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Behavioral models of binge-type eating

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Abstract

Purpose—To describe and evaluate behavioral models of binge-type eating. *Data identification:* Studies were identified using Medline and hand searches of bibliographies of identified articles.

Study selection—Isomorphic studies were selected that were judged to have some measure of construct validity.

Data extraction—Face and construct validity were assessed, as well as simplicity and cost of use.

Results of data synthesis—Several different models of binge-type eating exist, each with different strengths of validity and use. These include models using sham feeding, restriction/refeeding cycles and/or stress, limited access (LA) to optional foods, and eating induced by operant schedules of behavior.

Conclusions—We concur with Harry Harlow, who was quoted by Gerry Smith as saying: “You’d be crazy to use animal models, but you’d also be crazy not to use them.”

Keywords

Adjunctive behavior; Animal models; Binge; Bulimia; Eating disorders; Food intake; Limited access; Restriction; Schedule-induced behavior; Sham feeding; Stress; Stress

1. Introduction

Binge eating involves repeated, intermittent overconsumption of food in brief periods of time and is associated with a variety of health problems, including affective disorders, substance abuse, and obesity [1–3]. Although recent reports indicate progress in the pharmacological treatment of bingeing-related eating disorders [4], treatment options are limited and relapse rates are high [5,6].

One reason for the limited progress in the development of treatment strategies is that the physiological and neurological causes and consequences of repeatedly engaging in binge-type behavior are not clearly understood and cannot readily be studied in human subjects [7]. Well-characterized animal models are needed to advance our understanding of binge-type eating, as well as other disorders involving repeated, intermittent, excessive behavior, such as substance abuse. The goal of this review is to describe some of the bingeing models that currently exist and to propose guidelines for their evaluation.

2. Evaluation criteria

The evaluation of any animal model is facilitated by the use of clear classification schema and validation criteria. Smith [8] proposed that animal models of eating disorders be classified into

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four types: (1) etiologic, (2) isomorphic, (3) mechanistic, and (4) predictive. Etiologic models are based upon the same underlying cause as the human disorder. Because the cause(s) of human bingeing is/are not known, etiological models have not been developed.

Isomorphic models, in contrast, are designed to resemble the human symptomology. All of the currently available models are isomorphic, but vary in their similarities to human disordered binge-type eating. We have selected the diagnostic criteria for bulimia nervosa and the research criteria for binge eating disorder to guide our evaluation of the different models [9]. These bingeing-related eating disorders share the common feature of binge episodes that occur repeatedly over extended periods of time. Binge eating episodes are characterized by “eating, in a discrete period of time (e.g., within any 2-h period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances”. Bingeing can occur in the absence of hunger and involves some level of emotional distress, such as a sense of loss of control, disgust, guilt, depression, or embarrassment. Bulimia is distinguished from binge eating disorder by the presence of recurrent inappropriate compensatory behaviors, such as vomiting, fasting, or excessive exercise. Animal models, of course, cannot measure subjective feelings of distress such as those that characterize human bingeing disorders. However, valid measures relevant to depression, anxiety, stress, and fear do exist for animals and provide a means to evaluate distress that may be associated with bingeing in animal models [10,11].

Given the difficulties associated with operationalizing subjective feelings in animals, we have elected to use the following objective criteria to define binge-type eating in isomorphic models: (1) The behavior should occur repeatedly over an extended period of time. (2) Bingeing rats should consume more food in brief, discrete, periods of time than relevant controls do under similar circumstances. Ideally, the deprivation condition of the binge animals and the nonbinge animals should be comparable. (3) If compensatory behavior is present, it should be initiated by the animal rather than imposed by the investigator.

