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Sugar vs. Fat Bingeing: Notable Differences in Addictive-like Behaviors

Nicole M. Avena, Pedro Rada, Bartley G. Hoebel

Department of Psychology, Princeton University, Princeton, NJ 08540

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Send correspondence to:

Dr. Bartley G. Hoebel
Princeton University
Department of Psychology
Washington Road
Princeton, NJ 08540
Phone: (609) 258-4463
Fax: (609) 258-1113
E-mail: hoebel@princeton.edu

Abstract

Ingestion of different nutrients, such as fats vs. sugars, normally produces different effects on physiology, the brain and behavior. However, they do share certain neural pathways for reinforcement of behavior, including the mesolimbic dopamine (DA) system. When these nutrients are consumed in the form of binges, this can release excessive DA that causes compensatory changes that are comparable to the effects of drugs of abuse. In this paper, we review data obtained with animal models of fat and sugar bingeing. The concept of "food addiction" is described and reviewed from both clinical and laboratory animal perspectives. A theory is presented in which galanin, a fat-stimulated peptide, may have a role in preventing the emergence of opiate-like withdrawal signs, which are seen in sugar-bingeing rats, but not in fat-bingeing rats. Finally, we discuss the implications of bingeing on sugars and fats for obesity and eating disorders.

1. Introduction

Although binge-eating behavior is traditionally associated with eating disorders, it is becoming more prevalent in the United States through its emergence in a variety of clinical and non-clinical populations. Binge eating has been linked to obesity, which presently afflicts 33% of the adult U.S. population (1,2) and may also be a predictor of body-fat gain among children (3). Binge eating is also associated with increased frequency of body weight fluctuation, depression, anxiety and substance abuse (4-6). The presence of bingeing behavior in several different eating disorders, as well as in non-clinical populations, has made it important to study from a public-health perspective.

The DSM-IV defines binge eating as a series of recurrent binge episodes, where each episode is defined as eating a larger amount of food than normal during a short period of time (usually within any two-hour period) (7). Binge-eating episodes are associated with three or more of the following: 1) eating until feeling uncomfortably full, 2) eating large amounts of food when not physically hungry, 3) eating much more rapidly than normal, 4) eating alone because one is embarrassed by how much s/he is eating, 4) feeling disgusted, depressed, or guilty after overeating, or 5) marked distress or anxiety regarding binge eating.

Aside from diagnosed patients, there is also a far larger population of individuals who often binge on food, but perhaps not regularly enough to warrant a clinical diagnosis. It is not always clear where one draws the line between eating a large meal because the person is hungry and the food is tasty vs. a pathological

binge. However, the physiological consequences of binge eating may be similar, whether engaged in naturally due to hunger, casually for social or hedonic reasons, or regularly enough to warrant a diagnosis.

2. What are the common binge foods?

To put it simply, people usually binge on highly-palatable, caloric-rich food. These foods are typically high in fats, sugars, or often both (8,9). Binge episodes often involve consumption of bread or pasta, followed in frequency by sweets, fatty foods or salty snacks (10). Individuals with a preference for bingeing on sweet foods tend to binge more frequently.

Why don't people binge on broccoli? There must be some property of palatable "dessert" and "snack" foods rich in sugar and/or fat that promotes binge eating. Sugars and fats are well known to have different effects on physiology and brain chemistry (11), which may be related to their different effects on behavior. In order to understand the behavioral and neurochemical basis of binge eating on specific macronutrients, we turn to laboratory animal models of binge eating.

3. Animal models of binge eating

Binge eating is a multifaceted behavior, with emotional and cultural components that are difficult to reproduce with animal models. Nonetheless, animal models of binge eating are fundamental to understanding the physiological and neurochemical basis of this behavior.

3A. Animal models of sugar bingeing

Several laboratories have used limited access to sugar solutions to model binge eating (12-15). The findings all suggest that animals will engage in binge-type eating on a sweet food when it is offered intermittently. Our laboratory has developed a model of sugar bingeing (16), in which rats are maintained on daily 12-h food restriction, followed by access to a 25% glucose or 10% sucrose solution (similar to the sugar concentration of a soft-drink) and rodent chow. After a few days on this schedule, these animals escalate their daily intake of sugar (Fig. 1A) and begin to binge, as indicated by an increase in their intake of the sugar solution during the first hour of access. Animals that have *ad libitum* access to the sugar solution and chow consume a total daily amount similar to that consumed by the bingeing animals, but they do not engage in

discrete bingeing episodes. Body weight does not differ from normal in animals that are bingeing on sugar, indicating that the animals are able to regulate their calories and compensate for the excess energy by eating less rodent chow (Fig. 1 B and C).

