# Animal Models of Eating Disorders, Substance Use Disorders, and Addictions

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**Abstract**

Laboratory animal models are valuable in that they allow researchers to better understand the various biological and behavioral factors that may contribute to eating disorders and substance use disorders, as well as an opportunity to discover effective treatments for each. This chapter describes how animal models have been used to study features of anorexia nervosa, bulimia nervosa, and binge eating disorder, with a particular focus on the variables associated with the development of such behavior in animals. The second half of this chapter focuses on the various animal models that have been used to explore key characteristics of addiction. This chapter concludes with a brief discussion of the overlaps that exist between the two types of disorders and suggestions for future research directions.

**Keywords**

Addiction • Animal models • Anorexia nervosa • Bulimia nervosa • Binge eating • Binge eating disorder • Hyperactivity • Purging • Rat • Rodent

## 1.1 Introduction

Laboratory animal models allow researchers the unique opportunity to study both physical and psychological disorders in ways that would otherwise often be unfeasible among clinical samples. Further, such techniques allow researchers to isolate

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the biological mechanisms associated with a given disorder without the influence of many of the potentially confounding variables seen in humans, such as various social and cultural influences. As a result, animal models can serve as valuable tools in discovering the physiological bases of psychiatric disorders as well as viable treatment options. In some cases it is difficult, if not impossible, to model each characteristic of a specific disorder with the use of animals. Rather, animal models provide a method of replicating and investigating specific *symptoms* of a disorder. This chapter will discuss the behavioral symptoms of eating disorders and substance use disorders that have been explored through the use of animal models. Further, this chapter will describe how these symptoms have been isolated and studied by researchers, as well as some noteworthy findings that have been revealed as a result.

## 1.2 Animal Models of Eating Disorder Symptoms

### 1.2.1 Anorexia Nervosa

Anorexia nervosa (AN) is a psychiatric disorder characterized primarily by the refusal to maintain a healthy body weight and an unrelenting fear of gaining weight. In the United States, the prevalence of AN among adults is reported to be approximately 0.9 % and 0.3 % in women and men, respectively (Hudson, Hiripi, Pope, & Kessler, 2007). This disorder has been associated with a range of both medical and psychological comorbidities, including osteoporosis, bradycardia, anxiety, and depression (Attia, 2010). Although AN has been recognized by the *Diagnostic and Statistical Manual of Mental Disorders* for several decades, many questions remain regarding the biological alterations that may underlie and result from behaviors associated with AN and which treatment approaches are most effective for this disorder. The use of animal models may provide the field with new and unique insights into this complex disorder.

The primary animal model that is presently available for studying AN is activity-based anorexia (ABA). This model is based on the finding that rats given limited access to food (i.e., 1–2 h/day) and unlimited or nearly unlimited access to a running wheel will increase their running activity, particularly preceding scheduled food access (known as food anticipatory activity); lose a significant portion of their initial body weight; and, if the experimental protocol is not stopped, eventually die of self-starvation (Epling & Pierce, 1984; Routtenberg & Kuznesof, 1967). This model is thus able to capture three critical symptoms associated with AN: decreased calorie intake, hyperactivity, and weight loss (see Fig. 1.1). Female ABA rats also show changes in their hormonal cycles (Dixon, Ackert, & Eckel, 2003; Watanabe, Hara, & Ogawa, 1992), providing further congruence between this model and the feature of amenorrhea seen in AN. It should be noted that while hyperactivity is not considered a diagnostic criteria for AN, this feature has been reported in 31–80 % of individuals with AN (Hebebrand et al., 2003). Additionally, recent research shows that AN patients have significantly higher total energy expenditure and physical

