Chapter 23

Animal Models of Sugar and Fat Bingeing: Relationship to Food Addiction and Increased Body Weight

Nicole M. Avena, Miriam E. Bocarsly, and Bartley G. Hoebel

Abstract

Binge eating is a behavior that occurs in some eating disorders, as well as in obesity and in nonclinical populations. Both sugars and fats are readily consumed by human beings and are common components of binges. This chapter describes animal models of sugar and fat bingeing, which allow for a detailed analysis of these behaviors and their concomitant physiological effects. The model of sugar bingeing has been used successfully to elicit behavioral and neurochemical signs of dependence in rats; e.g., indices of opiate-like withdrawal, increased intake after abstinence, cross-sensitization with drugs of abuse, and the repeated release of dopamine in the nucleus accumbens following repeated bingeing. Studies using the model of fat bingeing suggest that it can produce some, but not all, of the signs of dependence that are seen with sugar binge eating, as well as increase body weight, potentially leading to obesity.

Key words: Binge eating, Dopamine, Fat, Food addiction, Nucleus accumbens, Sugar, Body weight

1. Introduction

1.1. Bingeing Behavior

Although binge-eating behavior has traditionally been associated with eating disorders, it is becoming more prevalent in the USA through its emergence in a variety of clinical and nonclinical populations. Bingeing is the main criteria for the diagnosis of binge-eating disorder, a disorder that affects approximately 6% of the population (1). Binge eating is also a hallmark of bulimia nervosa, a disorder characterized by cyclic binge eating and compensatory caloric purging. Further, binge eating has been linked to obesity, which presently afflicts 33% of the adult US population (2, 3). Binge eating may also be a predictor of body-fat gain among children, leading to a high risk for adult obesity (4). In addition to its relationship with obesity, binge eating is associated with increased frequency of body weight fluctuation, depression, anxiety, and substance abuse (5–7). Taken together, these studies suggest that

Firas H. Kobeissy (ed.), *Psychiatric Disorders: Methods and Protocols*, Methods in Molecular Biology, vol. 829,
DOI 10.1007/978-1-61779-458-2_23,

binge eating affects a significant proportion of our society, and it has deleterious consequences, making it important to study from a public-health perspective. Studies have correlated the increase in obesity with an increase in sugar consumption (8, 9) and fat consumption (10). These two nutrients are the focus of this protocol.

1.2. An Animal Model of Binge-Eating Sugar

Animal models of binge eating can be useful for studying the pathology underlying aberrant eating behaviors in human beings. Binge-eating behavior is observed in rats after just a few days of intermittent access to a sugar (e.g., 25% glucose or 10% sucrose) solution and chow. Rats have access to sugar and chow 12 h daily followed by 12 h of deprivation for approximately 1 month (11). Here, binge-eating behavior is defined as an increase in intake of the sugar solution during the first hour of access (animals have been shown to consume approximately 20% of their total daily sugar intake in the first hour of access). Further, sugar-bingeing rats gradually increase their total daily intake of sugar, eventually drinking as much in the 12-h access period as ad libitum-fed rats do in 24 h (~70 mL/day, see Fig. 1). We impose a 4-h delay between the onset of the dark cycle and the onset of food access in order to induce bingeing, as rats normally feed at the onset of the dark cycle and the delay will ensure that they will be hungry when the food is made available. Meal analyses demonstrate that in addition to escalated intake in the first hour, binge-eating rats show spontaneous binge episodes throughout the day while ad libitum-fed controls do not (12).

1.3. Binge Eating and Food Addiction

Food is a natural reward that activates neurochemical pathways in the brain that evolved to reinforce this behavior and others by making them pleasurable and motivating. Other reinforcers, including many drugs of abuse, exert their powerful reinforcing effects by usurping these brain pathways. Overlaps in the circuitry regulating food and drug intake have been well documented (13–18). Together, this overlapping circuitry, along with self-reports regarding feelings of compulsion to eat sweet or fat-rich foods, similar in some ways to an addict's compulsion to smoke cigarettes or drink alcohol, has inspired the study of "food addiction." The sugar binge eating model described in this chapter is a tool that can be used to study food addiction in the laboratory.

Bingeing is one criterion used by drug abuse researchers when classifying a substance as potentially addictive. Bingeing represents the transition from substance use to abuse (19), and it involves an escalation in the size and frequency of intake bouts, usually after a period of deprivation (19, 20). In addition to bingeing, other criteria, such as withdrawal, craving and cross-sensitization, have been described as behavioral signs of dependence on drugs of abuse. All of these criteria have been demonstrated using the animal model of sugar binge eating as described in this chapter (12, 21–29).

Rats maintained on the described sugar binge protocol also show neurochemical signs of dependence, including an increase in

