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Review

Evidence for sugar addiction: Behavioral and neurochemical effects of intermittent, excessive sugar intake

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Abstract

[Avena, N.M., Rada, P., Hoebel B.G., 2007. Evidence for sugar addiction: Behavioral and neurochemical effects of intermittent, excessive sugar intake. Neuroscience and Biobehavioral Reviews XX(X), XXX–XXX]. The experimental question is whether or not sugar can be a substance of abuse and lead to a natural form of addiction. ''Food addiction'' seems plausible because brain pathways that evolved to respond to natural rewards are also activated by addictive drugs. Sugar is noteworthy as a substance that releases opioids and dopamine and thus might be expected to have addictive potential. This review summarizes evidence of sugar dependence in an animal model. Four components of addiction are analyzed. ''Bingeing,'' ''withdrawal,'' ''craving'' and ''cross-sensitization'' are each given operational definitions and demonstrated behaviorally with sugar bingeing as the reinforcer. These behaviors are then related to neurochemical changes in the brain that also occur with addictive drugs. Neural adaptations include changes in dopamine and opioid receptor binding, enkephalin mRNA expression and dopamine and acetylcholine release in the nucleus accumbens. The evidence supports the hypothesis that under certain circumstances rats can become sugar dependent. This may translate to some human conditions as suggested by the literature on eating disorders and obesity.

Keywords: Binge eating; Dopamine; Acetylcholine; Opioids; Nucleus accumbens; Withdrawal; Craving; Behavioral sensitization; Rat

Contents

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1. Overview

Neural systems that evolved to motivate and reinforce foraging and food intake also underlie drug seeking and self-administration. The fact that some of these drugs can cause addiction raises the logical possibility that some foods might also cause addiction. Many people claim that they feel compelled to eat sweet foods, similar in some ways to how an alcoholic might feel compelled to drink. Therefore, we developed an animal model to investigate why some people have difficulty moderating their intake of palatable foods, such as sweet beverages.

In this animal model, rats are food deprived daily for 12 h, then after a delay of 4 h into their normal circadian-driven active period, they are given 12-h access to a sugar solution and chow. As a result, they learn to drink the sugar solution copiously, especially when it first becomes available each day.

After a month on this intermittent-feeding schedule, the animals show a series of behaviors similar to the effects of drugs of abuse. These are categorized as "bingeing," meaning unusually large bouts of intake (Colantuoni et al., 2001), opiate-like "withdrawal" indicated by signs of anxiety (Colantuoni et al., 2002) and behavioral depression, and "craving" measured during sugar abstinence as enhanced responding for sugar (Avena et al., 2005). There are also signs of both locomotor and consummatory "cross-sensitization" from sugar to drugs of abuse (Avena et al., 2004; Avena and Hoebel, 2003b). Having found these behaviors that are common to drug dependency with supporting evidence from other laboratories (Gosnell, 2005; Grimm et al., 2005; Wideman et al., 2005), the next question is why this happens.

A well-known characteristic of addictive drugs is their ability to cause repeated, intermittent increases in extracellular dopamine (DA) in the nucleus accumbens (NAc) (Di Chiara and Imperato, 1988; Hernandez and Hoebel, 1988; Wise et al., 1995). We find that rats with intermittent access to sugar will drink in a binge-like manner that releases DA in the NAc each time, like the classic effect of most substances of abuse (Avena et al., 2006; Rada et al., 2005b). This consequently leads to changes in the expression or availability of DA receptors (Colantuoni et al., 2001; Spangler et al., 2004).

Intermittent sugar access also acts by way of opioids in the brain. There are changes in opioid systems such as decreased enkephalin mRNA expression in the accumbens (Spangler et al., 2004). Signs of withdrawal seem to be largely due to the opioid modifications since withdrawal can be obtained with the opioid antagonist naloxone. Food deprivation is also sufficient to precipitate opiate-like withdrawal signs (Avena et al., unpublished; Colantuoni et al., 2002). This withdrawal state involves at least two neurochemical manifestations. First is a decrease in extracellular DA in the accumbens, and second is the release of acetylcholine (ACh) from accumbens interneurons. These neurochemical adaptations in response to intermittent sugar intake mimic the effects of opiates.

The theory is formulated that intermittent, excessive intake of sugar can have dopaminergic, cholinergic and opioid effects that are similar to psychostimulants and opiates, albeit smaller in magnitude. The overall effect of these neurochemical adaptations is mild, but well-defined, dependency (Hoebel et al., 1999; Leibowitz and Hoebel, 2004; Rada et al., 2005a). This review compiles studies from our laboratory and integrates related results obtained by others using animal models, clinical accounts and brain imaging to answer the question: can sugar, in some conditions, be "addictive"?

2. Defining addiction

Throughout this review we use several terms with definitions for which there is not universal agreement. Addiction research traditionally focuses on drugs of abuse, such as morphine, cocaine, nicotine and alcohol. However, recently a variety of "addictions" to non-drug entities, including gambling, sex, and in this review, food, have been investigated (Bancroft and Vukadinovic, 2004; Comings et al., 2001; Petry, 2006). The term "addiction" implies

psychological dependence and thus is a mental or cognitive problem, not just a physical ailment. "Addiction" is often used synonymously with the term "dependence" (Nelson et al., 1982) as defined by DSM-IV-TR (American Psychiatric Association, 2000). We will use the term dependence in its all-encompassing meaning to describe the results of a battery of animal studies that model human drug addiction in each of its major phases (Koob and Le Moal, 2005).

Drug dependence is characterized by compulsive, sometimes uncontrollable, behaviors that occur at the expense of other activities and intensify with repeated access. Dependence is difficult to demonstrate convincingly in laboratory animals, but criteria have been suggested using animal models. We have used models that were developed with rats for studying drug dependence and adapted them to test for signs of sugar dependence.

2.1. Bingeing

The diagnostic criteria for dependence can be grouped into three stages (American Psychiatric Association, 2000; Koob and Le Moal, 1997). The first, bingeing, is defined as the escalation of intake with a high proportion of intake at one time, usually after a period of voluntary abstinence or forced deprivation. Enhanced intake in the form of binges may result from both sensitization and tolerance to the sensory properties of a substance of abuse that occurs with its repeated delivery. Sensitization, which is described in greater detail below, is an increase in responsiveness to a repeatedly presented stimulus. Tolerance is a gradual decrease in responsiveness, such that more of the substance is needed to produce the same effect (McSweeney et al., 2005). Both are thought to influence the powerful, acute reinforcing effects of drugs of abuse and are important at the beginning of the addiction cycle since both can increase responding and intake (Koob and Le Moal, 2005).

2.2. Withdrawal

Signs of withdrawal become apparent when the abused substance is no longer available or is chemically blocked. We will discuss withdrawal in terms of opiate withdrawal, which has a clearly defined set of symptoms (Martin et al., 1963; Way et al., 1969). Anxiety can be operationally defined and measured in animals using the elevated plus-maze, in which anxious animals will avoid spending time on the open arms of the maze (File et al., 2004). This test has been extensively validated for both general anxiety (Pellow et al., 1985) and anxiety induced by drug withdrawal (File and Andrews, 1991). Behavioral depression in animals can also be inferred using the forced-swim test, which measures swimming escape efforts vs. passive floating (Porsolt et al., 1978). When signs of opiate withdrawal are precipitated with naloxone, it suggests that inactivation of opioid receptors is the cause. When the same signs are produced spontaneously during abstinence, one can surmise that it is due to lack of stimulation of some opioid system.