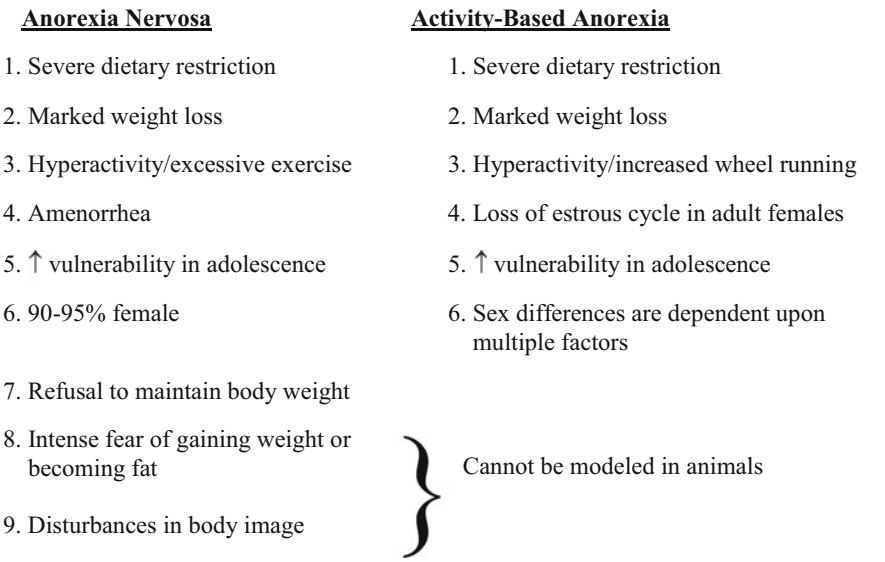


**Fig. 1.1** Behavioral similarities between individuals with anorexia nervosa and animals vulnerable to activity-based anorexia. Reprinted and adapted from *Anorexia nervosa: Symptoms, treatment, and neurobiology*, A translational approach to understanding anorexia nervosa, p. 167, 2012, N. Barbarich-Marsteller, with permission from Nova Science Publishers, Inc

activity patterns compared to either normal or overweight controls (Elbelt et al., 2013). Research using the ABA model has allowed investigators the opportunity to explore three main questions: (1) what factors might increase an animal's susceptibility to develop ABA, (2) how does ABA alter physiological mechanisms, and (3) what factors might protect against or attenuate ABA behavior and, ultimately, contribute to the recovery of body weight? (See Fig. 1.1.)

#### 1.2.1.1 Theories on Energy Expenditure

Two main theories have been proposed to explain why animals increase their energy expenditure when food is restricted. First, it has been proposed that animals may respond to calorie limitations with increased exercise as an adaptive strategy (Epling & Pierce, 1988). Indeed, one can imagine that when resources are limited, it would prove advantageous for survival to move in search of food. Recent research has supported this theory by demonstrating that ABA rats with access to sucrose, which is energy dense, run less than ABA rats with access to saccharin, which does not provide energy (Duclos, Ouerdani, Mormede, & Konsman, 2012). Evidence that food-restricted animals do not increase their running activity when given several small chances to feed throughout the day, as opposed to one meal or two shorter meals, provides further support for the idea that this behavior may be motivated by a search for food (Kanarek & Collier, 1983).

In addition to the possible evolutionary value of this behavior, it has been argued that running has reinforcing qualities (Belke & Wagner, 1996; Scheurink, Boersma,

Nergardh, & Sodersten, 2010), and it has been shown that running serves as a more potent reinforcer when animals are food restricted (Pierce, Epling, & Boer, 1986). Research from our laboratory has revealed increased extracellular dopamine (DA) release in the nucleus accumbens (NAc) of ABA rats when running compared to controls (Avena, Murray, Barbarich-Marsteller, & Rada (September, 2013). These findings contribute to the theory that animals may engage in high levels of exercise to experience the rewarding effects of running which may, in turn, be further enhanced by a state of hunger. While the two theories presented here are sometimes described as distinct or even competing, they may not be incompatible. As has been previously noted (Gutierrez, 2013; Garland et al., 2011), it is possible that adaptive coping strategies are promoted by natural sources of reinforcement.

#### 1.2.1.2 Variables Associated with the Development of ABA

Research investigating the factors that increase subjects' susceptibility to or serve to protect against developing ABA may provide unique insights into the complex set of variables that influence the development of AN in humans. To date, a number of characteristics have been identified as important when studying ABA in animals, including weight, age, and sex. Rats with a low baseline body weight, for example, tend to lose more weight when subjected to ABA-like conditions (1.5 h of food access and 2 h access to a running wheel) than rats of the same sex and age with a higher baseline body weight (Boakes & Dwyer, 1997). Likewise, differences in age have been shown to influence the progression of ABA, with younger animals tending to lose weight more rapidly (Boakes, Mills, & Single, 1999). Because this effect may be a function of low body weight, investigators have compared older female and younger male rats of similar weights and found that older female rats showed less body weight loss during ABA (Boakes et al., 1999), supporting the idea that older animals may be less susceptible to the detrimental effects of this model. This corresponds with findings that AN onset typically occurs earlier in life (Hudson et al., 2007).