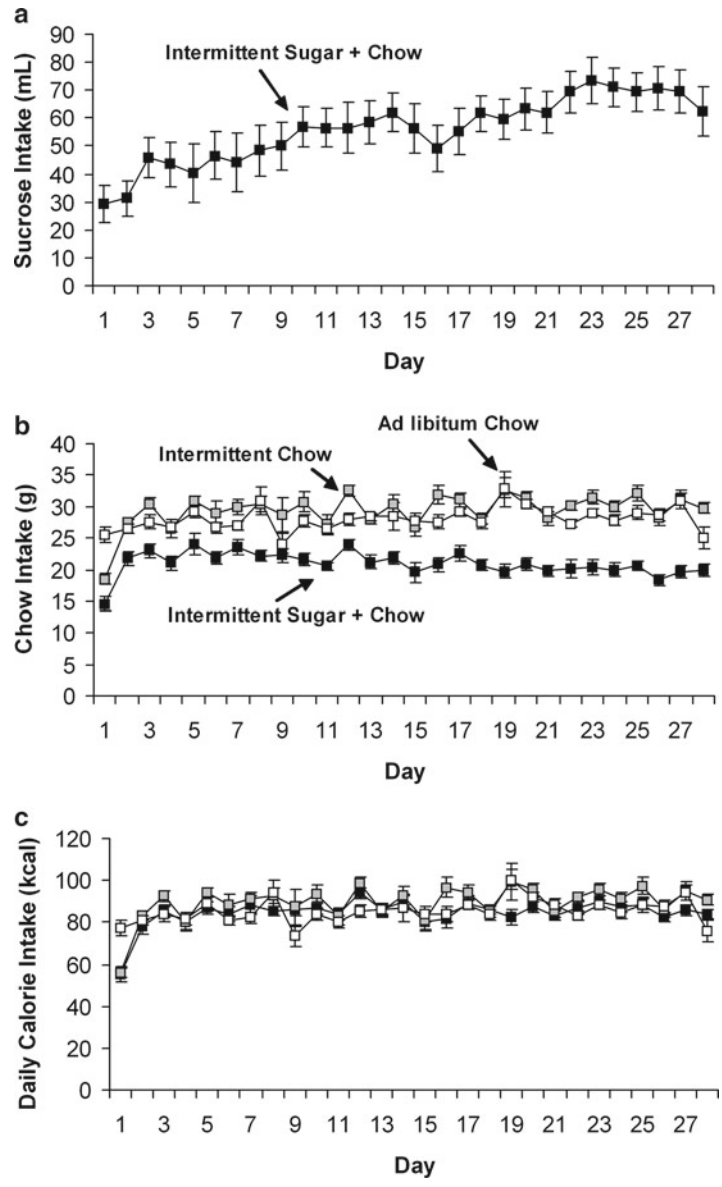

Fig. 1. Sugar and chow intake during the 28-day access period. (**a**) Rats with binge access to sugar and chow (i.e., intermittent sugar + chow) escalated their total daily sugar intake over time. (**b**) However, these rats ate fewer grams of chow than the intermittent chow and ad libitum chow control groups. (**c**) There was no difference among groups in total daily caloric intake. Adapted with permission from (12).

mu-opioid and D1 dopamine (DA) receptor binding in the nucleus accumbens (NAc), and increased D3 dopamine receptor mRNA in the NAc (25, 30). This is one area of the brain involved in motivation and reward for both eating and drug abuse (14, 31–35). Studies using in vivo microdialysis reveal that sugar-bingeing rats release DA in the NAc on days 1, 2, and 21 of bingeing on sugar

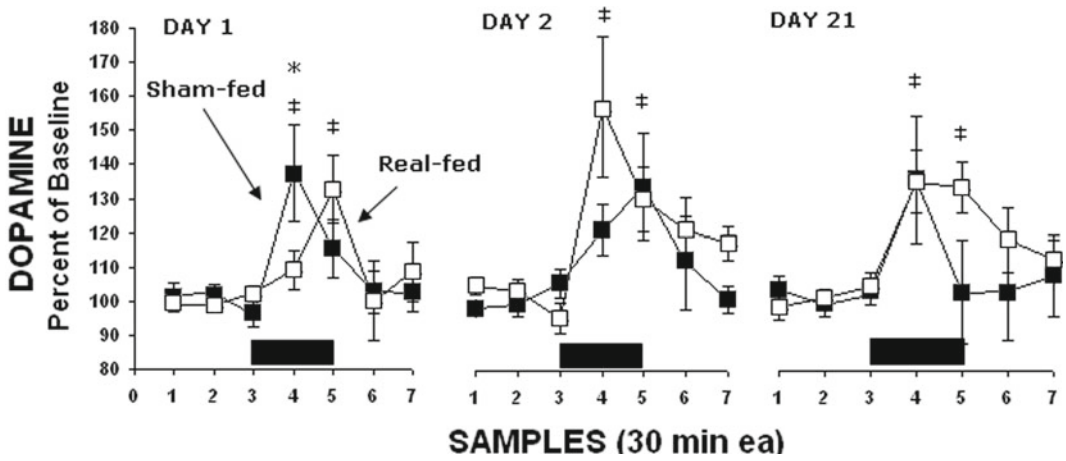

Fig. 2. Changes in extracellular DA in the NAc of sham-feeding and real-feeding rats during sucrose intake. The rectangles along the ordinate indicate when 10% sucrose was available. DA level is expressed as percentage of the mean baseline and is shown before, during and after unrestricted access to the sucrose. Significant differences between groups are indicated by asterisks ($p < 0.05$). Significant differences from baseline are indicated by (double dagger) ($p < 0.05$). Adapted with permission from (36).

(28), whereas nonbingeing rats show a blunted DA response that is more like the effect seen with a palatable food that is no longer novel (37). Further, this unabated release of DA with sugar bingeing can be elicited by the taste of sucrose, alone, as revealed by sham-feeding ((36), see Fig. 2). These neurochemical alterations are similar, albeit smaller in magnitude, to what is observed when rats repeatedly administer drugs of abuse.

After binge-eating sugar for approximately 1 month, rats show signs of opiate-like withdrawal. The opioid antagonist naloxone can be used to precipitate withdrawal signs, such as teeth-chattering, tremors, and ultrasonic vocalizations (24, 38). Signs of withdrawal can also emerge spontaneously by fasting the rats for 24–36 h (38). In both cases, the withdrawal behavior is coupled with an increase in the release of accumbens acetylcholine (ACh) and a decrease in DA (24, 38). This neurochemical imbalance in DA/ACh has been seen during withdrawal from drugs of abuse, such as alcohol, morphine, and nicotine (39–42). Further, following abstinence from sucrose, rats will exhibit a larger binge than ever before, indicating a "deprivation effect" and suggesting craving (43). In addition, cross-sensitization between rats maintained on the sugar-binge feeding schedules and amphetamine, alcohol, and cocaine, have been reported (21–23, 26).

