawal. This result occurs both when rats are given naloxone to precipitate opiate-like withdrawal [22] and after 36 h of food deprivation [19].

Serotonin

Hoebel and colleagues conducted seminal studies in rats that helped lay the groundwork for serotonin to be targeted in the treatment of abnormal eating [171, 172]. In the HD+Stress model fluoxetine, a selective-serotonin reuptake inhibitor (SSRI) that is approved for the treatment of bulimia, decreased intake of HD+noStress rats as potently as the binge-eating of HD+Stress rats at 2 h. At 4 h post-treatment, fluoxetine was still effective in the binge-eating rats, but not in HD+noStress controls [53]. Hence, a HD may impose long-lasting changes on satiety regulation, a key function of serotonin, despite normal body weight. Stress is known to transiently increase synaptic serotonin levels which may explain the prolonged anorectic efficacy of fluoxetine observed in the HD+Stress rats [53]. Conversely, fluoxetine is ineffective in reducing binge-type eating if the rats are in negative energy balance, possibly due to insufficient synaptic serotonin for SSRI action [173]. In addition, fluoxetine exerted the strongest anorectic effect in rats with sporadic extended (24h) access to palatable food relative to rats with a HD that never had palatable food or had it every day [54]. Hence, the role of intermittent palatable food to interact with a HD to disrupt serotonin function should not be underestimated.

GABA and Glutamate Receptors

The GABA-B receptor has garnered attention in the past decade due to the ability of agonists to reduce drug self-administration in animal studies, and for their potential in the treatment of substance use disorders [174, 175]. In the limited access model, the GABA-B agonist baclofen reduced intake of shortening, as well as high-fat (56%) solid emulsions, in rats with both daily and sporadic brief access at doses that stimulated or had no effect on chow intake [116, 121]. In contrast, baclofen had no effect on intake of three different sucrose solutions (3.2%, 10%, 32%) in rats with sporadic or daily limited access [121]. When fat and sucrose were mixed together baclofen reduced intake in rats with either sporadic or daily access when the sucrose concentration was low (3.2%, 10%) but had no effect in either group when the sucrose concentration was high (32%) [118]. Similar results have been reported by others. For instance, baclofen did not reduce consumption of a palatable food containing 40% fat and ~16% sucrose in a mouse model of binge eating [112]. In work reported by Hoebel and colleagues, baclofen reduced consumption of vegetable shortening in rats with 2-h daily access, but had no effect on intake of a sugar solution [111]. Thus, the intake reducing effects of baclofen in rats appear be specific to foods that are high in fat, with efficacy being attenuated by increasing concentrations of sugar.

None-the-less, recent clinical trials suggest the potential usefulness of baclofen in the treatment of binge eating [176, 177]. Specifically, baclofen significantly reduced binge size in open label [176] as well as placebo-controlled studies [177]. The types of food consumed and macronutrient composition of the binges were not assessed in those trials. However, the rat data suggest that baclofen may prove to be most effective for those people who binge primarily on fatty foods that are not high in sugar.

Work with the drug topiramate indicates that functional changes in GABA-A and glutamate receptors may underlie binge-type eating produced by a HD and stress. Using their modified HD+Stress model, Cifani et al. found that, while fluoxetine and sibutramine suppressed

binge-type eating, only topiramate selectively reduced intake in the HD+Stress group without affecting intake in the pure control, Stress-only, and HD-only groups [60]. The authors suspect it may be anti-craving properties of topiramate promoted by its activation of GABA-A receptors and inhibition of AMPA/kainate glutamate receptors that selectively suppressed binge-type eating [60, 178]. Overlooking it's unfortunate high side-effect profile, topiramate has been efficacious in reducing binge-eating clinically [179]. However, the rodent results are valuable in that they hint at the unique neurobiology created by the interaction of past caloric restriction, stress, and palatable food to alter the brain's control of eating. Further investigations into the role of GABA and glutamate on binge-eating are warranted.

HPA axis

In addition to the apparently strong influence that a HD has on subsequent binge eating, recent evidence also suggests that binge eating may reduce stress rendering it more difficult to extinguish the binge behavior. Bart Hoebel made the early prediction that "stress-induced release of DA may facilitate circuits in the NAc and other sites that process feeding stimuli and responses" ([57], pg. 182). Indeed, stress and specifically CORT, has since been shown to augment DA release in the NAc [58, 59]. As aforementioned, increased CORT levels are a hormonal marker of binge-eating rats in the HD+Stress model [41, 61]. Cifani et al., observed heightened CORT levels using their modified version of the HD + Stress model [60, 90]. Palatable food intake has been shown to blunt activation of the hypothalamic-pituitary-adrenal (HPA) axis [114, 180, 181]. In mice, energy restriction can increase sensitivity to stressors (accompanied by enhanced CORT release) and can increase intake of a high-fat diet in response to the stress [182]. Importantly, CORT is also increased during high-fat diet removal [2], as it is in withdrawal from addictive drugs [183]. This may set up a vicious addiction-like cycle of eating palatable food when stressed then suffering the consequences of palatable food withdrawal, a stressor in itself [180].