AN is also more prevalent among females (Hudson et al., 2007), leading some researchers to explore possible sex differences when studying the effects of ABA. However, the literature remains mixed regarding which sex is more or less vulnerable. While early research reported that female rats exhibit increased susceptibility to ABA compared to males due to characteristically high rates of running, this study did not report the ages of the rats or whether or not there were significant differences between the groups' baseline body weights (Pare, Vincent, Isom, & Reeves, 1978), which are now known to be key factors in the development of ABA. Additionally, while females do tend to run more (Boakes et al., 1999), males tend to lose weight more quickly, as females have also been shown to eat significantly more (Doerries, Stanley, & Aravich, 1991). Research investigating sex differences has also found this to be the case even when males had a higher baseline body weight (Doerries et al., 1991). Further, research comparing same age male and female rats did not show a significant difference between body weight loss, despite lower initial body weights and increased running observed among females, which the authors propose to be an indication that females may be less vulnerable than males to ABA.

Interestingly, it has been shown that while females remain consistent in their level of running activity despite declines in body weight, males tend to increase their wheel running as their body weight decreases (Boakes et al., 1999). Other research, however, has found that same-age females, weighing significantly less than their male counterparts, reach ABA removal criterion more quickly (Hancock & Grant, 2009), indicating that further research is needed to elucidate the sex differences that exist in this context and, more specifically, the factors that may contribute to them.

Baseline wheel running activity has also been shown to be a strong predictor of body weight loss for both mice and rats exposed to ABA conditions, with higher baseline rates predicting worse outcomes (Pjetri et al., 2012). This suggests that it may be relevant for clinicians to consider a patient's pre-morbid physical activity levels and, perhaps, that individuals involved in strenuous exercise routines may be more likely to develop AN-like symptoms when a diet is introduced. This theory has been tenuously supported by clinical research showing a higher prevalence of eating disorders among adolescent athletes compared to controls (Martinsen & Sundgot-Borgen, 2012), despite findings to the contrary (Martinsen, Bratland-Sanda, Eriksson, & Sundgot-Borgen, 2010; Reinking & Alexander, 2005).

The effects of stressful early life experiences, often modeled in animals with variations of maternal separation methods, have also been studied as a potential factor that may contribute to the development of ABA. However, this line of research has resulted in somewhat mixed findings. For example, rat pups separated from their dams for 180 min each day during the pre-weaning period show accelerated body weight loss, less food intake, and more pronounced increases in running activity compared to controls (15 min separation) (Hancock & Grant, 2009), suggesting that extended maternal separation during this developmental time period may increase an animal's vulnerability to ABA. Conversely, long maternal separation (3 h daily separation from dams) during pre-weaning has been shown to increase survival time in ABA in adult female rats compared to non-handling (Carrera, Cerrato, Sanchez, & Gutierrez, 2009). Finally, postnatal handling, which is known to increase maternal contact (licking and grooming behaviors) when the pup has been returned, has been shown to delay the amount of time before reaching removal criterion during ABA in adult females compared to non-handling (Carrera, Gutierrez, & Boakes, 2006). It is important to note that there are a number of variables to consider when interpreting these results which are beyond the scope of this chapter, including significant differences in baseline body weights (as seen in Carrera et al., 2006), as well as the implications of the control groups used.

Studies have also considered the protective role that certain factors may play in preventing or attenuating ABA behavior. For instance, social housing has been shown to decrease the deleterious effects of ABA and similar conditions on body weight loss compared to individual housing (Boakes & Dwyer, 1997; Ness, Marshall, & Aravich, 1995). Further, the palatability of the diet offered can affect weight loss, with a high-fat diet diminishing ABA (Brown, Avena, & Hoebel, 2008). These findings suggest the potential importance of social interaction as

well as diet composition in mediating the progression of ABA. Future research in this area may prove beneficial in informing prevention and/or attenuation strategies.