1.4. Sugar Bingeing and Body Weight

Body weight does not differ between rats that are bingeing on sugar and those with ad libitum access to chow or sugar; the rats are able to regulate their caloric intake and compensate for the excess energy obtained from sugar by eating less rodent chow (38).

This type of spontaneous bingeing/restricting behavior is similar to that of some patients with nonpurging type bulimia (44), particularly those who binge eat, but nonetheless maintain a normal body weight. While eliminating the variable of increased body weight is useful for some studies, it does not help with understanding the suggested link between binge eating and obesity. To study this relationship, we now discuss another animal model using a different primary nutrient: fat.

1.5. An Animal Model of Fat Bingeing

Corwin and colleagues have shown that rats with ad libitum access to rodent chow will binge on vegetable fat when it is presented for 2 h each day (45, 46). This effect is enhanced when the fat is offered on a more restricted schedule; e.g., 2 h, three times per week. Others have used diets rich in both fat and sugar (i.e., Oreo cookies), and find evidence of binge eating on these diets that is enhanced in response to stress (47, 48). Similarly, we describe here a model of binge eating in which limited daily access to sweet-fat chow in nondeprived animals leads to bingeing behavior, as defined by excessively large meals (49, 50). Unlike Corwin's model which uses pure fat, we used a sweet-fat diet, with the goal of capitalizing on the known effects that sugar bingeing can have on behavior and brain chemistry, and combining them with the effect that fat is expected to have on body weight. Rats with 2-h daily access to sweet-fat chow (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, rats consume, on average, 58% of their daily calories during the 2-h binge (49).

Although, as described above, sugar bingeing does not lead to obesity, binge eating a combination of sweet-fat does result in significant changes in body weight (49). These animals show daily self-imposed restriction of standard chow intake, resulting in fluctuations in daily body weight characterized by weight loss between binges. However, despite these fluctuations in body weight, animals with binge access to a sweet-fat diet weigh significantly more than control groups that either have standard chow or sweet-fat chow available ad libitum (see Fig. 3). This indicates a model of binge eating that is associated with weight gain and obesity. Further, this is a model of binge eating in the absence of hunger, which in many ways, more accurately reflects voluntary bingeing in humans when energy-deprivation is not driving food intake. The combination of these two nutrients, sugar and fat, constitutes a large proportion of the snacks and desserts that patients with eating disorders tend to overconsume, possibly contributing to body weight gain (51–54).

It is of interest to note that, contrary to our initial hypothesis, naloxone-precipitated withdrawal is not seen in rats binge eating the sweet-fat chow (12). This underscores the idea that not all palatable foods, and importantly, combinations of palatable foods, are

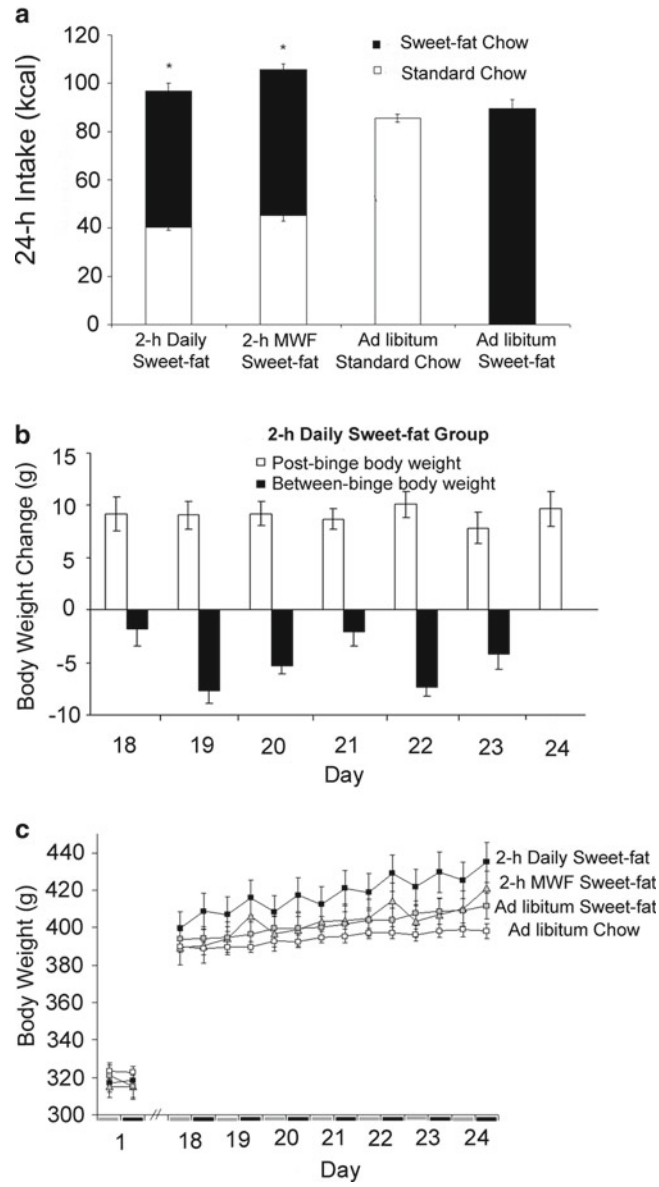

Fig. 3. Caloric intake and body weight alterations in a rat model of sweet-fat bingeing. (**a**) Total daily caloric intake during Week 3 of access expressed as calories derived from standard chow (*white*) vs. sweet-fat chow (*black*). The 2-h Daily Sweet-fat group and a group that received 2-h of sweet-fat 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 (asterisk = $p < 0.05$ 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 with permission from (49).

alike in terms of their effects on behavior and the brain. However, other models of bingeing on a fat-rich food suggest that there may be a link between addiction and overeating of fat (55–60). More research is needed to define the exact role that fat consumption has in addiction-like behavior.

