Published in final edited form as:

Appetite. 2010 December ; 55(3): 734–737. doi:10.1016/j.appet.2010.09.010.

The study of food addiction using animal models of binge eating*

Nicole M. Avena

University of Florida, College of Medicine, Department of Psychiatry, Gainesville, FL 32608, United States, Princeton University, Department of Psychology, Princeton, NJ 08540, United States

Nicole M. Avena: navena@princeton.eu

Abstract

This review summarizes evidence of “food addiction” using animal models of binge eating. In our model of sucrose bingeing, behavioral components of addiction are demonstrated and related to neurochemical changes that also occur with addictive drugs. Evidence supports the hypothesis that rats can become dependent and “addicted” to sucrose. Results obtained when animals binge on other palatable foods, including a fat-rich food, are described and suggest that increased body weight can occur. However, the characterization of an addiction-like behavioral profile in animals with binge access to fat requires further exploration in order to dissociate the effect of increased body weight from the diet or schedule of feeding.

Keywords

Bingeing; Craving; Withdrawal; Cross-sensitization; Body weight; Fat; Sugar; Obesity; Rats

The concept of food addiction

As reported at the Columbia University Seminar on Appetitive Behavior, the obesity epidemic has various proposed causes, one of which is the concept of “food addiction.” This theory posits that people can become addicted to food, in ways similar to how some people are addicted to drugs. It is thought that food addiction can lead to overeating, which can result in increased body weight or obesity in select individuals. Stories of “food addiction,” particularly “sugar addiction,” abound in the popular press (Appleton, 1996; Bennett & Sinatra, 2007; Rufus, 2004). There are clinical accounts in which self-identified food addicts use food to self-medicate; they often eat in order to escape a negative mood state (Ifland et al., 2009). The idea of food as an addictive substance has even permeated food marketing, with one study claiming that some commercials targeting children depict food as a source of extreme pleasure and addiction (Page & Brewster, 2009).

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Based on a presentation by Nicole Avena at the Columbia University Seminar on Appetitive Behavior. September 17, 2009, Harry R. Kissileff, Chairman, supported in part by GlaxoSmithKline and The New York Obesity Research Center, St. Luke’s/ Roosevelt Hospital. This research was supported by USPHS grants DK-079793 (NMA), MH-65024 (Bartley G. Hoebel), and AA-12882 (BGH). Appreciation is extended to Dr. Bart Hoebel and Miriam Bocarsly for their suggestions on the manuscript.

From a scientific standpoint, the reality of food addiction in humans as it relates to drug addiction has been a topic of debate (Gold, Graham, Cocores, & Nixon, 2009). The criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) pertaining to substance abuse have been applied to food addiction in humans through the development of the Yale Food Addiction Scale (Gearhardt, Corbin, & Brownell, 2009). In support of the food addiction theory as it might relate to obesity, clinical studies have shown that food craving in normal weight and obese patients activates areas of the brain similar to those indicated in drug craving (Pelchat, Johnson, Chan, Valdez, & Ragland, 2004; Wang, Volkow, Thanos, & Fowler, 2004). This is clearly a burgeoning line of research that will continue to grow as more corollaries are drawn relating addiction to overeating.

Modeling food addiction in laboratory animals: a focus on binge eating

Laboratory animal models have been used to study food addiction. Beginning in Bart Hoebel's laboratory, we adapted models that were developed with rats for studying drug dependence to test for signs of food dependence, with the eventual goal of identifying the neurochemistry associated with these behaviors. Addiction in humans is a complex disorder; for simplicity it is discussed in three stages (American Psychiatric Association, 2000; Koob & Le Moal, 1997). *Bingeing* is defined as a bout of intake in a relatively short period of time, usually after abstinence or deprivation. Signs of *withdrawal* can become apparent when the abused substance is no longer available or chemically blocked; we discuss withdrawal in terms of opiate withdrawal, which has a clearly defined set of behavioral signs (Martin, Winkler, Eades, & Pescor, 1963; Way, Loh, & Shen, 1969). Finally, *craving* occurs when motivation to obtain a particular substance is enhanced, usually after an abstinence period.