### 1.2.2 Bulimia Nervosa and Binge Eating Disorder

Bulimia nervosa (BN) is marked by (1) excess consumption of food during a distinct period of time (*binge eating*) which is accompanied by a sense of loss of control and (2) behaviors such as vomiting, laxative use, and intense exercise (*purging*), which are employed to compensate for the excess calories consumed while bingeing. The following section will discuss the various animal models that have been used to study these two criteria. It should be noted that models of binge eating are relevant to both BN and binge eating disorder (BED) as this symptom is a feature of both disorders.

#### 1.2.2.1 Binge Eating

Over the last several decades, a number of paradigms have been used to model binge eating in animals. The results of such research have revealed a number of key factors related to this behavior, including a history of food restriction, availability of palatable food, and stress.

Several research efforts have sought to characterize the role of dieting in the development of binge-related eating disorders. While it appears that dieting is not necessary for the onset of binge eating, a considerable number of individuals who report binge eating also report prior dieting (Manwaring et al., 2006; Spurrell, Wilfley, Tanofsky, & Brownell, 1997). In animals, cycles of food restriction and subsequent refeeding have been associated with increased consumption of both chow and palatable food during test meals following weight restoration and the normalization of food access (Hagan & Moss, 1991; Hagan & Moss, 1997). It is interesting to note that when spontaneously tested (without an acute period of food deprivation), only rats with both a history of food restriction and access to palatable food during refeeding showed increased food intake during the test meal, mostly in the form of palatable food (Hagan & Moss, 1997). The presence of palatable food appears to play a major role in binge eating behavior among animals. In our laboratory, binge eating has been elicited by limiting rats' food access to 12 h per day (Avena, Rada, & Hoebel, 2006; Bocarsly & Avena, 2012). During this time, rats are provided unlimited access to palatable food and standard rodent chow. Food is presented 4 h after the start of the dark cycle (4 h after they typically begin to feed), and thus, animals are hungry and exhibit binge intake of the palatable food. This pattern of overeating does not develop in rats that are only provided chow during the 12 h access period, nor does it develop in rats with ad libitum access to the palatable food. Though not universally supported (Raymond, Bartholome, Lee, Peterson, & Raatz, 2007), there is clinical research to suggest that individuals with BED and BN also tend to consume high amounts of palatable foods during binge meals (Bartholome, Raymond, Lee, Peterson, & Warren, 2006; Kales, 1990; Rosen, Leitenberg, Fisher, & Khazam, 1986; Yanovski et al., 1992).

Binge eating has also been modeled in rats by coupling food restriction and refeeding with an environmental stressor. For example, it has been shown that while an increase in food intake occurs among female rats following 1 week of restricted food access (2 h/day) this increase was greatest among rats that were assigned to the 1 week 2 h/day food restriction schedule and were subsequently placed in a small, movement-limiting cage (Inoue et al., 1998). Similarly, while a 48 h period of food and water deprivation caused food intake to increase in rats, a shorter, 12 h period of food and water deprivation coupled with a 10 min swim test in cold water produced both a greater increase in food intake and a marked increase in high-fat diet consumption in particular (Vaswani, Tejwani, & Mousa, 1983). The role of palatable food in mediating the binge eating response was further shown by Hagan et al., (2002) who found that while the combination of food restriction, refeeding, and a foot shock did not significantly increase chow intake in female rats, hyperphagia was reported when rats were given access to a palatable food (Oreo cookies). In a fascinating study by Cifani, Polidori, Melotto, Ciccocioppo, and Massi (2009), researchers found that both a history of several food restriction/refeeding cycles and a stressor, which involved allowing animals to see and smell but not eat palatable food, resulted in significant increases in palatable food intake. The authors propose that this form of stress may resemble that experienced by humans when encountering what are considered to be "forbidden food" items. Collectively, this line of research has led to the notion that a history of the combination of food restriction, stress, and access to palatable food may promote binge eating. Interestingly, a recent laboratory study assessing the effects of stress on eating in humans found that patients with BED exhibited increased initial eating rate and an decreased eating deceleration when exposed to stress unlike participants without BED (Schulz & Laessle, 2012). Likewise, clinical research has shown stress to increase intake of sweet high-fat foods among emotional eaters (Oliver, Wardle, & Gibson, 2000).