2. Materials

2.1. Sugar Bingeing

1. Sucrose or glucose.
2. Prepare a 25% (w/v) glucose or 10% (w/v) sucrose solution with tap water (see Notes 6–8).
3. Adult male or female rats (e.g., Sprague-Dawley rats) weighing at least 250 g (see Note 1).
4. Standard laboratory rodent chow (e.g., LabDiet #5001, PMI Nutrition International, Richmond, IN; 10% fat, 20% protein, 70% carbohydrate, 3.01 kcal/g).
5. Scale accurate to 0.1 g.
6. Hanging wire-mesh cages or plastic-bottom cages with removable food hoppers (e.g., Allentown Caging Equipment; see Note 2).
7. Rodent vivarium with a 12-h light/dark cycle, maintained at 21°C.
8. 100-mL graduated (in 1-mL increments) drinking tubes: e.g., glass drinking tubes (Lab Products) or tubes made from 100-mL polyethylene graduated cylinders (Fisher Scientific) by cutting off the flange and filing the top flat.
9. Rubber stoppers with sipper tubes (steel-ball tip valves preferred; see Note 3).

2.2. Sweet-Fat Bingeing

1. Sweet-fat nutritionally complete rodent chow (e.g., Research Diets, New Brunswick, NJ, #12451).
2. Adult male rats (e.g., Sprague-Dawley rats) weighing at least 250 g.
3. Standard laboratory rodent chow (e.g., LabDiet #5001, PMI Nutrition International, Richmond, IN; 10% fat, 20% protein, 70% carbohydrate, 3.01 kcal/g).
4. Scale accurate to 0.1 g.
5. Hanging wire-mesh cages or plastic-bottom cages with removable food hoppers (e.g., Allentown Caging Equipment, see Note 2).
6. Housing room with 12-h light/dark cycle, maintained at 21°C.
7. Hopper to provide high-fat diet, or appropriate container if using an alternative diet (see Notes 4 and 5).

3. Methods

3.1. Sugar Bingeing

1. Acclimate rats to their home-cage environment for at least 5 days prior to the onset of the experiment.
2. Divide rats into experimental and control groups (at least $n = 8–10$ per group) of similar body weight (<10% variation between groups) and individually house animals. Provide water ad libitum to all rats throughout the experiment (see Notes 9 and 10).
3. The main experimental group with binge access to sugar will have a 12-h deprivation period (no food, water only), followed by 12-h access to a 10% sucrose or 25% glucose solution plus pelleted standard rodent chow and water. The feeding period should be timed such that access starts 4 h into the dark cycle. Maintain rats on this binge-feeding schedule for 21–28 days to elicit the dependence-like signs described above (see Background Information and Notes 11 and 12).
4. At the same time, maintain control groups of rats, which may include:
   (a) *Ad libitum sugar solution and chow*. This group is highly recommended as a control because it allows for the contrast of behavior and neurochemistry in normal feeding and binge-feeding. Further, including this control group allows for the confirmation of binge behavior as indicated by increased first hour intake in the binge animals compared to the free-feeding rats.
   (b) *Intermittent chow*. This group has 12-h food deprivation followed by 12-h access to standard rodent chow (no sugar solution) and water. It allows for the control of intermittent access to food, coupled with a period of deprivation.
   (c) *Ad libitum chow* (without sugar access) (see Note 13).
5. Record the 1-h intake of sugar solution after the first hour of access, and record the daily intake before removing the solution at the end of the 12-h access period. Record the volume to the nearest milliliter by reading it directly off the graduated drinking tube (see Note 14).
6. Average data and analyze using analysis of variance (ANOVA) (see Notes 15 and 16).

3.2. Sweet-Fat bingeing

1. Acclimate rats to their environment for at least 5 days prior to the onset of the experiment.
2. Obtain or prepare a nutritionally complete sweet-fat diet (see Note 17).

3. Divide rats (at least $n = 8–10$ per group) into experimental and control groups of similar body weight (<10% variation between groups) and individually house animals in hanging wire cages (see Notes 2 and 8). Provide water ad libitum to all rats throughout the experiment (see Note 9).
4. The fat-binge group receives access to sweet-fat chow from 6 to 8 h after the onset of the dark cycle, daily. For the other 22 h of the day, all rats have ad libitum access to standard rodent chow.
5. At the same time, maintain control groups of rats, which may include:
   (a) *Ad libitum sweet-fat diet*. This group is highly recommended as a control because it allows for the contrast of behavior and neurochemistry in normal feeding and binge-feeding conditions. Further, including this control group allows for the confirmation of binge behavior as indicated by increased first hour intake in the binge animals compared to the free-feeding rats.
   (b) *Ad libitum chow* (with no access to sweet-fat diet).
   (c) *Limited intermittent fat-binge group*. This group receives access to sweet-fat chow from 6 to 8 h after the onset of the dark cycle 3 days/week (Monday/Wednesday/Friday). This feeding pattern has also been shown to elicit binge eating (49, 61) (see Note 18).
6. Record the 1-h intake of fat diet using a scale, after the first hour of access, as well as daily intake.
7. Average data and analyze using ANOVA (see Note 15).