To address this, Cottone et al. found that rats with intermittent access to palatable food elicit symptoms of withdrawal when the palatable food is not available, symptoms reversed by antagonism of corticotropin-releasing factor (CRF)-1-receptors [4]. The same process may be occurring in eating disorders characterized by bingeing. In obese individuals with BED cortisol levels are high relative to obese individuals without BED [184, 185]; blood cortisol levels in response to stress predict greater intake of sweets [186]; and salivary cortisol levels are positively correlated with binge-eating severity [187]. Besides activating stress responses, CORT is also implicated in the motivation to seek rewarding substances [158, 188–190]. Hence, anything that can arrest this cycle (e.g., substitution of palatable food with a healthful reward and/or pharmacologically targeting HPA-activation) may prove to be therapeutically useful in the treatment of bingeing by preventing relapse. More research is needed to determine if abnormal HPA hormone activation to stress is a pre-existing risk factor for binge-eating as one study suggests it might be [185].

Still the CORT elevations in the HD+Stress model and in individuals with BED suggest that binge-eating linked to stress involves dysfunction in the HPA axis. Thus, targeting stress hormones may be effective in treating binge eating. Nociceptin/orphanin is an endogenous ligand of the nociceptin opioid-receptor (a.k.a., OP4, ORL1). Its anti-stress and appetite enhancing actions, both reversible by CRF have dubbed it a functional CRF antagonist [191]. Interestingly, low but not high doses significantly reduce binge-eating of HD+Stress rats [192]. Although the effects were described as "slight" by the investigators, it suggests that we should not overlook the approach of treating binge-eating with appetite enhancing drugs, if they can also pharmacologically reduce stress. Thus, dosing may be critical. An additional attractive feature of this molecule is that unlike CRF antagonists, it may be exerting therapeutic effects without inhibiting the HPA axis [191].

Salidroside is a glucoside in Rhodiola rosea L. (a.k.a, Golden Root, Roseroot), a plant known in East Europe and Asia for its ‘adaptogenic’ anti-stress properties [193, 194]. In the HD+Stress model, doses of this compound had no effect on the chow or palatable food intake of pure control, Stress-only, or HD-only rats but completely abolished the binge-type eating of palatable food in the HD+Stress rats. Also because it did not affect the intake of non-cycled rats either when sated or food deprived [62], the effect cannot be due to suppression of a general increase in intake (hunger or palatability-induced) as is typical of serotonergic agents [62]. Although the compound can increase monoamines and *B*-endorphin, its anti-binge eating effect is attributed to a blunting of stress [195] since the compound also abolished the typical CORT elevation of these binge-eating rats [62]. Direct antagonism of the CRF-1 receptors may also be promising targets given evidence that they reduce stress-induced palatable food-seeking in rats [190, 196].

Summary/conclusions

Several take home messages can be derived from this overview. First, all three of the models described herein demonstrate that mere exposure to palatable food does not induce behavioral and neuronal changes indicative of pathological conditions such as addiction. Rather, it appears that repeated, intermittent bouts of excessive palatable food consumption are required for aberrant behavior and brain changes to be established. This is repeatedly demonstrated by comparison to the control groups that are consuming the same palatable food. The data derived from the use of these models clearly show that behavioral and neuronal consequences of bingeing on the palatable food are different from those that result from simply consuming the palatable food in a non-binge manner. Second, although the palatable food does not appear to be sufficient for bingeing and its associated neuronal alterations to develop, the palatable food does appear to be necessary. This is elegantly demonstrated by the sugar addiction model. When rats had access to only chow under the same conditions that promoted sugar addiction (12-h access starting 4 h into the dark cycle in rats that were 12-h food deprived), behavioral and neuronal measures consistent with addiction were not observed [19]. In addition, as reported with the HD+Stress model even when bingeing on chow occurred, it had to first be primed by palatable food [43]. Third, some form of intermittent access to the palatable food, as opposed to continuous access, appears necessary for bingeing to develop. The mechanisms that account for the powerful effect of intermittency on palatable food intake are not known, but are under investigation at this time. Fourth, while much work is still to be done, the models described here have already made progress in elucidating some of the neurotransmitters, their receptors, and brain regions that appear to be involved in binge eating. While several different candidates have been studied, DA and the opioid peptides within mesocorticolimbic circuits enjoy the greatest support from the models presented here. Fifth, while genetic traits undoubtedly contribute to binge risk, all three models provide strong evidence that repeatedly engaging in binge-type behavior has neuronal and behavioral consequences. In short, it appears that bingeing can induce a state that serves to perpetuate the behavior once initiated. Sixth, all of models demonstrate that binge-type consumption of palatable food can occur independent of obesity.

Finally, the results from these three models indicate that investigators ought not to limit what we attempt to model in laboratory animals by believing that certain behaviors are exclusive to humans. If we replicate the human environment as closely as possible in rats, e.g., by simulating a HD, stress, human diets, etc., we should not be surprised if animals exhibit ‘complex’ binge-eating characteristics such as ‘out of control’ behavior with food [8, 70], depression [54], and seemingly irrational behavior like tolerating aversive consequences for palatable food [85, 197]. Biasing “human-animal” dualistic thinking ought not to stagnate progress in the quest to understand and treat disorders characterized by binge eating

[198–200]. To borrow Hoebel's words when referring to James Old's hypotheses on motivation, we should not shy away from testing even "the most farout, twinkly-eyed ideas…" ([201], pg.654).

Research Highlights

- Three rat models of binge-type eating and their neuronal outcomes are described
- The outcomes associated with bingeing are different from non-bingeing.
- Binge-type eating can occur independent of obesity.

Acknowledgments

Support for the studies described here provided by MH67943 (RLC), MH60310 (RLC), Penn State Institute for Diabetes and Obesity (RLC), National Eating Disorders Association (NMA) and DK079793 (NMA), DK066007 (MMB), P30DK056336 (MMB) and NEDA Laureate Award (MMB).

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