3B. Animal models of fat bingeing

Animals will also binge on pure fat, which suggests that binge eating is not exclusive to sweet taste. Corwin and colleagues have shown that sated rats with *ad libitum* access to rodent chow will binge on a vegetable fat (shortening) when it is presented for 2 h each day (17), and this effect is enhanced when the fat is offered only 3 times per week. A similar finding has been reported with shortening that is trans-fat free (18). Rats with restricted access to vegetable fat do not show alterations in body weight or body-fat accrual compared with chow-fed controls (17,19); however, they do show elevated plasma leptin levels (19).

3C. Animal models of bingeing on sweet-fat mixtures

The combination of sweet and fat activates multiple taste receptors, postingestive signals and neuropeptide systems. Sugar/fat combinations, in the form of cookies or sugar-fat mixtures, have been used by Boggiano and others to induce binge eating in laboratory models (20,21). We have developed a model of binge eating using a nutritionally complete sweet-fat diet in animals that are not food-restricted (22). Rats with 2-h daily access to a sweet-fat food (Research Diets #12451 pellets, 45% fat, 20% protein, 35% carbohydrate, 4.7 kcal/g) binge on it, even though they have *ad libitum* access to standard rodent chow for the other 22 h/day. By Week 3 of access, the bingeing behavior is most pronounced, and these animals consume, on average, 58% of their daily calories during the 2-h period of access to the sweet-fat food (Fig. 2A). These animals self-restrict their intake of standard chow, similar to the effects we have reported with sugar (23) and others have reported with fat (17,19) or sugar-rich diets (14). Cyclic bingeing and self-imposed food restriction results in fluctuations in daily body weight characterized by weight loss between binges (Fig. 2B). However, even taking into consideration the self-restriction of standard rodent chow between binges, an overall increase in body weight occurs in rats bingeing on sweet-fat pellets when compared with control groups that are fed only standard rodent chow or *ad libitum* access to the same sweet-fat pellets (Fig. 2C). Thus, this model represents binge eating that can result in increased body weight.

4. Food addiction

Many scientists have speculated that obesity and eating disorders, such as bulimia and anorexia, may have properties of an “addiction” (24-30). Moreover, several popular self-help books have been written on the topic of “sugar addiction” (31-34). Clinical and laboratory animal studies reveal similarities between overeating and drug addiction.

4A. Clinical support for the theory of food addiction

A recent clinical study suggests that carbohydrates can have abuse potential for “carbohydrate cravers” (35). Likewise, craving-related changes in response to palatable foods have been identified using brain imaging techniques, and these changes are similar to those seen during drug craving (36,37). Dopamine (DA) has been suggested to have a common role in drug abuse and obesity (28). Positron emission tomography (PET) scans reveal that obese subjects show a reduction in striatal D_2 receptor availability that is correlated with the body weight of the subject (38), and similar in magnitude to the reductions reported in drug-addicted subjects (39). Opioids have also been the focus of clinical studies (25). Appetite dysfunctions in the form of either binge eating or self starvation can affect endogenous opioid activity (40). Collectively, these clinical studies support the view that overeating can affect behavior and brain systems in a manner that resembles aspects of an addiction.

4B. Behavioral evidence of sugar dependence in laboratory animals

Many of the behaviors and neurochemical changes that are characteristic of drug abuse are also apparent in our animal model of sugar bingeing described above and summarized in Table 1. This model is reviewed and related to the substance abuse literature in greater detail elsewhere (16).