Similar to studies investigating the effects of maternal separation on the development of ABA, research has explored the effects of maternal contact in early life on the development of binge eating. For example, 6- and 9-week-old female rats that had been separated from their mothers for 6 h/day for 3 weeks after birth exhibited significantly increased food intake following a period of restricted feeding compared to control rats who had been handled early in life (Iwasaki, Inoue, Kiriike, & Hikiji, 2000). This effect was not observed in female rats tested at either 3 or 12 weeks, nor was it shown in male rats at any time, indicating both age- and sex-specific effects. Additional evidence demonstrates that while hyperphagia was initially observed in both non-handled and maternally separated offspring during a period of refeeding following food restriction, only maternally separated rats continued to exhibit this response over multiple cycles (Ryu et al., 2008). Female offspring with lower levels of maternal care (measured by licking and grooming behaviors) during early life have also been shown to be more likely to binge eat palatable food after experiencing a shock, whether or not they had undergone food restriction. However, rats that had been food restricted exhibited this behavior sooner (Hancock, Menard, & Olmstead, 2005). Notably, these results were only

observed when this paradigm was introduced during adolescence but not in adulthood, which corresponds with evidence that the average onset for BN is during late adolescence (Hudson et al., 2007). Collectively, these findings suggest the relevance of early life stressors and maternal contact for binge eating behavior.

Corwin et al. (1998) have shown that food deprivation and stress are not necessary establishing operations for bingeing; by simply offering palatable food to rats on a limited access schedule (e.g., 2 h daily or 2 h 3 days a week), rats demonstrate excessive consumption. Likewise, binge eating has been modeled by providing intermittent access to a cafeteria-style diet including a variety of different foods, many of which are rich in fat and sugar (Leigh, Stock, Lacey, & Wilson, 1998). Wilson and Cantor (1987) have also elicited hyperphagia in food-satiated rats. When placed on an intermittent schedule of reinforcement, the reinforcer being electrical brain stimulation, most rats markedly increased their food intake. The authors suggest that, in this case, overeating may be seen as a type of adjunctive behavior engaged in between the receipt of reinforcers.

The number of animal models available to study binge eating behavior offers researchers unique opportunities to isolate and explore certain variables of interest. For instance, while binge eating may be related to increased body weight in certain models, our laboratory has noticed that sugar-bingeing animals tend to reduce their chow intake, effectively compensating for the excess calories taken in while bingeing (Avena, Rada, & Hoebel, 2008). Recent research by Hargrave and Kinzig (2012) has investigated the effects of enlarging the stomach by implanting and inflating chronic gastric balloons in the stomachs of rats, which may serve as an alternative model of binge eating that does not affect body weight. Such models can provide clinically relevant insights as body weight is not always increased in individuals who binge eat (Masheb & White, 2012). This also allows researchers to discriminate between the effects of binge eating versus those that may result from being overweight or obese. The different models that have been developed also provide the means to study subjects who engage in both binge eating and periods of self-imposed food restriction, as well as those that only report binge eating. Researchers may also wish to manipulate when palatable food is made available (i.e., every day or a few times a week) to reflect the clinical reality or the order of life events being studied (food restriction preceding stress or vice versa). Finally, the diversity of animal models allows investigators opportunities to study the effects of different stressors (i.e., early life stressors, acute, chronic) on binge eating behavior.

#### 1.2.2.2 Purging

While the compensatory behaviors associated with BN represent a greater challenge to replicate among animals, it has been possible to explore the effects of this behavior through the use of the sham feeding technique. This method involves the implantation of an intragastric fistula which allows the contents of the stomach to be drained during meals. Studies employing this technique have shown sham feeding to increase food intake in both rats (Davis & Campbell, 1973) and monkeys (Gibbs & Falasco, 1978). Such findings suggest that purging may inhibit normal

post-ingestive feedback processes that signal satiety and, thus, increase food consumption. Interestingly, cues associated with prior sham feeding have also lead to increased consumption during real feeding (Van Vort & Smith, 1987).