2.3. Craving

The third stage of dependence, craving, occurs when motivation is enhanced, usually after an abstinence period (Vanderschuren and Everitt, 2005; Weiss, 2005). "Craving" remains a poorly defined term that is often used to describe the intense desire to self-administer drugs in humans (Wise, 1988). For lack of a better word, we will use the term "craving" as defined by increased efforts to obtain a substance of abuse or its associated cues as a result of dependence and abstinence. "Craving" often has reference to motivation, which can be measured using operant conditioning. If abstinence makes the animal significantly increase its lever pressing, one can take this as a sign of enhanced motivation.

2.4. Sensitization

In addition to the above diagnostic criteria, behavioral sensitization is thought to underlie some aspects of drug dependence (Vanderschuren and Kalivas, 2000). Behavioral sensitization is typically measured as increased locomotion in response to repeated administrations of a drug. For example, after repeated doses of amphetamine followed by abstinence, a challenge dose, which has little or no effect in naïve animals, causes marked hyperactivity (Antelman and Caggiula, 1996; Glick et al., 1986). Animals sensitized to one substance often show cross-sensitization, which is defined as an increased locomotor response to a different drug or substance. Cross-sensitization can also be manifest in consummatory behavior (Piazza et al., 1989). Animals sensitized to one drug may show increased intake of a different drug. In other words, one drug acts as a "gateway" to another. For example, animals sensitized to amphetamine show accelerated escalation of cocaine intake (Ferrario and Robinson, 2007), and animals sensitized to nicotine consume more alcohol compared with non-sensitized animals (Blomqvist et al., 1996). This behavior is thought to occur when different drugs activate the same neural circuitry, and it is a reason why many clinicians require complete drug abstention as a condition of treatment for addicts (Wise, 1988).

The first question addressed by this review is whether any of these operationally defined behavioral characteristics of substance dependence can be found with intermittent sugar access. The second question explores neural systems to discover how sugar might have effects like a drug of abuse.

3. Drugs of abuse and palatable food activate a common subset of neural systems

Overlaps in the brain circuitry activated by food and drug intake suggests that different types of reinforcers

(natural and artificial) stimulate some of the same neural systems (Hoebel, 1985; Hernandez and Hoebel, 1988; Kelley et al., 2002; Le Magnen, 1990; Volkow and Wise, 2005; Wise, 1989). There are several regions in the brain involved in the reinforcement of both feeding and drug intake (Kalivas and Volkow, 2005; Kelley et al., 2005; Koob and Le Moal, 2005; Mogenson and Yang, 1991; Wise, 1997; Yeomans, 1995), and many neurotransmitters have been studied in these and related brain regions (Harris et al., 2005; Kalivas, 2004; Leibowitz and Hoebel, 2004; Schoffelmeer et al., 2001; Stein and Belluzzi, 1979). This review will focus on DA, the opioids, and ACh in the NAc shell, which so far, are the neurotransmitters that we have found to be involved with the reinforcing effects of intermittent sugar intake.

3.1. Dopamine

It is well established that addictive drugs activate DA-containing neurons in areas of the brain that process behavior reinforcement. This has been shown for drugs delivered systemically (Di Chiara and Imperato, 1988; Radhakishun et al., 1983), and for drugs infused locally (Hernandez and Hoebel, 1988; Mifsud et al., 1989). The mesolimbic DA projection from the ventral tegmental area (VTA) to the NAc has a role in reinforcement functions (Wise and Bozarth, 1984). The NAc is important for several components of "reward" including food seeking and reinforcement of learning, incentive motivation, stimulus salience and signaling a stimulus change (Bassareo and Di Chiara, 1999; Berridge and Robinson, 1998; Salamone, 1992; Schultz et al., 1997; Wise, 1988). Agents that directly or indirectly stimulate DA cell bodies in the VTA reinforce local self-administration, including opioids such as enkephalin (Glimcher et al., 1984), non-opioid peptides such as neurotensin (Glimcher et al., 1987) and many drugs of abuse (Bozarth and Wise, 1981; Gessa et al., 1985; McBride et al., 1999). Some addictive drugs also act at DA terminals (Cheer et al., 2004; Mifsud et al., 1989; Nisell et al., 1994; Westerink et al., 1987; Yoshimoto et al., 1992). Thus, any substance that repeatedly causes the release of DA or reduces DA reuptake at terminals via these circuits may be a candidate for abuse.

A variety of foods can release DA in the NAc, including lab chow, sugar, saccharin, and corn oil (Bassareo and Di Chiara, 1997; Hajnal et al., 2004; Liang et al., 2006; Mark et al., 1991; Rada et al., 2005b). The rise in extracellular DA can outlast the meal in food-deprived rats (Hernandez and Hoebel, 1988). However, in satiated animals, this DA release appears to be contingent on novelty since it wanes with repeated access, even when the food is palatable (Bassareo and Di Chiara, 1997; Rada et al., 2005b). An exception, which is described below (Section 5.3), is when animals are food deprived and fed sugar intermittently.

Extracellular DA decreases in reaction to drug withdrawal (Acquas et al., 1991; Acquas and Di Chiara, 1992; Rada et al., 2004; Rossetti et al., 1992). The behavioral symptoms of withdrawal from dopaminergic drugs are less well defined than those observed during withdrawal from opiates. Therefore, it may be easier to discern the signs of withdrawal when using foods that release both DA and opioids. Sugar is one such food.

3.2. Opioids

Opioid peptides are heavily expressed throughout the limbic system and exert some of their effects on reinforcement processing by interacting with DA systems (Bozarth and Wise, 1986; Di Chiara and Imperato, 1986; Haber and Lu, 1995; Leibowitz and Hoebel, 2004; Levine and Billington, 2004; Miller and Picket, 1980). The opioid peptide enkephalin in the NAc has been related to reward (Bals-Kubik et al., 1989; Bozarth and Wise, 1981; Olds, 1982) and can activate both mu and delta receptors to increase the release of DA (Spanagel et al., 1990). Morphine alters gene expression of endogenous opioid peptides while increasing opioid peptide production in the NAc (Przewlocka et al., 1996; Spangler et al., 2003; Turchan et al., 1997). Opioids are also important components of this system as cotransmitters with GABA in some accumbens and dorsal striatal outputs (Kelley et al., 2005).

Repeated use of opiates, or even some non-opiate drugs, can result in mu-opioid receptor sensitization in several regions, including the NAc (Koob et al., 1992; Unterwald, 2001). A mu-receptor antagonist injected into the NAc will attenuate the rewarding effects of heroin (Vaccarino et al., 1985), and systemically such drugs have been used as a treatment for alcoholism and heroin dependence (Deas et al., 2005; Foster et al., 2003; Martin, 1975; O'Brien, 2005; Volpicelli et al., 1992).