4. Notes

1. Studies have been conducted in male (21, 24, 28, 38) and female (22, 43) Sprague-Dawley rats; both sexes will binge.
2. Wire bottom cages are preferred because solid bottom cages retain the animals' feces and urine, which introduces confounding factors into the experiment. Consumption of bedding material (which is often caloric in nature) and fecal boli make it difficult to truly food deprive the rat. Further, gastric distension that results from filling the stomach with bedding or other substances collected in the bottom of the cage can cause the release of feeding peptides and neurotransmitters (62), potentially confounding studies. Additionally, measurements of food intake are less accurate in solid bottom cages; wire cages allow for the collection and weighing of pieces of chow that have been spilled, and allows the researcher to ensure food was

ingested and not hidden in the bedding. Wire food hoppers are recommended to hold standard rodent chow. Hoppers can be easily removed from the cage, allowing for easy facilitation of the 12-h deprivation period without too much disturbance to the rat's environment.

3. Rubber stoppers with steal ball tubes (e.g., Lab Products, Inc.) are preferred for providing fluid to the rats because they prevent unintentional fluid spillage. Further, the best practice for accurately measuring fluid intake is to attach the rubber stoppers and steal ball tubes to graduated cylinders. Cylinders can be mounted to the outside of a wire cage using a spring. Cylinders must be mounted vertically on the cage for accurate reading to the meniscus of the solution. Mounting bottles on the outside of the cage allows the researcher to take frequent readings of the fluid volume without disturbing the rat or risking fluid spillage.
4. Our research has been done predominately using binge consumption of a pelleted nutritionally complete diet. However, Corwin and colleagues have a well-developed model of binge consumption of pure vegetable fat (45, 46).
5. Containers to administer the high-fat diet should be chosen depending on the consistency of the diet. For example, metal hoppers can be used for pelleted diets and jars can be used to administer a Crisco or lard diet. Containers should limit spillage and allow for the collection of any stray food substances. Further, diet should be easy to remove from the cage, with little disruption to the rat, in order to smoothly facilitate daily food measurements.
6. Binge behavior has been observed with both lucose (25, 43) and sucrose (12, 21, 23, 38, 43, 63).
7. To prepare the 10% w/v sucrose solution, slowly dissolved 100 g of sucrose in approximately 800 mL of tap water while using a spin bar (i.e., a spinning magnet) to stir it, then, fill the container to 1,000 mL with tap water.
8. Prepare only enough sugar solution for each day. Store extra solution at 4°C for a maximum of 3 days, otherwise bacteria and mold can begin to form. Drinking bottles for sugar solutions should be emptied, rinsed, and refilled with new solution each day to avoid bacterial and mold growth. Bacteria can inhibit intake and possibly make rats sick. Each week bottles and drinking tubes should be sterilized using a laboratory dishwasher or commercial cage washing device.
9. There is some variability in chow, sugar, and fat intakes from rat to rat, so it is advisable to use at least 8–10 rats/group.
10. Rubber stoppers with sipper tubes and steel-ball tip valves work best to prevent leakage of the sugar solution. Water can also be

provided using these tubes and stoppers, or it can be made available using automatic watering systems.

11. Each rat is typically given 100 mL/day of the sugar solution, and those rats that drink almost all of it are given more on subsequent days. Ample amounts of chow should also be provided. Male Sprague-Dawley rats consume about 30–35 g of chow each day, nearing 100 kcal, with fluctuation depending on body weight and age. The goal is to always provide more sugar solution and chow than the rats will consume. By the end of 1 month, some rats may increase sucrose consumption to a degree that larger drinking tubes (e.g., 250 mL) are required.
12. Intermittent sugar access always begins 4 h into the dark cycle. Animals typically engage in a large meal at the onset of the dark cycle. By delaying access to chow and sugar until 4 h into the dark period, the rat spontaneously engages in a binge when food is provided. Water is always provided ad libitum, which ensures that sugar solution consumption is not driven by dehydration, but rather palatability and motivation.
13. Chow intake can also be recorded so comparisons can be made with control animals that do not have access to sugar. Hoppers containing chow can be weighed to determine the amount consumed, after returning dropped pieces of the pellets to the hopper to correct for spillage.
14. Graduated cylinders or bottles should hold at least 100 mL of solution. By the end of 1 month, some rats may consume more than this each day and may require larger bottles (e.g., 250 mL). It is anticipated that rats maintained on this intermittent sugar-access protocol usually reach an asymptote in daily intake after about 10 days, and binge on sucrose as seen in the 1-h daily intake (Figs. 1 and 4). These rats also have increased 1-h intake by day 20 compared to control rats (Fig. 4), which is suggestive of bingeing behavior.
15. Intake data can also be converted into calories. For reference, 1 mL of 10% sucrose solution has 0.4 kcal. 1 mL of 25% glucose solution has 0.97 kcal.
16. The time frame for completing an experiment is about 1 month (signs of opioid-like withdrawal are noted after 1 month of sugar bingeing). Daily time commitments for routine preparation and administration and removal of the sugar solution will vary depending on the number of subjects being tested, but generally requires about 1 h/day.
17. A pelleted diet can be purchased from Research Diets (Research Diets, New Brunswick, NJ. #12451; 45% fat, 20% protein, 35% carbohydrate, 4.7 kcal/g). This is the diet we have used successfully.