We believe that binge eating is a salient component of food addiction. Binge eating can be seen in obese individuals (Stunkard, 1959), a candidate population for having food addiction. Moreover, it is known that food restriction can enhance intake and reinforcing effects of many drugs of abuse (Carr, 2007), and the binge/ intoxication stage is a part of the addiction cycle (Koob and Volkow, 2010). It has also been proposed that binge eating shares similarities with conventional drug addiction (Cassin & von Ranson, 2007; Davis & Carter, 2009). Therefore, the models described herein incorporate binge eating, and the findings suggest that this distinguishing feature is associated with the resultant addiction-like state.

An animal model of sugar bingeing

Our most studied model is that of sucrose bingeing. In this model, rats are maintained on a diet of 12-h access to a 10% sucrose solution (or 25% glucose in earlier studies) and standard rodent chow, followed by 12-h of sucrose and chow deprivation, for about one month. We have published extensively using this model and relating it to a variety of factors associated with addictive behavior. What follows is a summary of those findings (also see Table 1); details can be found in our review papers (Avena, 2007; Avena, Rada, & Hoebel, 2008a).

Behavioral signs of addiction following bingeing on sugar

After a month of binge eating sugar (sucrose or glucose), rats show a series of behaviors similar to the effects of drugs of abuse, including the escalation of daily sugar intake and increase in sugar intake during the first hour of daily access (i.e., a binge). Sucrose-bingeing rats regulate their caloric intake by decreasing their chow consumption, which compensates for the extra calories obtained from sugar, resulting in a normal body weight (Avena, Bocarsly, Rada, Kim, & Hoebel, 2008).

When administered a relatively high dose of the opioid antagonist naloxone, somatic signs of withdrawal, such as teeth chattering, forepaw tremor, and head shakes are observed, as well as anxiety as measures by reduced time spent on the exposed arm of an elevated plus-maze (Colantuoni et al., 2002). Signs of opiate-like withdrawal also emerge when all food is removed 24 h; these include somatic signs such as those described in response to naloxone (Colantuoni et al., 2002) and anxiety (Avena, Bocarsly, et al., 2008). Removal of sugar has been reported by others to decrease body temperature in rats (Wideman, Nadzam, & Murphy, 2005), which is another sign of opiate-like withdrawal, and signs of aggressive behavior can occur in rats with a history of intermittent access to sugar (Galic & Persinger, 2002).

Craving is measured during sugar abstinence as enhanced responding for sugar (Avena, Long, & Hoebel, 2005). After 2 weeks of forced abstinence from sugar, rats with binge access lever press for 23% more sugar than they ever did before (Avena et al., 2005), suggesting a change in the motivational impact of sugar that persists throughout a period of abstinence and leads to enhanced intake. Research from other laboratories suggests that the motivation to obtain sugar increases with the duration of abstinence (Grimm, Fyall, & Ossincup, 2005).

Forced abstinence in sugar-bingeing rats also causes a tendency to become hyperactive and substitute another drug of abuse if made available. Hyperactivity as a sign of dopaminergic sensitization was shown in sugar-bingeing rats that were given a challenge dose of amphetamine (Avena & Hoebel, 2003). Sugar-induced sensitization of the dopamine (DA) system has also been reported using cocaine as the challenge drug (Gosnell, 2005). Further, rats previously bingeing on sugar drink more 9% alcohol compared to control groups with access to *ad libitum* sugar, *ad libitum* chow, or binge (12 h) chow only (Avena, Carrillo, Needham, Leibowitz, & Hoebel, 2004). Thus, it can be concluded that sugar bingeing acts as a gateway to enhanced alcohol use.