Ingestion of palatable foods has effects via endogenous opioids in a variety of sites (Dum et al., 1983; Mercer and Holder, 1997; Tanda and Di Chiara, 1998), and the injection of mu-opioid agonists in the NAc increases intake of palatable foods rich in fat or sugar (Zhang et al., 1998; Zhang and Kelley, 2002). Opioid antagonists, on the other hand, decrease ingestion of sweet food and shorten meals of palatable, preferred foods, even at doses that have no effect on standard chow intake (Glass et al., 1999). This opioid–palatability link is further characterized by theories in which the reinforcing effect is dissociated into a dopaminergic system for incentive motivation and an opioid "liking" or "pleasure" system for hedonic responses (Berridge, 1996; Robinson and Berridge, 1993; Stein, 1978). Evidence that opioids in the NAc influence hedonic reactions comes from data showing that morphine enhances rats' positive facial taste reactivity for a sweet solution in the mouth (Pecina and Berridge, 1995). The dissociation between the "wanting" and "liking" systems is also suggested by studies in humans (Finlayson et al., 2007).

3.3. Acetylcholine

Several cholinergic systems in the brain have been implicated in both food and drug intake, and related to

DA and the opioids (Katz and Valentino, 1984; Kelley et al., 2005; Rada et al., 2000; Yeomans, 1995). Focusing on ACh interneurons in the NAc, systemic administration of morphine decreases ACh turnover (Smith et al., 1984), a finding that was confirmed by *in vivo* microdialysis in freely-behaving rats (Fiserova et al., 1999; Rada et al., 1991a, 1996). Cholinergic interneurons in the NAc may selectively modulate enkephalin gene expression and peptide release (Kelley et al., 2005). During morphine withdrawal, extracellular ACh increases in the NAc while DA is low, suggesting that this neurochemical state could be involved in the aversive aspects of withdrawal (Pothos et al., 1991; Rada et al., 1991b, 1996). Likewise, both nicotine and alcohol withdrawal increase extracellular ACh, while decreasing DA in the NAc (De Witte et al., 2003; Rada et al., 2001, 2004). This withdrawal state may involve depression, since M1-receptor agonists injected in the NAc can cause behavioral depression in the forced-swim test (Chau et al., 1999).

ACh in the NAc has also been implicated in food intake. We theorize that its overall muscarinic effect is to inhibit feeding at M1 receptors since local injection of the mixed muscarinic agonist arecholine will inhibit feeding, and this effect can be blocked by the relatively specific M1 antagonist pirenzapine (Rada and Hoebel, unpublished). Feeding to satiety increases extracellular ACh in the NAc (Avena et al., 2006; Mark et al., 1992). A conditioned taste aversion also increases ACh in the NAc and simultaneously lowers DA (Mark et al., 1991, 1995). D-fenfluramine combined with phentermine (Fen-Phen) increases extracellular ACh in the NAc at a dose that inhibits both eating and cocaine self-administration (Glowa et al., 1997; Rada and Hoebel, 2000). Rats with accumbal ACh, toxin-induced lesions are hyperphagic relative to non-lesioned rats (Hajnal et al., 2000).

DA/ACh balance is controlled in part by hypothalamic systems for feeding and satiety. Norepinephrine and galanin, which induce eating when injected in the paraventricular nucleus (PVN), lower accumbens ACh (Hajnal et al., 1997; Rada et al., 1998). An exception is neuropeptide-Y, which fosters eating when injected into the PVN, but does not increase DA release nor lower ACh (Rada et al., 1998). In accord with the theory, the satiety-producing combination of serotonin plus CCK injection into the PVN increases accumbens ACh (Helm et al., 2003).

It is very interesting that when DA is low and extracellular ACh is high, this apparently creates not satiety, but instead an aversive state (Hoebel et al., 1999), as during behavioral depression (Rada et al., 2006), drug withdrawal (Rada et al., 1991b, 1996, 2001, 2004) and conditioned taste aversion (Mark et al., 1995). We conclude that when ACh acts as a post-synaptic M1 agonist it has effects opposite to DA, and thus may act to impede dopaminergic functions (Hoebel et al., 1999; Rada et al., 2007) causing satiety when DA is high and behavioral depression when DA is relatively low.

4. Behavioral similarities between drug self-administration and intermittent, excessive sugar intake

The concept of "sugar addiction" has been bandied about for many years. Clinical accounts of "sugar addiction" have been the topic of many best-selling books and the focus of popular diet programs (Appleton, 1996; DesMaisons, 2001; Katherine, 1996; Rufus, 2004). In these accounts, people describe symptoms of withdrawal when they deprive themselves of sugar-rich foods. They also describe food craving, particularly for sugar and other carbohydrates, which can trigger impulsive eating. This leads to a vicious cycle of self-medication with sweet foods that may result in obesity or an eating disorder.

Although the idea of food addiction has been popular in the media and proposed to be based on brain neurochemistry (Hoebel et al., 1989; Le Magnen, 1990), this phenomenon has only recently been systematically studied in the laboratory.

As outlined in the overview in Section 1, we use a feeding schedule that induces rats to binge on a sugar solution, then apply the criteria for drug dependence that are presented in Section 2 and test for the behavioral and neurochemical commonalities given in Section 3. Rats are given 12-h access to an aqueous 10% sucrose solution (25% glucose in some experiments) and lab chow, followed by 12 h of deprivation daily for three or more weeks (i.e., Daily Intermittent Sugar and Chow). These rats are compared with control groups such as Ad libitum Sugar and Chow, Ad libitum Chow, or Daily Intermittent Chow (12-h access to lab chow followed by 12-h deprivation). For the intermittent access groups, availability is delayed 4 h into the animal's active period in order to stimulate feeding, which normally ensues at the onset of the dark cycle. Rats maintained on the Daily Intermittent Sugar and Chow regimen enter a state that resembles drug dependence on several dimensions. These are divided into behavioral (Section 4) and neurochemical (Section 5) similarities to drug dependence.

4.1. "Bingeing": escalation of daily sugar intake and large meals

Escalation of intake is a characteristic of drugs of abuse. This may be a combination of tolerance, in which more of an abused substance is needed to produce the same euphoric effects (Koob and Le Moal, 2005), and sensitization, such as locomotor sensitization, in which the substance produces enhanced behavioral activation (Vezina et al., 1989). Studies using drug self-administration usually limit access to a few hours per day, during which animals will self-administer in regular intervals that vary as a function of the dose received (Gerber and Wise, 1989) and in a manner that keeps extracellular DA elevated above a baseline, or "trigger point," in the NAc (Ranaldi et al., 1999; Wise et al., 1995). The length of daily access has been shown to critically affect subsequent

self-administration behavior. For example, the most cocaine is self-administered during the first 10 min of a session when access is at least 6 h per day (Ahmed and Koob, 1998). Limited periods of access, to create "binges," have been useful, because the pattern of self-administration behavior that emerges is similar to that of a "compulsive" drug user (Markou et al., 1993; Mutschler and Miczek, 1998; O'Brien et al., 1998). Even when drugs, such as cocaine, are given with unlimited access, humans or laboratory animals will self-administer them in repetitive episodes or "binges" (Bozarth and Wise, 1985; Deneau et al., 1969). However, experimenter-imposed intermittent access is better than ad libitum access for experimental purposes, since it becomes very likely that the animal will take at least one large binge at the onset of the drug-availability period. Moreover, a period of food restriction can enhance drug intake (Carr, 2006; Carroll, 1985) and has been shown to produce compensatory neuroadaptations in the mesoaccumbens DA system (Pan et al., 2006).