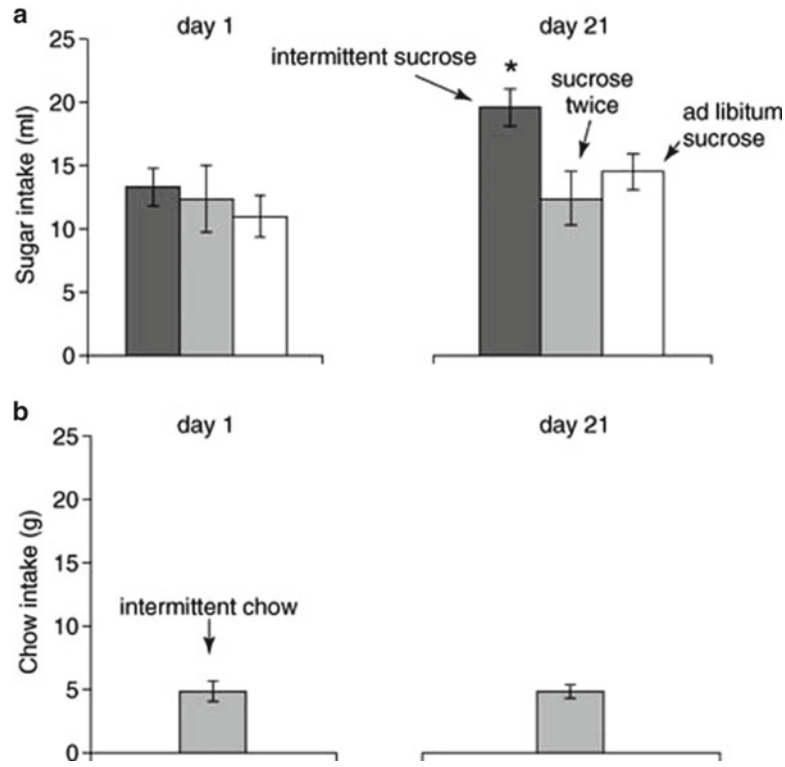

Fig. 4. Sucrose solution and chow intake during the first hour of daily access on days 1 and 21. (**a**) For the sugar drinking groups, there was no significant difference in intakes on day 1 (*left panel*), but by day 21 (*right panel*), only the bingeing rats (i.e., intermittent sucrose) showed a difference in intake relative to day 1. Rats with ad libitum sucrose and chow or ad libitum chow with sucrose solution for 1 h only on days 1 and 21 drank the same amount on day 21 as on day 1. (**b**) Rats with intermittent access to chow did not show a binge-eating effect on chow consumption; asterisk = $p < 0.05$. Adapted with permission from (28).

18. Food intake should be measured daily at 6 and 8 h after the onset of the dark cycle (i.e., before and after the 2-h access to the sweet-fat chow) for all groups. Hoppers containing chow can be weighed to determine the amount consumed, after returning dropped pieces of the pellets to the hopper to correct for spillage.

Acknowledgments

Supported by USPHS grants MH-65024 (to B.G.H. et al.), DA-10608 (to B.G.H.), DA-031230 (to N.M.A), AA-019623 (fellowship to M.E.B), and the National Eating Disorders Association (to N.M.A).