Briefly, rats given daily intermittent access to a sugar solution and chow escalate their sugar intake and increase their intake during the first hour of daily access, which we define as a “binge” (15). Sugar-bingeing rats show signs of opiate-like withdrawal when administered a relatively high dose of the opioid antagonist naloxone (3 mg/kg, s.c.). Somatic signs of withdrawal, such as teeth chattering, forepaw tremor, and head shakes, as well as behavioral manifestations of anxiety, are observed (41). Similar signs of opiate-like

withdrawal emerge spontaneously without the use of an opioid antagonist, when all food is removed for 24 h (23,41). Sugar-bingeing rats lever press for 23% more sugar in a test after 2 wks without sugar than they ever did before (42), suggesting a change in the motivational impact of sugar that persists and increases throughout a period of abstinence. We have also shown that rats bingeing on sugar develop locomotor cross-sensitization to a low, challenge dose of amphetamine (0.5 mg/kg, i.p.) that has little or no effect on naïve animals (43). When rats are bingeing on sugar and then forced to abstain, they subsequently show enhanced intake of 9% alcohol (44), suggesting that intermittent access to sugar can be a gateway to alcohol use.

Other researchers have obtained supportive behavioral findings using similar models of sugar bingeing. Signs of anxiety have been reported in rats with limited access to a high-sucrose diet (14). The mere removal of sugar has been reported to decrease body temperature (45). Also, aggressive behavior has been observed during removal of a diet that involves intermittent sugar access (46). Using operant conditioning, Grimm and colleagues (47) find that sucrose seeking increases during a month of sugar abstinence in rats that had intermittent sugar access. Intermittent sucrose access cross-sensitizes not only with amphetamine (43), but also with cocaine (48), and facilitates sensitization to the DA agonist quinpirole (49). These results support the theory that the DA system is sensitized by intermittent sugar access; this is important since enhanced mesolimbic dopaminergic neurotransmission plays a role in the behavioral effects of sensitization as well as cross-sensitization (50), and may contribute to addiction (51,52).

4B2. Neurochemical evidence of sugar dependence

The evidence described above suggests that sugar bingeing can produce behaviors that are similar to those observed in drug-dependent rats. Concomitant neurochemical changes may result in, or perpetuate, these behaviors. These signs are also summarized in Table 1, and are explained in greater detail in an earlier review (16).

We have found changes in DA, acetylcholine (ACh) and opioid systems in sugar-bingeing rats that are similar to those observed with some drugs of abuse. Autoradiography reveals increased D_1 receptor binding in the nucleus accumbens (NAc) and decreased D_2 receptor binding in the striatum relative to chow-fed rats (15). Rats with intermittent sugar and chow access also have decreased D_2 receptor mRNA in the NAc, and increased D_3 receptor mRNA in the NAc and dorsal striatum compared with chow-fed controls (53). Sugar-

bingeing rats have a significant decrease in enkephalin mRNA (53), while mu-opioid receptor binding is significantly enhanced in the NAc shell, cingulate, hippocampus and locus coeruleus (15).

One of the strongest neurochemical commonalities between sugar bingeing and drugs of abuse is their effect on extracellular DA. A hallmark of drugs that are abused in repeated increase in extracellular DA, whereas during normal feeding the DA response fades out after repeated exposure to a food (54). When rats are bingeing on sugar, the release of DA is recurrent, which may make the brain adapt as it does to a drug of abuse. Rats that are bingeing on sugar apparently release DA every day, as measured on days 1, 2 and 21 of access (55). 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.

Withdrawal from drugs, such as morphine, nicotine and alcohol, is often accompanied by alterations in DA/ACh balance in the NAc, specifically DA decreases while ACh increases (56-58). 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 (41) or after 36 h of food deprivation (23).

Others have reported supportive findings. There is a decrease in D_2 receptor binding in the NAc of rats with restricted access to sucrose and chow compared with rats fed restricted chow only (59), and alterations occur in accumbens DA turnover and DA transporter binding in rats maintained on an intermittent sugar-feeding schedule (12,60).

4B3. Is there evidence of dependence on fat or sweet-fat combinations?

The literature suggests that, like sugar, a similar addictive-like state may emerge with fat. Le Magnen (29) noted that naloxone could precipitate withdrawal in rats fed an cafeteria-style diet *ad libitum*, which contains a variety of fat- and sugar-rich foods (e.g., cheese, cookies, chocolate chips). More recently, Teegarden and Bale (61) show that mice given *ad libitum* access to diets high in fat or carbohydrate for 4 weeks, and then forced to abstain, endure an aversive environment to gain access to their preferred food. They conclude that withdrawal of such a diet elevates the stress state and reduces reward, contributing to dietary relapse.