The behavioral findings with sugar are similar to those observed with drugs of abuse. Rats fed daily intermittent sugar and chow escalate their sugar intake and increase their intake during the first hour of daily access, which we define as a "binge" (Colantuoni et al., 2001). The animals with ad libitum access to a sugar solution tend to drink it throughout the day, including during their inactive period. Both groups increase their overall intake, but the limited-access animals consume as much sugar in 12 h as ad libitum-fed animals do in 24 h. Detailed meal pattern analysis using operant conditioning (fixed-ratio 1) reveals that the animals with limited access consume a large meal of sugar at the onset of availability and larger, fewer meals of sugar throughout the access period, compared with animals drinking sugar ad libitum (Fig. 1; Avena and Hoebel, unpublished). Rats fed Daily Intermittent Sugar and Chow regulate their caloric intake by decreasing their chow intake to compensate for the extra calories obtained from sugar, which results in a normal body weight (Avena and Hoebel, 2003b; Colantuoni et al., 2002).

4.2. "Withdrawal": anxiety and behavioral depression induced by an opioid antagonist or food deprivation

As described in Section 2, animals can show signs of opiate withdrawal after repeated exposure when the substance of abuse is removed, or the appropriate synaptic receptor is blocked. For example, an opioid antagonist can be used to precipitate withdrawal in the case of opiate dependency (Epejo et al., 1994; Koob et al., 1992). In rats, opiate withdrawal causes severe somatic signs (Martin et al., 1963; Way et al., 1969), aggression (Kantak and Miczek, 1986), and anxiety (Schulteis et al., 1998),

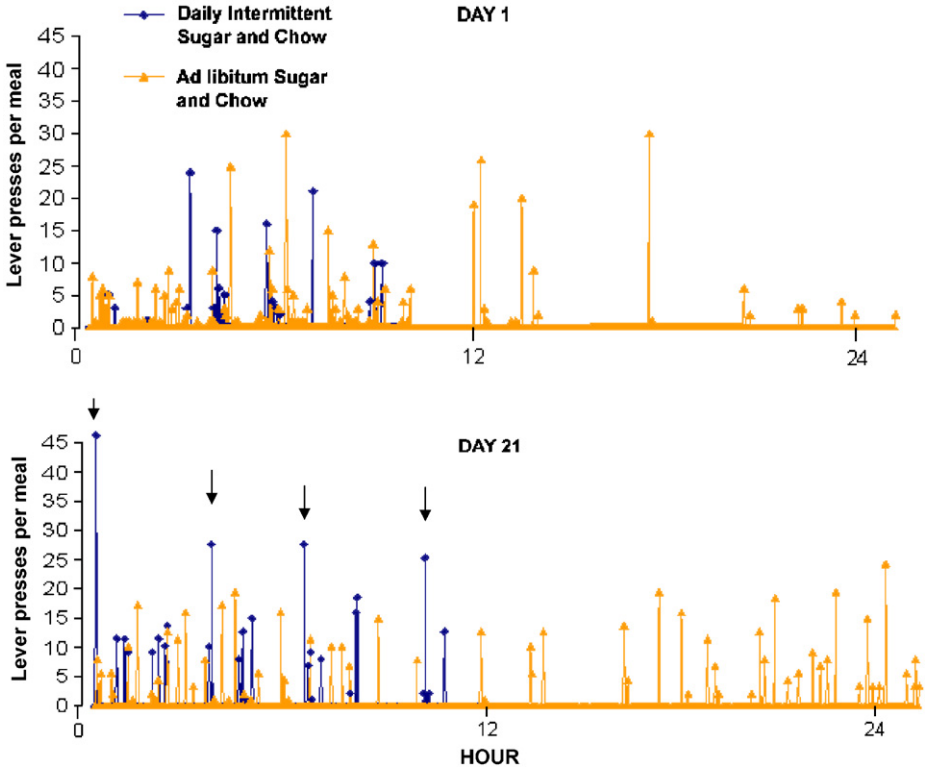

Fig. 1. Meal analysis of two representative rats living in operant chambers. The one maintained on Daily Intermittent Sucrose and Chow (blue/black lines) had increased intake of sugar compared with the one given Ad libitum Sucrose and Chow (orange/gray lines). Hour 0 is 4 h into the dark phase. Each lever press delivered 0.1 mL of 10% sucrose. A sugar meal is defined as ending when the rat does not press for 2 min. Both rats consumed several meals of about equal size on day 1 (top panel). Note that the rat with sugar available 24 h also drinks during the inactive (light) phase. By day 21 (bottom panel), the rat with sucrose and chow available for only 12 h consumed an initial "binge" of sucrose (indicated by the first arrow), followed by fewer, but larger meals, than the rat with sucrose and chow available ad libitum. Sugar-bingeing rats are the ones that show signs of dependency in a battery of tests.

decreases in body temperature (Ary et al., 1976), as well as a motivational syndrome characterized by dysphoria and depression (De Vries and Shippenberg, 2002; Koob and Le Moal, 1997).

Some of these signs have been noted after intermittent access to sugar when withdrawal is precipitated with an opioid antagonist, or when food and sugar are removed. 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 are observed (Colantuoni et al., 2002). These animals are also anxious, as measured by reduced time spent on the exposed arm of an elevated plus-maze (Fig. 2; Colantuoni et al., 2002).

Behavioral depression has also been found following naloxone administration in intermittent sugar-fed rats. In this experiment, rats were given an initial 5-min forced-swim test in which escape (swimming and climbing) and passive (floating) behaviors were measured. Then the rats were divided into four groups that were fed Daily Intermittent Sucrose and Chow, Daily Intermittent Chow, Ad libitum Sucrose and Chow, or Ad libitum Chow for 21 days. On day 22, at the time that the intermittent-fed rats would normally receive their sugar and/or chow, all rats were instead injected with naloxone (3 mg/kg, s.c.) and were then placed in the water again for another test. In the group that had been fed Daily Intermittent Sucrose and Chow, escape behaviors were significantly suppressed compared with Ad libitum Sucrose and Chow or Ad libitum Chow controls (Fig. 3; Kim, Avena and Hoebel, unpublished). This decrease in escape efforts, which were replaced by passive floating, suggests the rats were experiencing behavioral depression.

Signs of opiate-like withdrawal also emerge when food and sugar are removed for 24 h. Again this includes somatic signs such as teeth chattering, forepaw tremor and head shaking (Colantuoni et al., 2002) and anxiety as measured with an elevated plus-maze (Avena et al., unpublished). Spontaneous withdrawal from the mere removal of sugar has been reported using decreased body temperature as the criterion (Wideman et al., 2005). Also, signs of aggressive behavior have been found in response to removing a diet that involves intermittent sugar access (Galic and Persinger, 2002).

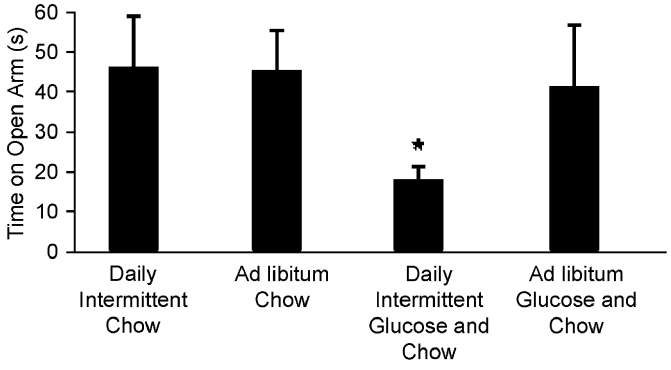

Fig. 2. Time spent on the open arms of an elevated plus-maze. Four groups of rats were maintained on their respective diets for one month and then received naloxone (3 mg/kg, s.c.). The Daily Intermittent Glucose and Chow group spent less time on the open arms of the maze. $*p<0.05$ compared with the Ad libitum Chow group. From Colantuoni et al., 2002.