Insights into purging behavior may also be gleaned from research investigating captive gorillas that have been shown to regurgitate and then reingest their food (Gould & Bres, 1986). This behavior was exhibited least by gorillas that were both born in captivity and reared by their mothers compared to those born in captivity but hand-reared and those captured in the wild and thus may have also experienced maternal separation. While this may not be an ideal model of BN, this finding does provide further support for theories that stressful early life experiences, and maternal separation in particular, may alter feeding behavior later in life.

## 1.3 Animal Models of Substance Use Disorders and Addictions

Numerous animal models have been developed over the years to study the various behaviors that characterize addiction. Similar to those used within the field of eating disorders, animal models employed within the context of understanding drug abuse and addiction often focus on specific symptoms that can be replicated in the laboratory. These symptoms may be informed by the diagnostic criteria used to classify substance use disorders (SUDs) and/or clinical observations. For example, while relapse is not listed as a diagnostic criterion for addiction, it remains a subject of interest within the field. The following section describes how animal models have been used to provide insight into some of the key aspects of addiction.

### 1.3.1 Tolerance

According to the DSM-5, tolerance is defined as "requiring a markedly increased dose of the substance to achieve the desired effect or a markedly reduced effect when the usual dose is consumed" (American Psychiatric Association [APA], 2013). While tolerance may at first seem to represent a challenge to researchers as it may be thought to have its basis in subjective experience and appraisal, behavioral models have been developed to assess this characteristic of addiction in animals. One method for measuring tolerance is a tilting plane test. When studying tolerance to alcohol consumption, for example, Nikander and Pekkanen (1977) placed rats on a plane thats angle would regularly increase until the rat could no longer hold its ground. The angle at which the rat slid (the "sliding angle") was used to indicate the point at which the animal was intoxicated. As alcohol intake increases and tolerance for lower doses develops, rats are better able to coordinate motor functions and stay on the plane for longer periods of time. Similarly, Tiffany and Maude-Griffin (1988) administered varying levels of morphine to rats to see which dosages would elicit stronger analgesic effects (a common effect of morphine). Following morphine administration, a tail flick test is administered to determine how long it takes for the rat to move its tail from under a hot beam of

light. A rat that is considered tolerant to the lower doses of morphine will flick its tail quickly from under the hot beam of light but will be slower when administered a higher dose. Thus, at least two distinct animals models have been used to assess the presence of tolerance in response to exposure to drugs of abuse.

### 1.3.2 Withdrawal

Unlike tolerance, assessing the presence of withdrawal syndrome does not necessarily require much experimental manipulation. Withdrawal may be elicited, for example, by taking a drug away from an animal after a certain period of use or by administering the appropriate antagonist. One symptom that has been observed in response to withdrawal from several different drugs of abuse is anxiety (Emmett-Oglesby, Mathis, Moon, & Lal, 1990). Therefore, withdrawal has been measured through the use of experimental tests that are thought to detect anxiety in animals. One such method involves training rats to lever press for food in response to feelings of anxiety (Gauvin et al., 1996). For example, rats have been given pentylenetetrazole (an anxiogenic drug) and saline and taught to lever press for food only in response to the effects of pentylenetrazole (i.e., the anxiety). Similarly, the animal will lever press in response to withdrawal-induced anxiety.

Behavioral coding has also been used to identify characteristics of withdrawal in animals. For instance, withdrawal in rats has been shown to produce wet dog shakes, writhing (or abdominal stretching), jumping, stereotyped head bobbing, sweeping tail movements, yawning, and increases in irritability (defined as episodes of conflict-induced vocalizations). Teeth chatter episodes (separated by at least 3 s), discrete episodes of chewing (without anything in mouth), lacrimation, piloerection, ptosis, salivation, and diarrhea have all been observed among animals during withdrawal (Rasmussen, Beitner-Johnson, Krystal, Aghajanian, & Nestler, 1990). In chimpanzees, symptoms of withdrawal are similar to those observed among humans. After several weeks of chronic ethanol intake, hyperreflexia and irritability were noted when blood alcohol levels neared zero. Concomitant symptoms include photophobia, rapid respiration, sweaty palms and feet, decreased responsiveness to auditory stimuli, and, in severe cases, convulsions (Pieper, Skeen, McClure, & Bourne, 1972). Again, symptoms such as these can be coded to provide a measure of the severity of withdrawal produced by a particular substance.