Mechanistic models are based upon neurobiological mechanisms involved in the development and/or maintenance of bingeing. Although mechanisms have been proposed, the neurobiological causes and consequences of bingeing are not known. Thus, mechanistic models are not available. Although not specifically designed as mechanistic models of bingeing, however, pharmacological and genetic studies of ingestive behavior in animals provide a foundation for explanations of neurobiological mechanisms that may contribute to bingeing in humans. In animal studies, for instance, central PYY and peripheral ghrelin are potent orexigenic peptides; in active and/or short-term recovered bulimics, cerebrospinal fluid PYY and plasma ghrelin are elevated [12,13]. Conversely, levels and/or secretion of some anorexic peptides and neurotransmitters, such as leptin, CCK, and serotonin, are reduced in bulimic patients [14–18].

Predictive models are used to test interventions. Most behavioral models of bingeing can be used to examine basic mechanisms and to develop pharmacological interventions. Because there currently are few effective treatments for bingeing-related disorders, there is a great need for models that can be used to this end. Such models should accurately predict effective treatment and should also be inexpensive, simple to use, and reliable [19].

The Smith classification schema maps well onto the validation criteria for animal models in psychiatry described in McKinney [20]. These criteria provide a means to judge the face validity of a model and are as follows: (1) similarity of the inducing conditions (etiologic), (2) similarity of the behavioral states produced (isomorphic), (3) common underlying neurobiological mechanisms (mechanistic), and (4) reversal by clinically effective treatment techniques (predictive). Because the currently available models are all isomorphic, none meet

all four of McKinney's criteria [20]. This is because our understanding of etiology, basic mechanisms, and treatment of bingeing is so limited. For this review, then, the assessment of face validity was necessarily based upon similarity of symptomology between the model and the clinical disorder.

In addition, Willner [19] has suggested that behavioral models be evaluated for their predictive (generally assessed as an increase or decrease in symptoms in response to drug tests) and construct validity (the theoretical rationale upon which they are based). Strong predictive validity has not yet been established for any of the models that we will describe because few of the agents that reduce bingeing in animals have been tested in human clinical trials. We based our assessment of construct validity upon the binge-inducing stimulus in each of the models. That is, if the means used to induce bingeing in the model was related to an established correlate of bingeing in humans, then, the model was assumed to have at least some measure of construct validity.

3. Models

3.1. Sham-feeding

Van Vort [21] and Smith [8] provide compelling arguments for the use of sham feeding as a behavioral model of bingeing. Sham feeding is achieved by equipping rats with chronic fistulas (typically a gastric fistula), which allows liquid food to drain from an opening before entering the intestinal tract. Under these conditions, rats consume large amounts of liquid food in brief periods of time, relative to controls with the fistula closed. Furthermore, this effect can be demonstrated repeatedly over extended periods of time [8]. Smith [8] and Van Vort [21] argue that the drainage of food from the open fistula serves as a model of purging, although they correctly note that this is entirely due to the experimental manipulation and not initiated by the animal. The face validity of this model is good, as is the theoretical rationale behind it.

The strength of the model lies in its ability to separate positive orosensory feedback, which stimulates feeding, from negative intestinal feedback, which inhibits feeding [22]. The sham-feeding preparation has been used by several laboratories but was refined and used by Smith [23] to study the control of food intake in the context of meals. There is evidence that levels of several neuromodulators thought to be involved in the control of meal size are altered in the bingeing-related eating disorders (see Ref. [18] for a review). Thus, the usefulness of the sham-feeding model for examining basic mechanisms relevant to bingeing cannot be denied.

3.2. Models based on cycles of dieting and overeating

A history of dieting and overeating is thought to contribute to future binge eating in some people (e.g., Refs. [24–26]). In animals, food deprivation or restriction is a standard method of increasing subsequent intake (also referred to as rebound hyperphagia). Restriction/refeeding (R/R) cycles generally consist of several days of limited food access followed by a few days of ad libitum access. Body weight generally decreases during the restriction phase and returns to normal during the refeeding phase. Rats may go through more than one cycle. In-and-of-itself feeding, induced by food deprivation, would not be a very good model of binge-type eating, as food intake is not greater than "... most [animals] would eat during a similar period of time and under similar circumstances." [9]. That is, simply eating more because one has been deprived of food does not qualify as a binge. Furthermore, even if high-fat, palatable food is provided during the refeeding period, effects in rats have been reported to dissipate with time [27].