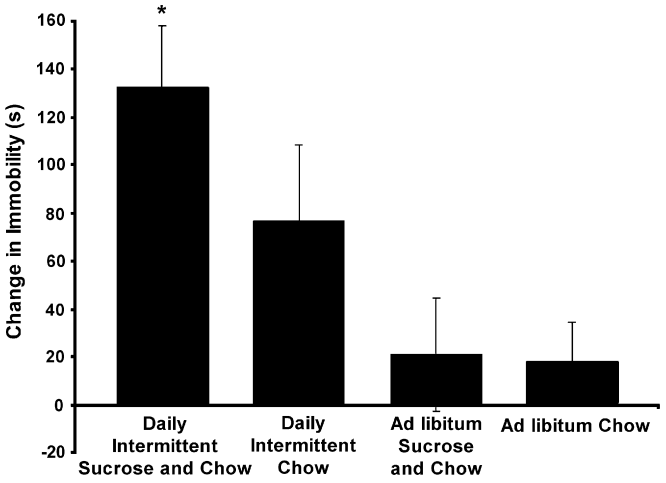

Fig. 3. Rats that have been maintained on Daily Intermittent Sucrose and Chow are more immobile than control groups in a forced-swim test during naloxone-precipitated withdrawal. $*p<0.05$ compared with Ad libitum Sugar and Chow and Ad libitum Chow groups.

4.3. "Craving": enhanced responding for sugar following abstinence

As described in Section 2, "craving" in laboratory animals can be defined as enhanced motivation to procure an abused substance (Koob and Le Moal, 2005). After self-administering drugs of abuse and then being forced to abstain, animals often persist in unrewarded operant responding (i.e., resistance to response extinction), and increase their responding over time for cues previously associated with the drug (i.e., incubation) (Bienkowski et al., 2004; Grimm et al., 2001; Lu et al., 2004). Additionally, if the drug becomes available again, animals will take more than they did prior to abstinence (i.e., the "deprivation effect") (Sinclair and Senter, 1968). This increase in motivation to procure a substance of abuse may contribute to relapse. The power of "craving" is evidenced by results showing that animals will sometimes face adverse consequences to obtain a substance of abuse such as cocaine or alcohol (Deroche-Gamonet et al., 2004; Dickinson et al., 2002; Vanderschuren and Everitt, 2004). These signs in laboratory animals mimic those observed with humans in which the presentation of stimuli previously associated with a drug of abuse increases self-reports of craving and the likelihood of relapse (O'Brien et al., 1977, 1998).

We used the "deprivation effect" paradigm to investigate sugar consumption after abstinence in sugar-bingeing rats. Following 12-h daily access to glucose for four weeks, rats

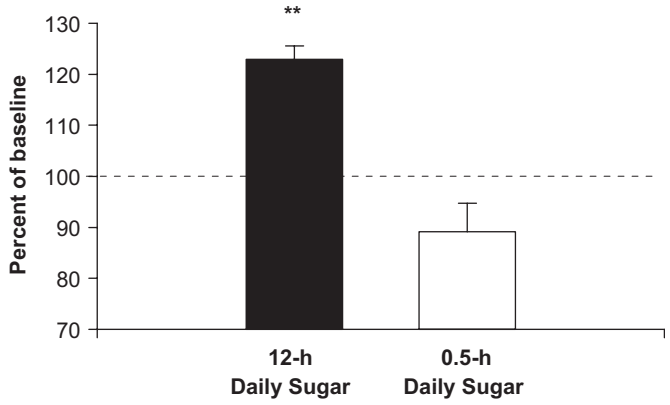

Fig. 4. After 14 days of abstinence from sugar, rats that previously had 12-h daily access significantly increased lever pressing for glucose to 123% of pre-abstinence responding, indicating increased motivation for sugar. The group with 0.5-h daily access did not show increased responding after abstinence. $^{**}p<0.01$. From Avena et al., 2005.

lever press for 23% more glucose in a test after two weeks of abstinence than they ever did before (Fig. 4; Avena et al., 2005). A group with 0.5-h daily access to glucose did not show the effect. This provides a cogent control group in which rats are familiar with the taste of glucose, but have not consumed it in a manner that leads to a deprivation effect. The results suggest a change in the motivational impact of sugar that persists throughout two weeks of abstinence, leading to enhanced intake.

Additionally, like the drugs described above, the motivation to obtain sugar appears to "incubate," or grow, with the length of abstinence (Shalev et al., 2001). Using operant conditioning, Grimm et al. (2005) found that sucrose seeking (lever pressing in extinction and then for a sucrose-paired cue) increases during abstinence in rats after intermittent sugar access for 10 days. Remarkably, responding for the cue was greater after 30 days of sugar abstinence compared with 1 week or 1 day. These results suggest the gradual emergence of long-term changes in the neural circuitry underlying motivation as a result of sugar self-administration and abstinence.

4.4. "Cross-sensitization": increased locomotor response to psychostimulants during sugar abstinence

Drug-induced sensitization may play a role in the enhancement of drug self-administration and is implicated as a factor contributing to drug addiction (Robinson and Berridge, 1993). In a typical sensitization experiment, the animal receives a drug daily for about a week, then the procedure stops. However, in the brain there are lasting, even growing, changes apparent a week or more later when a low, challenge dose of the drug results in hyperlocomotion (Kalivas et al., 1992). Additionally, cross-sensitization from one drug to another has been demonstrated with several drugs of abuse, including amphetamine sensitizing rats to cocaine or phencyclidine (Greenberg and Segal, 1985; Kalivas and Weber, 1988; Pierce and Kalivas, 1995; Schenk et al., 1991), cocaine cross-sensitizing with alcohol (Itzhak and Martin, 1999), and heroin with cannabis (Pontieri et al., 2001). Other studies have found this effect with non-drug substances. Behavioral cross-sensitization between cocaine and stress has been demonstrated (Antelman and Caggiula, 1977; Covington and Miczek, 2001; Prasad et al., 1998). Also, increases in food intake (Bakshi and Kelley, 1994) or sexual behaviors (Fiorino and Phillips, 1999; Nocjar and Panksepp, 2002) have been observed in animals with a history of drug sensitization.