References

1. Hudson, J. I., Hiripi, E., Pope, H. G., Jr., and Kessler, R. C. (2007) The prevalence and correlates of eating disorders in the national comorbidity survey replication. *Biol Psychiatry* **61**, 348–58.
2. Ogden, C. L., Yanovski, S. Z., Carroll, M. D., and Flegal, K. M. (2007) The epidemiology of obesity. *Gastroenterology* **132**, 2087–102.
3. Stunkard, A. J. (1959) Eating patterns and obesity. *Psychiatr Q* **33**, 284–95.
4. Tanofsky-Kraff, M., Cohen, M. L., Yanovski, S. Z., Cox, C., Theim, K. R., Keil, M., Reynolds, J. C., and Yanovski, J. A. (2006) A prospective study of psychological predictors of body fat gain among children at high risk for adult obesity. *Pediatrics* **117**, 1203–9.
5. Ramacciotti, C. E., Coli, E., Paoli, R., Gabriellini, G., Schulte, F., Castrogiovanni, S., Dell'Osso, L., and Garfinkel, P. E. (2005) The relationship between binge eating disorder and non-purging bulimia nervosa. *Eat Weight Disord* **10**, 8–12.
6. Grucza, R. A., Przybeck, T. R., and Cloninger, C. R. (2007) Prevalence and correlates of binge eating disorder in a community sample. *Compr Psychiatry* **48**, 124–31.
7. Galanti, K., Gluck, M. E., and Geliebter, A. (2007) Test meal intake in obese binge eaters in relation to impulsivity and compulsivity. *Int J Eat Disord* **40**, 727–32.
8. Yudkin, J. (1972) Sweet and Dangerous, Peter H. Wyden, Inc, New York.
9. Bray, G. A., York, B., and DeLany, J. (1992) A survey of the opinions of obesity experts on the causes and treatment of obesity. *Am J Clin Nutr* **55**, 151S–54S.
10. Bray, G. A., and Popkin, B. M. (1998) Dietary fat intake does affect obesity! *Am J Clin Nutr* **68**, 1157–73.
11. Avena, N., Rada, P., and Hoebel, B. (2006) Unit 9.23C Sugar bingeing in rats, *in* "Current Protocols in Neuroscience" (Crawley, J., Gerfen, C., Rogawski, M., Sibley, D., Skolnick, P., and Wray, S., Eds.), John Wiley & Sons, Inc., Indianapolis pp. 9.23C.1–9.23C.6.
12. Avena, N. M., Rada, P., and Hoebel, B. G. (2008) Evidence of sugar addiction: Behavioral and neurochemical effects of intermittent, excessive sugar intake. *Neurosci Biobehav Rev* **32**, 20–39.
13. Hoebel, B. G. (1985) Brain neurotransmitters in food and drug reward. *Am J Clin Nutr* **42**, 1133–50.
14. Hernandez, L., and Hoebel, B. G. (1988) Feeding and hypothalamic stimulation increase dopamine turnover in the accumbens. *Physiol Behav* **44**, 599–606.
15. Kelley, A. E., Bakshi, V. P., Haber, S. N., Steininger, T. L., Will, M. J., and Zhang, M. (2002) Opioid modulation of taste hedonics within the ventral striatum. *Physiol Behav* **76**, 365–77.
16. Le Magnen, J. (1990) A role for opiates in food reward and food addiction, *in* "Taste, Experience, and Feeding" (Capaldi, P. T., Ed.), American Psychological Association, Washington, D. C. pp. 241–52.
17. Volkow, N. D., and Wise, R. A. (2005) How can drug addiction help us understand obesity? *Nat Neurosci* **8**, 555–60.
18. Wise, R. A. (1989) Opiate reward: sites and substrates. *Neurosci Biobehav Rev* **13**, 129–33.
19. Ahmed, S. H., and Koob, G. F. (1998) Transition from moderate to excessive drug intake: change in hedonic set point. *Science* **282**, 298–300.
20. Heyser, C. J., Schulteis, G., and Koob, G. F. (1997) Increased ethanol self-administration after a period of imposed ethanol deprivation in rats trained in a limited access paradigm. *Alcohol Clin Exp Res* **21**, 784–91.
21. Avena, N. M., Carrillo, C. A., Needham, L., Leibowitz, S. F., and Hoebel, B. G. (2004) Sugar-dependent rats show enhanced intake of unsweetened ethanol. *Alcohol* **34**, 203–9.
22. Avena, N. M., and Hoebel, B. G. (2003) A diet promoting sugar dependency causes behavioral cross-sensitization to a low dose of amphetamine. *Neuroscience* **122**, 17–20.
23. Avena, N. M., and Hoebel, B. G. (2003) Amphetamine-sensitized rats show sugar-induced hyperactivity (cross-sensitization) and sugar hyperphagia. *Pharmacol Biochem Behav* **74**, 635–9.
24. Colantuoni, C., Rada, P., McCarthy, J., Patten, C., Avena, N. M., Chadeayne, A., and Hoebel, B. G. (2002) Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. *Obes Res* **10**, 478–88.
25. Colantuoni, C., Schwenker, J., McCarthy, J., Rada, P., Ladenheim, B., Cadet, J. L., Schwartz, G. J., Moran, T. H., and Hoebel, B. G. (2001) Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. *Neuroreport* **12**, 3549–52.
26. Gosnell, B. A. (2005) Sucrose intake enhances behavioral sensitization produced by cocaine. *Brain Res* **1031**, 194–201.
27. Grimm, J. W., Fyall, A. M., and Osincup, D. P. (2005) Incubation of sucrose craving: effects of reduced training and sucrose pre-loading. *Physiol Behav* **84**, 73–9.