Despite this limitation, studies of R/R cycles have been conducted that are potentially relevant to human bingeing. For instance, Hoebel et al. used R/R protocols to examine neurobiological and behavioral consequences that result from bingeing on sweet or high-fat foods [28–30].

Their findings indicate that repeated R/R cycles that include palatable foods can alter dopamine and opioid binding, alter the balance between dopamine and acetylcholine in the nucleus accumbens, and induce a withdrawal-like condition during restriction. If confirmed, this would suggest mechanistic consequences of bingeing that could serve to maintain the behavior. The Hoebel studies also support the possibility that R/R cycles may induce neurological profiles that overlap with those induced by drugs of abuse. Leigh et al. [31] used a somewhat different approach, in that their rats were never food deprived. Instead, they exposed rats to alternating cycles of cafeteria diet access and chow to model the negative effects of bulimia on fertility. Taken together, these studies suggest that repeated, periodic overconsumption of palatable foods can induce neural and biological changes that may have important relevance to bingeing-related eating disorders.

Hagan and Moss [32,33] and Hagan et al. [34,35] have developed a bingeing model in which R/R cycles are used as preparation for a later manipulation. For instance, Hagan and Moss [33] subjected rats to 12 R/R cycles, with cookies available during the refeeding phase. Thirty days after the end of the last cycle, those rats that had a history of restriction with refeeding on chow and cookies ate more chow and cookies under nonrebound conditions than rats without the R/R history did. This shows that restriction can have impacts on consumption long after restriction has ceased in animal studies, a finding that models previous reports in humans (see Ref. [26] for a review).

3.3. Models based on stress

Several lines of evidence suggest a connection between stress and binge-type eating in humans [36–39]. Therefore, stress is a reasonable component to include in behavioral models of bingeing. A variety of stressors, such as tail pinch, shock, noise [40], maternal separation, and overcrowding, has been used to stimulate food intake in animal models. Stress-based models can be divided into the immediate, where the effect on intake is seen during or shortly after the stress, and the historic, where there is an extended period of time between the stress and intake assessment. Within these categories, the stress can be classified as acute, if it is applied only once, or chronic, if the animal has been repeatedly exposed to the stressor or exposed for more than a brief period of time. Stressors can also be more or less severe.

3.3.1. Immediate acute stressors—Perhaps, the best studied of the immediate acute stress models is the tail-pinch model, in which pinching a rat's tail increases the rat's intake while the tail is being pinched and/or for up to 30 min afterwards. Tail-pinch-induced feeding is reduced by a variety of pharmacological compounds, several of which have relevance to bingeing. For instance, plasma opioid concentrations have been reported to be lower in bulimics than in controls [41], and opiate antagonists have been reported to reduce binge symptomology in human trials ([42–45], but see Ref. [46]; see also Ref. [47] for a review). Likewise, opiate antagonists reduce tail-pinch-induced eating (see Ref. [48] for a review of early studies). On the other hand, CCK reduced TP-induced feeding [48] but had no effect on binge intakes in a small clinical study at dosages previously reported to reduce food intake in healthy subjects [44]. These findings indicate that the predictive validity of the tail-pinch model cannot be evaluated with confidence until more comparative data are available. Should it prove to have good predictive validity, the tail-pinch model would be potentially useful for therapeutic screening, as it is relatively simple and inexpensive to use.

Shock is another manipulation used to induce stress. Although there have been conflicting reports about the effect of shock on food intake [49,50], recent investigations by Hagan et al. [34,35] suggest the usefulness of shock in models of bingeing. The Hagan shock protocol is designed to model not only the cycles of dieting and bingeing that often occur in people with

bingeing-related eating disorders, but also to examine the contribution of stress to binge behavior.