In terms of neurochemistry, it appears that binge eating of fat has affects on the accumbens DA and enkephalin systems that are similar to those observed with sugar bingeing. Limited exposure to fat (corn oil)

will repeatedly release DA in the NAc, and this effect is due to the taste of the oil (62). Rats with limited daily access to a sweet-fat diet show a significant decrease in enkephalin mRNA in the NAc (63), similar to the finding reported above with sugar (53). The role of opioids in the paraventricular nucleus of the hypothalamus (PVN) has been studied using a binge model (64), and the findings suggest that D-Ala2, NMe-Phe4, Gly-ol5-enkephalin (DAMGO) increases fat intake in fat-preferring animals, while having no effect In sucrose-preferring animals. These results indicate a complex role for PVN opioids in food intake with preference and nutrient type affecting the ability of these compounds to change behavior.

Based on this neurochemistry and the behaviors described above, it seems logical that fat-bingeing might also produce addictive-like behaviors. However, the data are not clear. Although fat offered *ad libitum* has been reported to produce some addictive-like behaviors (29,61), the effects of fat bingeing have not been reported. We have investigated whether behavioral signs of dependence emerge when animals binge using a variety of different high-fat diets and sweet-fat combinations. We have tested rats with limited (12-h or 2-h) access to a sweet-fat diet (Research Diets #12451, 45% fat, 20% protein, 35% carbohydrate), 12-h access to a sweet-fat mixture (35.7% vegetable fat, 64.3% sucrose), or 12-h access to vegetable fat (100% Crisco vegetable shortening), all with chow concurrently available. Control groups were fed these diets *ad libitum*, or given standard chow *ad libitum*. After 21-25 days on the diets, animals were administered 3 mg/kg s.c. naloxone, then observed for somatic signs of distress and anxiety in the elevated plus-maze. These procedures gave positive results in our previous reports with sugar bingeing (41), but no significant evidence of opiate-like withdrawal was found with any of these fat-rich dietary options, in either the bingeing or *ad libitum* groups. In other studies, we attempted to elicit spontaneous opiate-like withdrawal signs by food-depriving the rats maintained on fat-rich diets for 24-36 h. Again, although signs of anxiety and somatic indications of distress have been reported following fasting in sugar-bingeing rats (23), this was not observed in rats that had been bingeing with a high-fat source in the diet.

Although we have not noted signs of opiate-like withdrawal in fat-bingeing rats, that does not mean that excessive fat intake cannot produce addictive-like behaviors. Withdrawal is not a necessary criterion for drug craving, just like hunger is not necessary for food craving (37). Moreover, different classes of drugs (e.g., DA agonists vs. opiates) result in specific behavioral and physiological withdrawal signs. Thus, it may be that different macronutrients may also produce different withdrawal signs. It has yet to be determined whether or

not bingeing on fat can precipitate other addictive-like behaviors, including abnormal motivation due to abstinence and cross-sensitization.

5. Why do signs of opiate-like withdrawal emerge with sugar but not fat bingeing?

The relative lack of opiate-like withdrawal signs after fat bingeing underscores the importance of opioid systems in differentiating sugars and fats, and their subsequent affects on behavior. The neuropeptide galanin (GAL) and its binding sites are expressed in brain areas important for both drug and food reward (11). GAL is considered a fat-stimulated peptide because its expression is increased in these brain regions in response to a high-fat meal (65). In addition, hypothalamic injection of GAL promotes the intake of fat in preference to carbohydrate in some situations (66,67). Interestingly, peripheral injection of galnon, a synthetic GAL agonist, decreases opiate withdrawal signs in morphine-dependent mice (68). A single systemic injection of galnon in GAL knock-out mice is sufficient to reverse some of the biochemical changes brought about by morphine administration (69). Thus, GAL may be an endogenous negative regulator of opiate reward by attenuating some of the behavioral and neurochemical effects of opiates. Based on these data, it is possible that that lack of opiate-like withdrawal signs in fat-bingeing rats may be due to fat-induced endogenous GAL activation that can inhibit the relevant opioid effects.