We and others have found that intermittent sugar intake cross-sensitizes with drugs of abuse. Rats sensitized with daily amphetamine injections (3 mg/kg, i.p.) are hyperactive one week later in response to tasting 10% sucrose (Avena and Hoebel, 2003a). Conversely, rats fed Daily Intermittent Sucrose and Chow show locomotor cross-sensitization to amphetamine. Specifically, such animals are hyperactive in response to a low, challenge dose of amphetamine (0.5 mg/kg, i.p.) that has no effect on naïve animals, even after 8 days of abstinence from sugar (Fig. 5; Avena and Hoebel, 2003b). Rats maintained on this feeding schedule but administered saline were not hyperactive, nor were rats in control groups (Daily Intermittent Chow, Ad libitum Sucrose and Chow, Ad libitum Chow) given the challenge dose of amphetamine. Intermittent sucrose access also cross-sensitizes with cocaine (Gosnell, 2005) and facilitates the development of sensitization to the DA agonist quinpirole (Foley et al., 2006). Thus, results with three different DA agonists from three different laboratories support the theory that the DA system is sensitized by intermittent sugar access, as evidenced by cross-sensitization. This is important since enhanced mesolimbic dopaminergic neurotransmission plays a major role in the behavioral effects of sensitization as well as cross-sensitization (Robinson and Berridge, 1993), and may contribute to addiction and comorbidity with polysubstance abuse.

4.5. "Gateway effect": increased alcohol intake during sugar abstinence

Numerous studies have found that sensitization to one drug can lead not only to hyperactivity, but also to subsequent increased intake of another drug or substance (Ellgren et al., 2007; Henningfield et al., 1990; Hubbell et al., 1993; Liguori et al., 1997; Nichols et al., 1991; Piazza et al., 1989; Vezina, 2004; Vezina et al., 2002; Volpicelli et al., 1991). We refer to this phenomenon as "consummatory cross-sensitization." In the clinical literature, when one drug leads to taking another, this is sometimes referred to as a "gateway effect." It is particularly noteworthy when a legal drug (e.g., nicotine) acts as a gateway to an illegal drug (e.g., cocaine) (Lai et al., 2000).

Rats maintained on intermittent sugar access and then forced to abstain, subsequently show enhanced intake of 9% alcohol (Avena et al., 2004). This suggests that

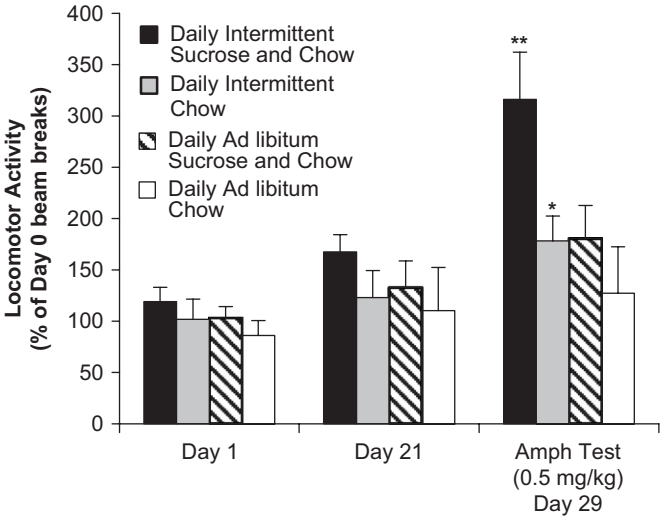

Fig. 5. Locomotor activity in a photocell cage plotted as percent of baseline beam breaks on day 0. Rats were maintained for 21 days on the specified diet regimens. Rats maintained on Daily Intermittent Sucrose and Chow were hyperactive 9 days later in response to a low dose of amphetamine, compared with control diet groups. $^{**}p<0.01$. Rats maintained on a diet of intermittent chow access were hyperactive in response to amphetamine compared with saline (data not shown), but not compared with other groups that received amphetamine $^{*}p<0.01$. From Avena and Hoebel, 2003b.

intermittent access to sugar can be a gateway to alcohol use. Others have shown that animals that prefer sweet-taste will self-administer cocaine at a higher rate (Carroll et al., 2007). As with the locomotor cross-sensitization described above, underlying this behavior are presumably neurochemical alterations in the brain, such as adaptations in DA and perhaps opioid functions.

5. Neurochemical similarities between drug self-administration and intermittent sugar intake

The studies described above suggest that intermittent sugar access can produce numerous behaviors that are similar to those observed in drug-dependent rats. In this section, we describe neurochemical findings that may underlie sugar dependency. To the extent that these brain alterations match the effects of drugs of abuse, it strengthens the case that sugar, in some cases, can resemble a substance of abuse.

5.1. Intermittent sugar intake alters D_1, D_2 and mu-opioid receptor binding and mRNA expression

Drugs of abuse can alter DA and opioid receptors in the mesolimbic regions of the brain. Pharmacological studies with selective D_1, D_2 and D_3 receptor antagonists and gene knockout studies have revealed that all three receptor subtypes mediate the reinforcing effects drugs of abuse. There is an up-regulation of D_1 receptors (Unterwald et al., 1994) and increase in D_1 receptor binding (Alburges et al., 1993; Unterwald et al., 2001) in response to cocaine. Conversely, D_2 receptor density is lower in NAc of monkeys that have a history of cocaine use (Moore et al., 1998). Drugs of abuse can also produce changes in gene expression of DA receptors. Morphine and cocaine have been shown to decrease accumbens D_2 receptor mRNA (Georges et al., 1999; Turchan et al., 1997), and increase D_3 receptor mRNA (Spangler et al., 2003). These findings with laboratory animals support clinical studies, which have revealed that D_2 receptors are down-regulated in cocaine addicts (Volkow et al., 1996a, b, 2006).

Similar changes have been reported with intermittent access to sugar. Autoradiography reveals increased D_1 receptor binding in the NAc and decreased D_2 receptor binding in the striatum of rats fed Daily Intermittent Glucose and Chow (Fig. 6; Colantuoni et al., 2001). This was relative to chow-fed rats, so it is not known whether ad libitum glucose would also produce this effect. Others have reported 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 (Bello et al., 2002). Rats with intermittent sucrose and chow access also have decreased D_2 receptor mRNA in the NAc compared with ad libitum chow controls (Spangler et al., 2004). In these animals, mRNA levels of the D_3 receptor are increased in the NAc and caudate-putamen.

Regarding the opioid receptors, mu-receptor binding is increased in response to cocaine and morphine (Bailey et al., 2005; Unterwald et al., 2001; Vigano et al., 2003). Mu-opioid receptor binding is also significantly enhanced after three weeks on the intermittent sugar diet, compared with ad libitum chow. This effect was observed in the accumbens shell, cingulate, hippocampus and locus coeruleus (Colantuoni et al., 2001).

5.2. Intermittent sugar intake alters enkephalin mRNA expression

Enkephalin mRNA in the striatum and the NAc is decreased in response to repeated injections of morphine (Georges et al., 1999; Turchan et al., 1997; Uhl et al., 1988). These changes within opioid systems are similar to those observed in cocaine-dependent human subjects (Zubieta et al., 1996).

Rats with intermittent sucrose access also display a significant decrease in enkephalin mRNA, although it is difficult to judge its functional significance (Spangler et al., 2004). This decrease in enkephalin mRNA is consistent with findings observed in rats with limited daily access to a sweet-fat, liquid diet (Kelley et al., 2003). Assuming this decrease in mRNA results in less enkephalin peptide being synthesized and released, it could account for a compensatory increase in mu-opioid receptors, as cited above.