### 1.3.3 Craving

The DSM-5 now includes craving, defined as "an intense desire or urge for the drug that may occur at any time but is more likely when in an environment where the drug previously was obtained or used," as a diagnostic criterion for SUDs (American Psychiatric Association, 2013). Measuring this construct in animals may serve as a proxy for the excessive time or effort humans may spend in attempts to get and take a particular substance when addicted. Markou et al. (1993) propose that

craving is "reflected in enhanced effectiveness of the drug as a reinforcer." Based on this conceptualization, craving can be determined by assessing, in various ways, how much effort animals will exert to receive a drug of abuse. For example, animals may first be provided access to a drug on a fixed-ratio schedule. Once the animals' level of responding is consistent, investigators may increase the level of responding necessary for the receipt of the drug by switching to a progressive ratio reinforcement schedule. Likewise, craving may be indicated by how quickly an animal traverses an runway to gain access to a drug (Vanderschuren & Ahmed, 2013). Craving has also been measured in animals using an experiment based on the extinction process. In this procedure, animals are first trained to lever-press for access to a drug, then the experimenter removes the drug to assess how much the animal will continue to respond without reinforcement.

An additional approach to determining craving in animals is through the use of choice paradigms. During this type of test, subjects are allowed to choose between two stimuli, one of which is the drug, and depending on the test, selection of one stimulus may prohibit animals from accessing the alternative stimuli until the following trial. The principles of classical conditioning have also been employed to study craving in animals; the conditioned reinforcement paradigm includes the pairing of a drug and a conditioned stimulus (CS) during training. Depending on an animal's level or rate of responding for the CS when the drug no longer accompanies it, an animal is considered to demonstrate more or less craving.

Investigators can also learn about addictive behavior by observing an animal's behavior following a period of abstinence from a drug. For example, animals may demonstrate a change in intake of or responding for the drug when it is reintroduced after abstinence (Koob, 2000). This is called the "deprivation effect" and may be used to indicate the presence of strong cravings or as a model of relapse. Other methods used to measure craving include second-order schedule paradigms and conditioned place preference tests (see review by Markou et al., 1993).

### 1.3.4 Use Despite Consequences

The DSM-5 includes several criteria that may fit under the broader category of "use despite consequences." For example, criterion 6 reads, "the individual may continue substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance." Additionally, criterion 9 reads, "The individual may continue substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (American Psychiatric Association, 2013)." To determine if animals would show persistent drug-seeking behavior despite adverse consequences, an experiment was designed in which animals were trained to lever press for an additional lever which, when pressed, would provide access to cocaine. After training with these contingencies, rats were presented with both a CS (a tone) and footshock. Later, drug seeking was tested in the presence of the CS. The results of this experiment showed that a subset of subjects continued to

exhibit drug-seeking behavior despite the presence of this cue. Interestingly, this effect was only observed after animals were given extended access to cocaine but not in animals given access to the drug for a more limited period (Vanderschuren & Everitt, 2004). Similarly, certain animals with extended access to ethanol continue to ingest the drug after a period of abstinence even when it is given a bitter taste by adding quinine (Wolffgramm, Galli, Thimm, & Heyne, 2000).

### 1.3.5 Relapse

Animal models have been helpful in identifying the various circumstances that may contribute to a relapse. For example, relapse has been elicited by stress, cues associated with the drug, as well as small doses of the drug (Deroche-Gamonet, Belin, & Piazza, 2004; Lynch, Nicholson, Dance, Morgan, & Foley, 2010). To determine the factors or conditions that may promote relapse, researchers have employed a reinstatement procedure which consists of allowing animals the chance to respond for access to a drug, subsequently removing the drug and assessing whether certain stimuli elicit responding again (Deroche-Gamonet et al., 2004; Lynch et al., 2010).