Addiction-like neurochemical changes following binge eating of sugar

Unlike drugs of abuse, which exert their effects on DA release each time they are administered (Di Chiara & Imperato, 1988; Pothos, Rada, Mark, & Hoebel, 1991; Wise et al., 1995), the effect of consumption of palatable food on DA release wanes with repeated access, unless the animal is food deprived (Bassareo & Di Chiara, 1999; Di Chiara & Tanda, 1997). However, rats bingeing on sugar continue to release DA, as measured by *in vivo* microdialysis on days 1, 2 and 21 of access (Rada, Avena, & Hoebel, 2005), and this unabated release of DA can be elicited by the taste of sucrose (Avena, Rada, Moise, &

Hoebel, 2006) and is enhanced when rats are at a reduced body weight (Avena, Rada, & Hoebel, 2008b). On the other hand, rats that binge on chow only, are fed sugar and/or chow *ad libitum*, or taste sugar only two times, develop a blunted DA response that is typical of a food that loses its novelty. These results are supported by findings of alterations in accumbens DA turnover and DA transporter in rats maintained on an intermittent sugar-feeding schedule (Bello, Sweigart, Lakoski, Norgren, & Hajnal, 2003; Hajnal & Norgren, 2002).

Thus, binge access to sugar causes recurrent increases in extracellular DA in a manner that is more like a drug of abuse than a food. Consequently, changes in the expression or availability of DA receptors emerge. Autoradiography reveals increased D₁ in the nucleus accumbens (NAc) and decreased D₂ receptor binding in the striatum (Colantuoni et al., 2001). Others have reported a decrease in D₂ receptor binding in the NAc of rats with intermittent access to sucrose (Bello, Lucas, & Hajnal, 2002). Rats bingeing on sugar show decreases in D₂ receptor mRNA in the NAc and increased D₃ receptor mRNA in the NAc (Spangler et al., 2004).

Regarding opioid receptors, mu-receptor binding is increased in response to cocaine and morphine (Bailey, Gianotti, Ho, & Kreek, 2005; Unterwald, Kreek, & Cuntapay, 2001; Vigano et al., 2003), and enkephalin mRNA in the striatum and the NAc is decreased in response to repeated injections of morphine (Georges, Stinus, Bloch, & Le Moine, 1999; Turchan, Lason, Budziszewka, & Przewlocka, 1997; Uhl, Ryan, & Schwartz, 1988). Likewise, in sugar-bingeing rats, mu-opioid receptor binding is significantly enhanced in the accumbens shell after 3 weeks of access (Colantuoni et al., 2001). Rats bingeing on sugar also have a significant decrease in enkephalin mRNA in the NAc (Spangler et al., 2004), which is consistent with findings in rats offered limited daily access to a sweet-fat, liquid diet (Kelley, Will, Steininger, Zhang, & Haber, 2003).

Drug withdrawal can be accompanied by alterations in DA/ acetylcholine (ACh) balance in the NAc, with ACh increasing while DA is suppressed, and this DA/ACh imbalance has been shown during withdrawal from several drugs of abuse (Hoebel, Avena, & Rada, 2007). Using our model of sugar bingeing, we have shown that rats with intermittent access to sugar show the same neurochemical imbalance in DA/ACh during withdrawal: (1) when the bingeing rats are given naloxone to precipitate opioid withdrawal (Colantuoni et al., 2002), and (2) after 36 h of total food deprivation (Avena, Bocarsly, et al., 2008). Thus, addiction-like neurochemical changes can result from drinking a sugar solution in a bingeing manner.

Bingeing on a fat-rich food

As noted above, rats bingeing on sucrose do not gain excess body weight, suggesting that sucrose bingeing might foster characteristics of addiction, but it alone is probably not responsible for obesity or weight gain. However, we have shown that when a highly palatable combination of sugar and fat is offered to rats, it instigates binge eating and also increases body weight (Berner, Avena, & Hoebel, 2008). We reduced the duration of palatable food access from 12 to 2 h in order to make the binge episodes more salient. Others have used this same access schedule with fat (shortening), but not observed changes

in body composition (Corwin, Wojnicki, Fisher, Dimitriou, Rice, & Young, 1998). In our study, rats were maintained for approximately one month on: (1) sweet-fat chow for 2-h/day followed by *ad libitum* standard chow, (2) 2-h sweet-fat chow 3 days/week and access to standard chow in the interim, (3) *ad libitum* sweet-fat, or (4) *ad libitum* standard chow. Both groups with limited (2-h) access to the sweet-fat chow exhibited bingeing behavior, and the body weight of these rats increased after the binge and then decreased between binges as a result of self-restricted intake of standard chow following binges. However, despite these fluctuations in body weight, the group with daily access to sweet-fat chow gained significantly more weight than the control group with standard chow available *ad libitum*.