5.3. Daily intermittent sugar intake repeatedly releases dopamine in the accumbens

One of the strongest neurochemical commonalities between intermittent sugar access and drugs of abuse has

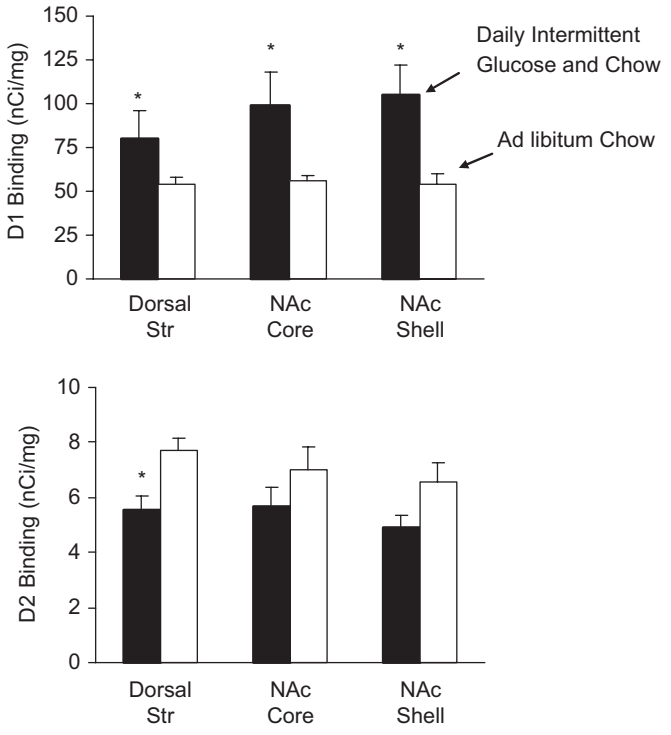

Fig. 6. Intermittent sugar access alters DA receptor binding at the level of the striatum. D_1 receptor binding (top panel) is increased in the NAc core and shell of animals exposed to Daily Intermittent Glucose and Chow (black bars) for 30 days compared with control animals fed chow ad libitum (white bars). D_2 receptor binding (bottom panel) is decreased in the dorsal striatum of the same animals. $^*p < 0.05$. From Colantuoni et al., 2001.

been found using *in vivo* microdialysis to measure extracellular DA. Repeated increase in extracellular DA is a hallmark of drugs that are abused. Extracellular DA increases in the NAc in response to both addictive drugs (De Vries and Shippenberg, 2002; Di Chiara and Imperato, 1988; Everitt and Wolf, 2002; Hernandez and Hoebel, 1988; Hurd et al., 1988; Picciotto and Corrigall, 2002; Pothos et al., 1991) and drug-associated stimuli (Ito et al., 2000). Unlike drugs of abuse, which exert their effects on DA release each time they are administered, the effect of eating palatable food on DA release wanes with repeated access when the food is no longer novel, unless the animal is food deprived (Bassareo and Di Chiara, 1999; Di Chiara and Tanda, 1997; Rada et al., 2005b). Thus normal feeding is very different than taking drugs because the DA response during feeding phases out.

However, and this is very important, rats fed daily intermittent sucrose and chow apparently release DA every day as measured on days 1, 2 and 21 of access (Fig. 7; Rada et al., 2005b). As controls, rats fed sucrose or chow ad libitum, rats with intermittent access to just chow, or rats that taste sucrose only two times, develop a blunted DA response as is typical of a food that loses it 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 et al., 2003; Hajnal and Norgren, 2002). Together, these results suggest that intermittent access to sugar and chow causes recurrent increases in extracellular DA in a manner that is more like a drug of abuse than a food.

An interesting question is whether the neurochemical effects observed with intermittent sugar access are due to its postingestive properties or whether the taste of sugar can be sufficient. To investigate orosensory effects of sugar, we used the sham-feeding preparation. Rats that are sham feeding with an open gastric fistula can ingest foods but not fully digest them (Smith, 1998). Although sham feeding does not completely eliminate post-ingestive effects (Berthoud and Jeanrenaud, 1982; Sclafani and Nissenbaum, 1985), it does allow the animals to taste the sugar while retaining almost no calories.

The results of sham feeding sugar for the first hour of access each day show that DA is released in the NAc, even after 3 weeks of daily bingeing, simply due to the taste of sucrose (Avena et al., 2006). Sham feeding does not further enhance the typical sugar-induced DA release. This supports other work showing that the amount of DA release in the NAc is proportional to the sucrose concentration, not the volume consumed (Hajnal et al., 2004).

5.4. Accumbens acetylcholine release is delayed during sugar binges and eliminated during sham feeding

As described in Section 3.3, accumbens ACh increases when feeding slows down (Mark et al., 1992). One could predict that when an animal takes a very large meal, as with the first sugar "binge," the release of ACh should be delayed until the satiation process begins as reflected in the gradual termination of the meal. This is what was observed; ACh release peaked when this initial "binge" meal was drawing to a close (Rada et al., 2005b).

Next we measured ACh release when the animal could take a large meal of sugar while sham feeding. Purging the stomach contents drastically reduced the release of ACh (Avena et al., 2006). This is predictable based on the theory that ACh is normally important for the satiation process (Hoebel et al., 1999; Mark et al., 1992). It also suggests that by purging, one eliminates the ACh response that opposes DA. Thus when "bingeing" on sugar is accompanied by purging, the behavior is reinforced by accumbens DA without ACh, which is more like taking a drug and less like normal eating.

5.5. Sugar "withdrawal" upsets dopamine/acetylcholine balance in the accumbens

The behavioral signs of drug withdrawal described in Section 2.2 are usually accompanied by alterations in DA/ACh balance in the NAc. During withdrawal, DA decreases while ACh is increased. This imbalance has been shown during chemically induced withdrawal with several drugs of abuse, including morphine, nicotine and alcohol

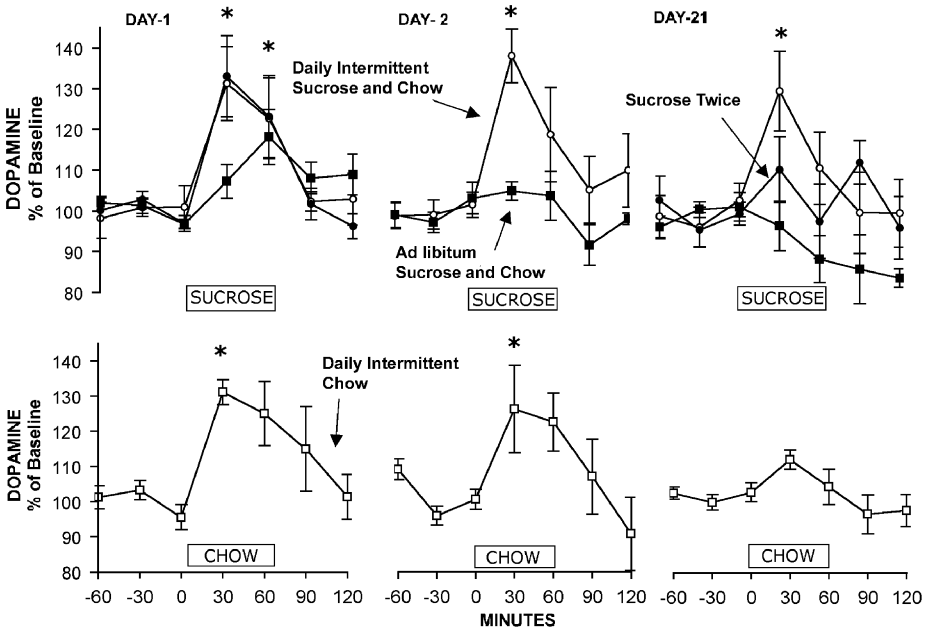

Fig. 7. Rats with intermittent access to sugar release DA in response to drinking sucrose for 60 min on day 21. Dopamine, as measured by *in vivo* microdialysis, increased for the Daily Intermittent Sucrose and Chow rats (open circles) on days 1, 2 and 21; in contrast, DA release was attenuated on day 21 in four control groups as follows: a group that only had 1-h access to sucrose on days 1 and 21 with ad libitum chow in the interim (filled circles), Ad libitum Sucrose and Chow group (filled squares), and Daily Intermittent Chow group (bottom panel). The bar on the ordinate indicates the hour (0–60 min) that sucrose or chow was available for the tests. $^{*}p<0.05$. From Rada et al., 2005b.