In the Hagan protocol, rats are exposed to repeated R/R cycles, as in her previous studies. In this new protocol, rats are also exposed to one session of acute food shock (0.6 mA) on the last refeeding day of each cycle [34]. Food intake is measured after the foot shock sessions and is compared to food consumption in rats with no food restriction history and to rats with no shock history. Rats with the shock history consume more of a palatable food (cookies) during the final feeding test than do rats without the shock history. Hagan et al. [35] also found that shock resulted in a larger increase in food intake in food-deprived animals with a R/R history than in food-deprived animals without a R/R history. Thus, cycles of restricted intake and refeeding on palatable foods interact with shock (stress) to induce binge-type eating in the Hagan model.

The Hagan model has strong construct validity, and may prove useful in the search for mechanistic antecedents to bingeing. Its use is limited primarily by its complexity, particularly, if a shock component is included. This limitation, however, is minor if the model proves to have good predictive validity. Face validity is limited only because the Hagan model has not yet been used to repeatedly induce binges over extended periods of time.

3.3.2. Immediate chronic stressors—Tail pinch and shock have in common that they are of short duration and increase intake during and/or immediately after that short time period. Longer lasting (chronic) immediate stressors can also increase food intake. Inoue et al. [51] found that placing a rat in an extremely small cage after a period of food deprivation enhanced rebound hyperphagia upon return to free-feeding. Space restriction significantly elevated 2-, 4-, and 24-h intakes above those achieved by rats who had experienced the food deprivation and returned to free-feeding in standard cages. The predictive validity of this model has yet to be determined, and, to our knowledge, follow-up studies have not been done.

3.3.3. Historic chronic stressors—Severe chronic stress early in life can change eating behavior in adult animals. This is relevant to evidence that stressful early-life events may increase vulnerability to the development of bingeing-related disorders in humans [39,37]. Rhesus monkeys raised under conditions of social isolation eat and drink more in 24 hours than do monkeys raised under normal conditions [52]. In rats, daily periods of early maternal separation enhanced rebound hyperphagia and palatable food intake later in life [53,54]. The effect was particularly strong for females. These models might be useful for elucidating the effects of early-life stressors on later disordered eating.

3.4. Limited access

The “forbidden foods” hypothesis of human binge eating suggests that the foods humans binge on are those to which they have limited their own access [55]. Kales [55] found that among bulimics, 69% of binge content, as opposed to 15% of nonbinge meal content, consisted of forbidden foods. Forbidden foods are generally high-fat, high-sucrose foods, such as snacks and desserts [9,55]. While self-imposed limited access (LA) to certain foods has been associated with bingeing, LA imposed by others may also contribute to subsequent increased consumption of those foods, even in the absence of hunger [56]. This has particular relevance to bingeing-related eating disorders, as eating in the absence of hunger has been associated with bingeing in humans [57].

Corwin and colleagues [58,59] have developed a behavioral model of bingeing in which LA to an optional source of dietary fat (vegetable shortening) is provided under non-food-deprived conditions for several weeks or months. In the Corwin protocol, the optional fat is made available under a variety of access conditions, ranging from continuous to only 2 h of access

three times a week. The rats in this protocol have unlimited access to chow and water; that is, the animals are never food deprived; only access to the optional fat is limited. The basic finding is that as access to the fat decreases, consumption of the fat increases when it is provided. When rats only have access to the fat for 2 h three times a week, intakes during the 2-h access period are very high, representing approximately 70% of the control 24-h energy consumption. Rats maintained on the Corwin protocol overeat on binge days and undereat on nonbinge days relative to controls. Thus, a binge/compensate behavior pattern develops, although the rats are never deprived of food; only their access to the optional fat is restricted. Rats cannot vomit (purge), thus, undereating is a method of compensating that is available to them. Recent work has shown that binge-type eating will occur under LA conditions, even if undereating did not occur on the previous day [60]. The Corwin protocol demonstrates that limiting access to a preferred fatty food, even in the absence of food deprivation, can invoke subsequent binge-type behavior in rats.