## 1.4 Overlaps Between Eating Disorders and Addictions

Eating and drug use are both motivating, appetitive behaviors with underlying similarities in their neural circuitry (Volkow & Wise, 2005), leading some researchers to investigate whether eating disorders may represent some form of an addictive behavior (Davis & Claridge, 1998; Kaye et al., 2013; Marrazzi & Luby, 1986). Although some do not consider this is a valid conceptual approach to the study of eating disorders (Wilson, 2010), there is support for this idea. From a reward perspective, food restriction, a feature of certain eating disorders, can increase the reinforcing effects of drugs of abuse (Carr, 2002). Eating disorders commonly begin during adolescence, a period of vulnerability for the development of addictive behaviors. Much like individuals with drug addiction, who forgo many activities and responsibilities in order to seek and consume drugs of abuse, individuals with eating disorders can adopt a similar pattern of behavior, with weight loss efforts, bingeing or rituals regarding food, and exercise occupying the majority of their time and energy. When food intake in AN does occur, it is often associated with anxiety, a symptom that is also often reported during periods of drug abstinence or withdrawal (Barbarich-Marsteller, Foltin, & Walsh, 2011). Likewise, eating disorder behavior is often engaged in despite serious consequences to one's health and is vulnerable to relapse. Thus, eating disorders share many commonalities with addiction.

Studies using animal models of eating disorders support the idea that aspects of addiction may be involved. In our laboratory, we have used a model of binge eating to show signs of "addiction" to sugar and other palatable foods (Avena et al., 2008),

**Table 1.1** Summary of findings in support of sugar addiction in rats using an animal model of sucrose or glucose bingeing

| Substance dependence | Animal model of sugar dependence |
|---|---|
| A. DSM-5 | |
| *Tolerance* | Escalation of daily sugar intake Colantuoni et al. (2001) |
| *Withdrawal* | Somatic signs (teeth chattering, tremor), anxiety measured by plus maze, ultrasonic distress vocalizations Colantuoni et al. (2002), Avena et al. (2008) |
| *Consuming more than intended* | Deprivation effect Avena, Long, and Hoebel (2005) |
| B. Behavioral signs | |
| *Locomotor cross-sensitization* | Amphetamine Avena and Hoebel (2003) |
| *Proclivity to consume other drugs of abuse* | Alcohol Avena, Carrillo, Needham, Leibowitz, and Hoebel (2004) |
| C. Neurochemical changes in the NAc | |
| *Repeated release of DA* | Rada, Avena, and Hoebel (2005), Avena, Rada, and Hoebel (2006) |
| *↑$D_1$ receptor binding* | Colantuoni et al. (2001) |
| *↓$D_2$ receptor binding* | Colantuoni et al. (2001) |
| *↑$D_3$ receptor mRNA* | Spangler et al. (2004) |
| *↓preproenkephalin mRNA* | Spangler et al. (2004) |
| *DA/ACh imbalance during withdrawal* | Colantuoni et al. (2002), Avena et al. (2008) |

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including signs of withdrawal, craving, and neurochemical changes in reward-related brain regions that are consistent with those seen when animals are given a drug of abuse (See Table 1.1). Likewise, rats prone to binge eating have been found more likely to traverse a shock grid for the receipt of palatable food than binge-resistant rats (Oswald, Murdaugh, King, & Boggiano, 2011), indicating use despite deleterious consequences. Clinical support for such findings comes in part from studies assessing food addiction using a self-report scale. For example, in a sample of obese individuals with BED, 41.5 % were considered to meet the criteria for "food addiction" (Gearhardt, White, Masheb, & Grilo, 2013). In terms of AN, it has been shown that ABA rats display withdrawal signs in response to an opioid antagonist (Kanarek, D'Anci, Jurdak, & Mathes, 2009). Future research incorporating models typically used to assess characteristics of addiction to study eating disorder pathology may shed additional light on similarities that may exist between these two disorders.

Several studies have also found increased substance use/abuse among eating disorder samples, particularly among individuals with bulimic symptoms (Krug et al., 2009; Root et al., 2010). Further, patients with substance use disorder and post-traumatic stress disorder who report bingeing have been found to demonstrate less success during drug abstinence (Cohen et al., 2010). Such findings suggest the

relevance of assessing and appropriately addressing the symptoms of both substance use disorders and eating disorders during treatment.

**Conclusion**

Animal models have been used to further our understanding of the symptoms associated with AN, BN, BED, as well as addiction. The clinical utility of these models lies in their ability to identify characteristics which may increase one's vulnerability to develop such symptoms, and to help researchers identify and explore the potential of promising treatment approaches. Further, the overlaps that have been identified between these two types of disorders present a possible guide for further study.

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