6. Implications for eating disorders and obesity

We began this review with a discussion relating binge eating to obesity. Indeed, the findings with animal models that have been presented suggest that binge eating of sugar, and possibly even fat, may have some addictive-like properties. However, sugar bingeing does not affect body weight, but a combination of sweet and fat does result in increased body weight (22). Thus, fat may be the macronutrient that results in excess body weight, and sweet-taste may be largely responsible for producing addictive-like behaviors that include a withdrawal syndrome. However, if there is a high level of fat in the diet, it is conceivable that this inhibits the occurrence of opiate-like withdrawal signs by increasing the expression of some fat-stimulated peptide, such as GAL.

7. Conclusion

This review presents and overview of animal models of binge eating, with a focus on dissecting the effects of bingeing on sugars vs. fats. Results from many laboratories are presented to support the concept that binge eating sugar can result in behavioral and neurochemical changes that are similar to those caused by some drugs of abuse. Access to fat can promote obesity and may produce some properties of an addictive-like state, but opiate-like withdrawal is less evident. This may be due to the protective effects of a fat-induced peptide, such as GAL, that inhibits the relevant opioid system.

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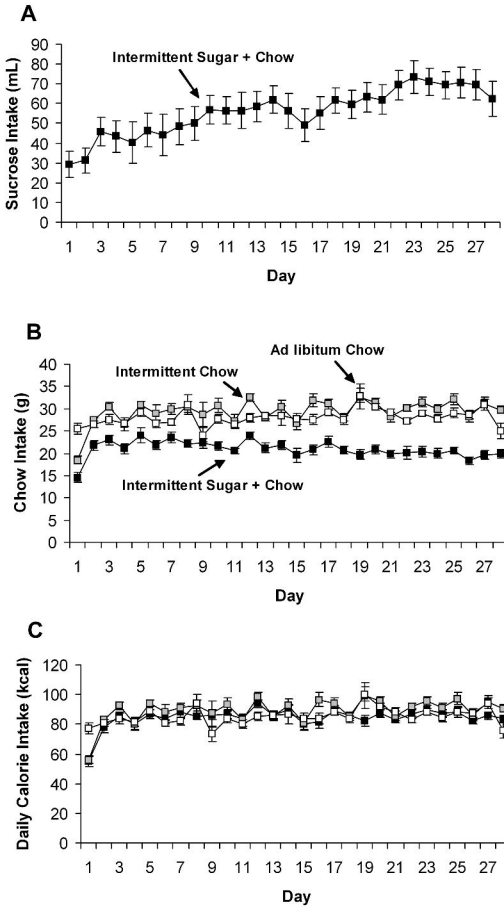
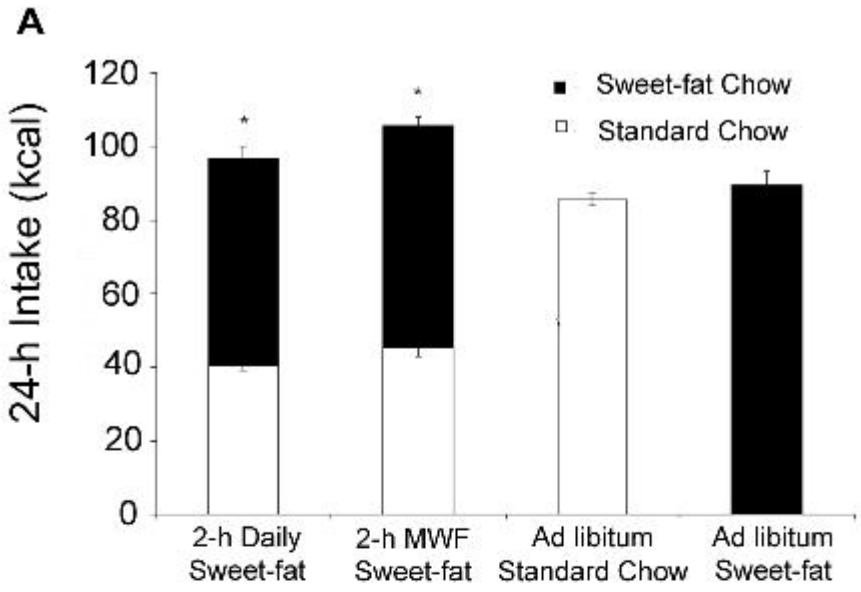
Figure Legends