Establishing these elevated intakes takes about 4 weeks. However, once the binge intakes are established, they are easily maintained. The studies typically last 4–8 weeks, and binge intakes remain reliably high. In addition, de Araujo-Held et al. [61] have provided evidence that behavior relevant to anxiety, as measured in the light/dark transition test, is increased in animals maintained on the binge protocol, relative to nonbinge controls. This protocol provides a means of establishing elevated intakes in discrete periods of time in non-food-deprived rats for extended periods of time. It includes a voluntary compensatory component and appears to invoke behavior relevant to distress. The phenomenon is not only robust, but also quite reliable, as Corwin et al. have demonstrated it in different strains and ages of rats, in males and females, and in mice [58,59,61,62]. The Corwin LA protocol appears to be a strong isomorphic model, with good construct validity. In addition, it is relatively simple and inexpensive to use.

LA protocols have been used to examine neurological consequences that may result when binge-type behavior is maintained for extended periods of time. Two peptides proposed to be involved in the regulation of fat intake, galanin [63] and enterostatin [64], had no effect on fat intake under LA conditions [58,65,66]. Recent work indicates that a GABA-B agonist can selectively reduce fat intake under LA conditions, without reducing intake in control rats maintained on a high-fat diet [67]. GABA-B agonists have little effect in other feeding protocols but reduce drug self-administration [68]. This is interesting because binge eating and substance abuse are intermittent excessive behaviors associated with loss of control that share clinical comorbidity [69–74]. Taken together, results using the Corwin protocol suggest that the neurobiology of fat consumption under LA binge-type conditions is very different from fat intake under nonbinge conditions and may overlap with the neurobiology of substance abuse.

3.5. Schedule-induced hyperphagia

Schedule-induced (also known as adjunctive; SI) behaviors were originally described by Skinner and Morse [75] but received extensive attention after an initial report by Falk [76]. SI behaviors are behaviors directed at a secondary reinforcer (e.g., drinking water) when an animal is responding under operant reinforcement schedules for a different primary reinforcer (e.g., lever pressing for food). SI behaviors can be induced reliably when interval (time-based) operant schedules are in effect and have been characterized as non-regulatory and excessive. SI water intake, for instance, is typically two to three times greater than control 24-h intake and can total up to half of the rat's body weight within a single, approximately, 3-h session [76,77].

Attempts to induce SI food intake were generally unsuccessful when water was used as the primary reinforcer [78,79]. However, when electrical brain stimulation was used as the primary reinforcer, adjunctive intake of a wet mash was at least 150% of control in 14 of 19 sated rats

tested. Eleven of these rats consumed more than 22 g of wet mash during a 3-h session [80]. The authors suggest that adjunctive eating may provide a model of environmentally induced snacking. The model may also provide a novel means to induce non-regulatory excessive eating, such as occurs during a binge. Follow-up investigations, unfortunately, have not been reported. As a model of bingeing, the approach is limited by the technology required to implement it. However, it does provide another means to induce elevated intakes in non-food-deprived rats and is worthy of further investigation.

3.6. Self-induced regurgitation

Purging (vomiting) is a typical compensatory behavior used by bulimic humans. To our knowledge, there is only one model in which animals “purge”. Fifty to eighty-four percent of gorillas spontaneously regurgitate and sometimes reingest recent meals and/or share the vomitus with other gorillas. This behavior is more likely to occur if the gorilla has recently consumed preferred foods [81]. Although this model is not readily used within most laboratory environments, and a binge component is lacking, it represents the only evidence we are aware of that animals will self-induce regurgitation after the consumption of preferred foods.