While the evidence of addiction in sugar-bingeing rats is well documented, the addiction-like behavioral and neurochemical changes associated with binge eating fat-rich foods have not yet been fully characterized. Others have reported that bingeing on fat (corn oil) can cause alterations in accumbens DA release, similar to that seen in our sugar-bingeing animals (Liang, Hajnal, & Norgren, 2006). Moreover, rats identified as binge-eating prone will tolerate higher levels of foot shock when it is paired with a fat-containing food (Oswald, Murdaugh, King, & Boggiano, 2010), suggesting that binge eating can be associated with an abnormal motivation to consume palatable food. We have not observed behavioral signs of opiate-like withdrawal in fat-bingeing rats using our limited access model. It is possible that properties inherent in fat counteract some effects on the opioid system (Avena, Rada, & Hoebel, 2009; Hawes et al., 2008). While more work is needed to understand the behavioral effects of binge eating of fat-rich foods and how they may differ from bingeing on other nutrients, models of binge access to sweet-fat foods are advantageous in that they may inform research on obesity in relation to addiction-like characteristics.

There are very few studies on the addiction-like effects of binge eating on fat-rich foods, but a growing number of studies have assessed the effect of *ad libitum* access to fat-rich foods. Rats with *ad libitum* access to a cafeteria-style diet show signs of compulsivity as measured by food intake during rest periods and changes in the microstructure of feeding behavior (Heyne, Kiesselbach, Sahun, McDonald, Gaiffi, Dierssen, & Wolffgramm, 2009). *Ad libitum* access to a cafeteria-style diet has been reported to produce signs of opiate-like withdrawal (Le Magnen, 1990). Also, when given *ad libitum* access to a high-fat diet, mice show signs of anxiety and willingness to endure an aversive environment in order to gain access to the high-fat food, as well as changes in limbic corticotrophin-releasing factor (CRF) and reward-related signaling expression (Teegarden & Bale, 2007; Teegarden, Nestler, & Bale, 2008). CRF systems have been identified as having a critical role in the withdrawal syndrome that emerges upon removal of palatable food (Cottone et al., 2009). Recently, Kenny's group reported evidence of downregulation of D₂ receptors in rats with *ad libitum* or limited access to a cafeteria style diet, with the effects most pronounced in rats that were obese (Johnson & Kenny, 2010).

Summary and conclusions

The models of binge eating in rats described herein provide tools with which to study the concept of food addiction and its resultant neurochemistry. The data suggest that binge intake of sugar can have dopaminergic, cholinergic and opioid effects that are similar to

those seen in response to some drugs of abuse, albeit smaller in magnitude. Newer data generated from studies of bingeing on a sweet-fat chow show that it produces increased body weight, providing a potential link to obesity. These experiments from our laboratory, combined with research by others, contribute to the growing body of evidence in support of the concept of food addiction.

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Table 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-IV-TR	
<i>Tolerance</i>	Escalation of daily sugar intake (Colantuoni et al., 2001)
<i>Signs of withdrawal</i>	Somatic signs (teeth-chattering, tremor), Anxiety measured by plus-maze, Ultrasonic distress vocalizations (Colantuoni et al., 2002 and Avena et al., 2008)
<i>Consuming more than intended</i>	Deprivation effect (Avena et al., 2005)
B. Behavioral signs	
<i>Locomotor cross-sensitization</i>	Amphetamine (Avena and Hoebel, 2003)
<i>Proclivity to consume other drugs of abuse</i>	Alcohol (Avena et al., 2004)
C. Neurochemical changes in the NAc	
<i>Repeated release of DA</i>	Rada et al. (2005) and Avena et al. (2006)
↑ <i>D₁ receptor binding</i>	Colantuoni et al. (2001)
↓ <i>D₂ receptor binding</i>	Colantuoni et al. (2001)
↑ <i>D₃ receptor mRNA</i>	Spangler et al. (2004)
↑ <i>preproenkephalin mRNA</i>	Spangler et al. (2004)
<i>DA/ACh imbalance during withdrawal</i>	Colantuoni et al. (2002) and Avena et al. (2008)

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