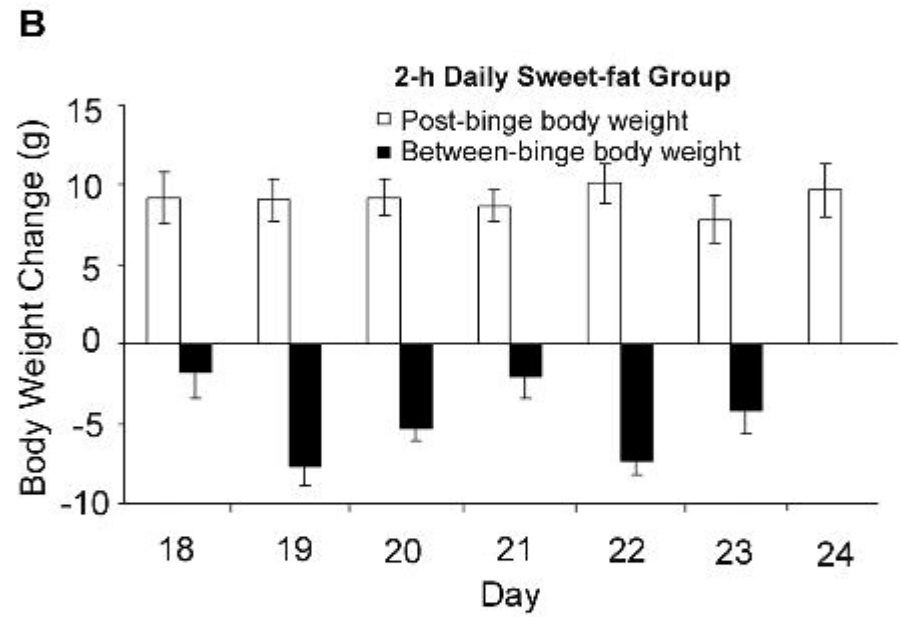
Figure 1. Sugar and chow intake during the 28-day access period in a rat model of sugar bingeing. A) Rats with intermittent sugar + chow escalated their total daily sugar intake over time. B) Rats with intermittent sugar + chow ate fewer grams of chow than the intermittent chow and *ad libitum* chow control groups; however, C) shows that there was no difference between groups in total daily caloric intake. Reprinted with permission from (23).

Figure 2. Caloric intake and body weight alterations in a rat model of fat bingeing. A) Total daily caloric intake during Week 3 of access expressed as calories derived from standard chow (white) vs. sweet-fat chow (black). The 2-h Daily Sweet-fat group and a group that received 2-h of sweet-fat chow only on Mondays, Wednesdays, and Fridays (2-h MWF Sweet-fat) both consume more than 50% of their daily calories from sweet-fat chow when it is available. *=$p<0.05$ compared with the Ad libitum Standard Chow group (mean ± SEM). B) A saw-tooth pattern emerges for the 2-h Daily Sweet-fat group in which they decrease in weight pre-binge and increase in weight post-binge each day. C) However, despite

this fluctuation in body weights throughout the day, the rats with 2-h daily sweet-fat gained significantly more total body weight than rats fed standard chow *ad libitum*. Adapted from (22).


A
Sucrose Intake (mL)
Intermittent Sugar + Chow
Day
B
Chow Intake (g)
Ad libitum Chow
Intermittent Chow
Intermittent Sugar + Chow
Day
C
Daily Calorie Intake (kcal)
Day


A
24-h Intake (kcal)
120
100
80
60
40
20
0
Sweet-fat Chow
Standard Chow
2-h Daily Sweet-fat
2-h MWF Sweet-fat
Ad libitum Standard Chow
Ad libitum Sweet-fat


B
2-h Daily Sweet-fat Group
Post-binge body weight
Between-binge body weight
Body Weight Change (g)
15
10
5
0
-5
-10
18
19
20
21
22
23
24
Day