4. Summary and conclusions

Bingeing models are distinguished from other ingestive behavior protocols, in that brief bouts of excessive food intake are stimulated by factors other than (or in addition to) palatability, food deprivation, and circadian rhythms. Models of binge-type eating offer a window into mechanistic factors that can stimulate feeding to excess, i.e., over-and-above what would be expected under normal conditions. Such models are needed to clarify the mechanisms that contribute to the development and maintenance of binge-type behavior patterns. The study of bingeing involving natural rewards, such as food, also offers the possibility of enhancing our understanding of mechanisms relevant to other rewards such as drugs of abuse.

The first requirement of any good model is that it be clear what the experimenters are modeling. Language is especially loose in the field of binge models. Few would say that binge behavior and bingeing-related eating disorders are the same thing, but the two are often confused in the translation into animal models. Binge eating is a simple behavior seen in most humans at some times and nearly all Americans on Thanksgiving, but the bingeing-related eating disorders share a pattern of chronic, pathological binge eating associated with psychological distress. A model of the disorder must, at the least, include multiple incidents of binge-type eating and provide some measure of associated distress. Models of bulimia nervosa would need to include some form of compensatory behavior such as purging, excessive exercise, or fasting. In this review, we have described protocols that model selective aspects of the bingeing-related eating disorders. Indeed, it is our belief that no single animal model can fully represent the complexity of factors involved in the human disorders.

Despite their limitations, however, behavioral models are needed to advance our understanding, not only of the causes but also of the effects of bingeing. The search for etiology has dominated the development of many animal models of human disorders. We would like to argue for the merits of modeling effect, as well, especially in the bingeing-related disorders. The factors that contribute to the development of binge-type eating are many and difficult to define, and patients usually present clinically after the behavior is well established. Neurochemical profiles in symptomatic and short-term recovered patients differ from the profiles of long-term recovered patients, suggesting that the neurochemical consequences of bingeing may contribute to the maintenance of the behavior and to relapse [18]. Understanding the consequences of bingeing, therefore, is a potentially fruitful approach that may provide insight into neurological mechanisms amenable to therapeutic intervention.

The models reviewed in this paper have been classified according to the manner in which brief bouts of excessive food intake are induced. Each model has strengths and weaknesses related to validity and use, which are summarized in Table 1. While the applicability of research generated with animal models to the human condition is invariably imperfect, we concur with Smith [8], that “being able to model [selected components] of these complex clinical syndromes will provide, at best, a partial answer to the perplexing questions raised by the psychopathology of these patients. In our current state of ignorance, however, partial answers are better than none.” We also concur with Harry Harlow, whose classic work regarding maternal separation set the stage for the development of animal models of psychiatric disorders. As quoted by Smith [8], Harlow reportedly defended the use of animal models by stating, “You’d be crazy to use animal models, but you’d also be crazy not to use them”.

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Table 1
Summary of behavioral models of binge-type eating

| | Validity | | Use | | Citations ^a |
|-----------------------------|-------------------|-----------|------------|-------------------|--------------------------|
| | Face [†] | Construct | Simplicity | Cost [‡] | |
| Sham feeding | ** | ** | * | * | Smith [8]; Van Vort [21] |
| Restriction/refeeding (R/R) | ** | ** | * | * | Hagan and Moss [33] |
| Tail-pinch | * | * | ** * | ** * | Morley et al. [48] |
| R/R + shock | ** | ** * | * | * | Hagan et al. [34, 35] |
| Crowding | * | * | ** | ** * | Inoue et al. [51] |
| Social isolation | * | ** | * | * | Miller et al. [52] |
| Maternal separation | * | ** | * | ** | Iwasaki et al. [53] |
| Limited access | ** * | ** | ** | ** * | Corwin et al. [58, 59] |
| Adjunctive eating | * | * | * | * | Wilson and Cantor [80] |

^aThese are not intended to be exhaustive, but only to provide examples.

[†]One star indicates that one of the proposed objective criteria for defining binge-type eating in isomorphic models was met; two stars indicate two criteria; three stars indicate three criteria.

[‡]More stars indicate lower cost.