28. Rada, P., Avena, N. M., and Hoebel, B. G. (2005) Daily bingeing on sugar repeatedly releases dopamine in the accumbens shell. *Neuroscience* **134**, 737–44.
29. Wideman, C. H., Nadzam, G. R., and Murphy, H. M. (2005) Implications of an animal model of sugar addiction, withdrawal and relapse for human health. *Nutr Neurosci* **8**, 269–76.
30. Spangler, R., Wittkowski, K. M., Goddard, N. L., Avena, N. M., Hoebel, B. G., and Leibowitz, S. F. (2004) Opiate-like effects of sugar on gene expression in reward areas of the rat brain. *Brain Res Mol Brain Res* **124**, 134–42.
31. Hernandez, L., and Hoebel, B. G. (1988) Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. *Life Sci* **42**, 1705–12.
32. Hoebel, B. G., Hernandez, L., Schwartz, D. H., Mark, G. P., and Hunter, G. A. (1989) Microdialysis studies of brain norepinephrine, serotonin, and dopamine release during ingestive behavior: theoretical and clinical implications, *in* "The Psychobiology of Human Eating Disorders: Preclinical and Clinical Perspectives" (Schneider, L. H., Cooper, S. J., and Halmi, K. A., Eds.), Annals of the New York Academy of Sciences, New York. pp.171–91.
33. Koob, G. F. (1999) Drug reward and addiction, *in* "Fundamental Neuroscience" (Zigmond, M., Bloom, F. E., Landis, S. C., Roberts, J. L., and Squire, L. R., Eds.), Academic Press, San Diego pp. 1254–79.
34. Wise, R. A. (1998) Drug-activation of brain reward pathways. *Drug Alcohol Depend* **51**, 13–22.
35. Wise, R. A. (1997) Drug self-administration viewed as ingestive behaviour. *Appetite* **28,** 1–5.
36. Avena, N. M., Rada, P., Moise, N., and Hoebel, B. G. (2006) Sucrose sham feeding on a binge schedule releases accumbens dopamine repeatedly and eliminates the acetylcholine satiety response. *Neuroscience* **139**, 813–20.
37. Bassareo, V., and Di Chiara, G. (1997) Differential influence of associative and nonassociative learning mechanisms on the responsiveness of prefrontal and accumbal dopamine transmission to food stimuli in rats fed ad libitum. *J Neurosci* **17**, 851–61.
38. Avena, N. M., Bocarsly, M. E., Kim, A., Rada, P., and Hoebel, B. G. (2008) After daily bingeing on a sucrose solution, prolonged food deprivation induces anxiety and accumbens dopamine/acetylcholine imbalance. *Physiol Behav* **94**, 309–15.
39. Rada, P., Jensen, K., and Hoebel, B. G. (2001) Effects of nicotine and mecamylamine-induced withdrawal on extracellular dopamine and acetylcholine in the rat nucleus accumbens. *Psychopharmacology (Berl)* **157**, 105–10.
40. Rada, P., Johnson, D. F., Lewis, M. J., and Hoebel, B. G. (2004) In alcohol-treated rats, naloxone decreases extracellular dopamine and increases acetylcholine in the nucleus accumbens: evidence of opioid withdrawal. *Pharmacol Biochem Behav* **79**, 599–605.
41. Rada, P., Pothos, E., Mark, G. P., and Hoebel, B. G. (1991) Microdialysis evidence that acetylcholine in the nucleus accumbens is involved in morphine withdrawal and its treatment with clonidine. *Brain Res* **561**, 354–6.
42. Rada, P. V., Mark, G. P., Taylor, K. M., and Hoebel, B. G. (1996) Morphine and naloxone, i.p. or locally, affect extracellular acetylcholine in the accumbens and prefrontal cortex. *Pharmacol Biochem Behav* **53**, 809–16.
43. Avena, N. M., Long, K. A., and Hoebel, B. G. (2005) Sugar-dependent rats show enhanced responding for sugar after abstinence: evidence of a sugar deprivation effect. *Physiol Behav* **84**, 359–62.
44. American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision (DSM-IV-TR), American Psychiatric Association, Washington, DC.
45. Corwin, R. L., Wojnicki, F. H., Fisher, J. O., Dimitriou, S. G., Rice, H. B., and Young, M. A. (1998) Limited access to a dietary fat option affects ingestive behavior but not body composition in male rats. *Physiol Behav* **65**, 545–53.
46. Dimitriou, S. G., Rice, H. B., and Corwin, R. L. (2000) Effects of limited access to a fat option on food intake and body composition in female rats. *Int J Eat Disord* **28**, 436–45.
47. Boggiano, M. M., Chandler, P. C., Viana, J. B., Oswald, K. D., Maldonado, C. R., and Wauford, P. K. (2005) Combined dieting and stress evoke exaggerated responses to opioids in binge-eating rats. *Behav Neurosci* **119**, 1207–14.
48. Boggiano, M. M., and Chandler, P. C. (2006) Binge eating in rats produced by combining dieting with stress. *Curr Protoc Neurosci* **Chapter 9**, Unit9 23A.
49. Berner, L. A., Avena, N. M., and Hoebel, B. G. (2008) Bingeing, Self-restriction, and Increased Body Weight in Rats With Limited Access to a Sweet-fat Diet. *Obesity (Silver Spring)* **16**, 1998–2002.
50. Berner, L. A., Bocarsly, M. E., Hoebel, B. G., and Avena, N. M. (2009) Baclofen suppresses binge eating of pure fat but not a sugar-rich or sweet-fat diet. *Behav Pharmacol* **20**, 631–4.
51. Allison, S., and Timmerman, G. M. (2007) Anatomy of a binge: food environment and

characteristics of nonpurge binge episodes. *Eat Behav* **8**, 31–8.

52. Guertin, T. L., and Conger, A. J. (1999) Mood and forbidden foods' influence on perceptions of binge eating. *Addict Behav* **24**, 175–93.
53. Hadigan, C. M., Kissileff, H. R., and Walsh, B. T. (1989) Patterns of food selection during meals in women with bulimia. *Am J Clin Nutr* **50**, 759–66.
54. Kales, E. F. (1990) Macronutrient analysis of binge eating in bulimia. *Physiol Behav* **48**, 837–40.
55. Kelley, A. E., Will, M. J., Steininger, T. L., Zhang, M., and Haber, S. N. (2003) Restricted daily consumption of a highly palatable food (chocolate Ensure(R)) alters striatal enkephalin gene expression. *Eur J Neurosci* **18**, 2592–8.
56. Liang, N. C., Hajnal, A., and Norgren, R. (2006) Sham feeding corn oil increases accumbens dopamine in the rat. *Am J Physiol Regul Integr Comp Physiol* **291**, R1236–9.
57. Teegarden, S. L., and Bale, T. L. (2007) Decreases in dietary preference produce increased emotionality and risk for dietary relapse. *Biol Psychiatry* **61**, 1021–9.
58. Teegarden, S. L., Nestler, E. J., and Bale, T. L. (2008) Delta FosB-mediated alterations in dopamine signaling are normalized by a palatable high-fat diet. *Biol Psychiatry* **64**, 941–50.
59. Johnson, P. M., and Kenny, P. J. (2010) Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat Neurosci* **13**, 635–41.
60. Cottone, P., Sabino, V., Steardo, L., and Zorrilla, E. P. (2009) Consummatory, anxiety-related and metabolic adaptations in female rats with alternating access to preferred food. *Psychoneuroendocrinology* **34**, 38–49.
61. Corwin, R. L., and Buda-Levin, A. (2004) Behavioral models of binge-type eating. *Physiol Behav* **82**, 123–30.
62. Mazda, T., Yamamoto, H., Fujimura, M., and Fujimiya, M. (2004) Gastric distension-induced release of 5-HT stimulates c-fos expression in specific brain nuclei via 5-HT3 receptors in conscious rats. *Am J Physiol Gastrointest Liver Physiol* **287**, G228–35.
63. Avena, N. M., Rada, P., and Hoebel, B. G. (2008) Underweight rats have enhanced dopamine release and blunted acetylcholine response in the nucleus accumbens while bingeing on sucrose. *Neuroscience* **156**, 865–71.