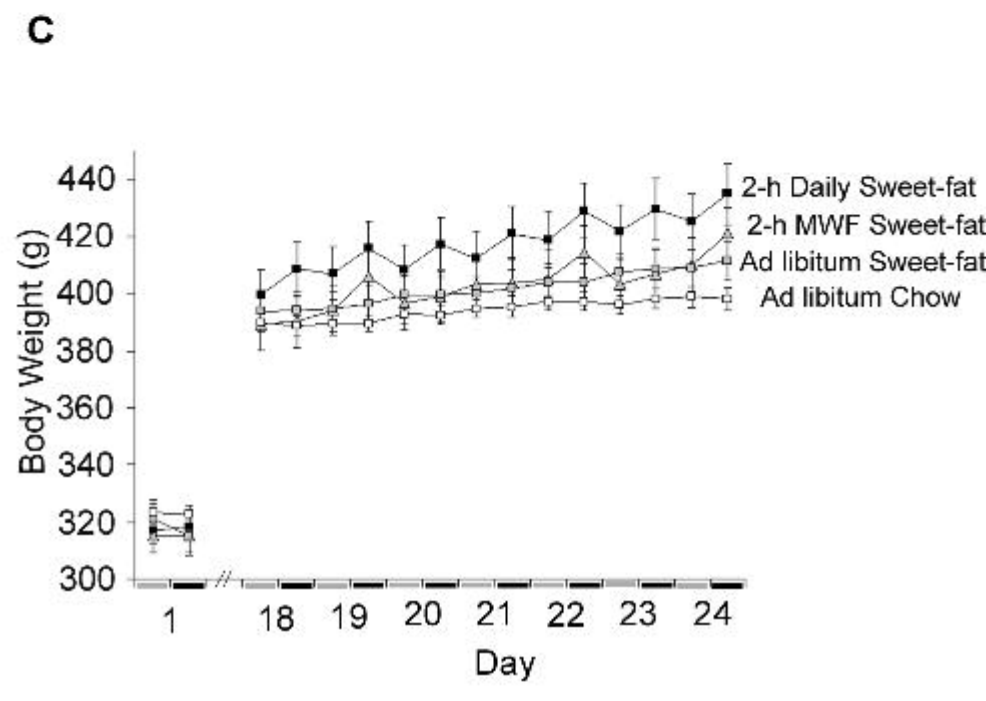

C
Body Weight (g)
440
420
400
380
360
340
320
300
2-h Daily Sweet-fat
2-h MWF Sweet-fat
Ad libitum Sweet-fat
Ad libitum Chow
1
18
19
20
21
22
23
24
Day

Table 1
Signs of Dependence Observed in Sugar-bingeing Rats

Behavioral Signs		
Sign	*Result*	*Reference*
Tolerance	Escalation of sugar intake over time	Colantuoni et al., 2001; Rada et al., 2005
Sensitization	Large meals of sugar in the form of binges	Colantuoni et al., 2001; Rada et al., 2005; Avena et al., 2008
Opiate-like withdrawal	Anxiety, somatic indications	Colantuoni et al., 2002; Avena et al., 2008
	Decreased body temperature	Wideman et al., 2005
Deprivation effect	Increase intake of sugar following an abstinence period	Avena et al., 2005
Incubation of responding	Temporal increase in responding for cues associated with sugar	Grimm et al., 2005
Cross-sensitization	Locomotor sensitization to amphetamine	Avena and Hoebel, 2003
	Locomotor sensitization to cocaine	Gosnell, 2005
	Consummatory sensitization to alcohol	Avena et al., 2004

Neurochemical Signs		
Neurotransmitter	*Result*	*Reference*
Dopamine	Repeated release in NAc	Rada et al., 2005, Avena et al., 2006
	Increased D1 receptor binding in the striatum	Colantuoni et al., 2001
	Decreased D2 receptor binding in the striatum Decreased D2 receptor binding in the NAc	Colantuoni et al., 2001 Bello et al., 2002
	Decreased D2 receptor mRNA in the NAc	Spangler et al., 2004
	Decreased D3 receptor mRNA in the STR and NAc	Spangler et al., 2004
	Increased DAT in the NAc and VTA	Bello et al., 2003
	Increased DAT mRNA in the VTA	Bello et al., 2003
	DA turnover in the NAc	Hajnal and Norgren, 2002
Acetylcholine	Delay in rise in NAc No rise in NAc when sham feeding	Rada et al., 2005 Avena et al., 2006
Opioids	Respond to naloxone with signs of opiate-withdrawal	Colantuoni et al., 2002

	Increased mu-opioid receptor binding in the NAc, cingulate, hippocampus, and LC	Colantuoni et al., 2001
	Decreased enkephalin gene expression in the NAc	Spangler et al., 2004

STR= striatum, DAT= dopamine transporter

Adapted from (70).