(Rada et al., 1996, 2001, 2004). Mere abstinence from an abused substance is also sufficient to elicit neurochemical signs of withdrawal. For example, rats that are forced to abstain from morphine or alcohol have decreased extracellular DA in the NAc (Acquas and Di Chiara, 1992; Rossetti et al., 1992) and ACh increases during spontaneous morphine withdrawal (Fiserova et al., 1999). While withdrawal from an anxiolytic drug (diazepam) precipitated by a bendodiazepine-receptor antagonist does not lower extracellular DA, it does release accumbens ACh (Rada and Hoebel, 2005).

Rats that have intermittent access to sugar and chow show the morphine-like neurochemical imbalance in DA/ACh during withdrawal. This was produced two ways. When given naloxone rats with intermittent sucrose access show a decrease in accumbens DA release coupled with an increase in ACh release (Colantuoni et al., 2002). The same thing occurs after 36 h of food deprivation (Fig. 8; Avena et al., unpublished). One way to interpret deprivation-induced neurochemical imbalance is that perhaps without food to release opioids, the animal suffers a similar type of withdrawal-like state as seen when the up-regulated mu-opioid receptors are blocked with naloxone.

6. Discussion and clinical implications

Food is not ordinarily like a substance of abuse, but intermittent bingeing and deprivation may change that. Based on the observed behavioral and neurochemical similarities between the effects of intermittent sugar access and drugs of abuse, we suggest that sugar, as common as it is, nonetheless meets many of the criteria for a substance of abuse and may be addictive for some individuals when consumed in a "binge-like" manner. This conclusion is reinforced by the changes in limbic system neurochemistry that are similar for drugs and for sugar. The effects we observe are smaller in magnitude than those produced by drugs of abuse such as cocaine or morphine; however, the fact that these behaviors and neurochemical changes can be elicited with a natural reinforcer is interesting. It is not clear from this animal model if intermittent sugar access can result in neglect of social activities as proposed by the definition of dependency in the DSM-IV-TR (American Psychiatric Association, 2000). Nor is it known whether rats will continue to self-administer sugar despite physical obstacles, such as enduring pain to obtain sugar, as some rats do for cocaine (Deroche-Gamonet et al., 2004). Nonetheless, the extensive series of experiments revealing similarities between sugar- and drug-induced behavior and neurochemistry, as chronicled in Sections 4 and 5, lends credence to the concept of "sugar addiction," gives precision to its definition, and provides a testable model.

6.1. *Bulimia nervosa*

The feeding regimen of Daily Intermittent Sugar and Chow shares some aspects of the behavioral pattern in people diagnosed with binge-eating disorder or bulimia. Bulimics often restrict intake early in the day and then binge later in the evening, usually on palatable foods (Drewnowski et al., 1992; Gendall et al., 1997). Bulimic patients will binge on excessive amounts of non-caloric

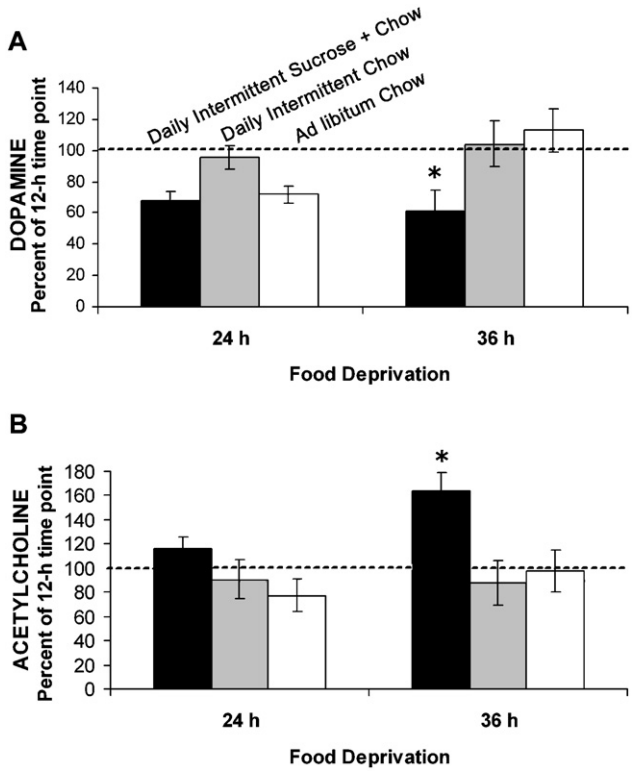

Fig. 8. Extracellular DA and ACh following 24 and 36 h of fasting. (A) After 36 h of fasting, DA release in the Daily Intermittent Sucrose and Chow group (black bar) was significantly less than both the intermittent chow (gray bar) and ad libitum chow (white bar) control groups. (B) Extracellular ACh was significantly increased in the Daily Intermittent Sucrose and Chow group at the 36 h fasting point compared with both control groups. $*p<0.05$.

sweeteners (Klein et al., 2006), suggesting that they derive benefits from sweet orosensory stimulation. These patients later purge the food, either by vomiting or laxative use, or in some cases by strenuous exercise (American Psychiatric Association, 2000). Bulimic patients have low β-endorphin levels (Brewerton et al., 1992; Waller et al., 1986), which might foster eating with a preference or craving for sweets. They also have decreased mu-opioid receptor binding in the insula compared with controls, which correlates with recent fasting behavior (Bencherif et al., 2005). This contrasts with the increase in the NAc observed in rats following a binge. Cyclic bingeing and food deprivation may produce alterations in mu-opioid receptors, which help perpetuate bingeing behavior. In support, appetite dysfunctions in the form of binge eating and self-starvation can stimulate endogenous opioid activity (Aravich et al., 1993).

The finding described in Section 5.3, that intermittent sugar access repeatedly releases DA in response to the taste of sugar, may be important for understanding the bingeing behaviors associated with bulimia. DA has been implicated in bulimia by comparing it to hypothalamic self-stimulation, which also releases DA without calories (Hoebel et al., 1992). Bulimic patients have low central DA activity as reflected in analysis of DA metabolites in the spinal fluid, which also indicates a role for DA in their abnormal responses to food (Jimerson et al., 1992). We have shown that purging leaves DA unopposed by satiety-associated ACh in the accumbens (Section 5.4). This neurochemical state may be conducive to exaggerated binge eating. Moreover, the findings that intermittent sugar intake cross-sensitizes with amphetamine and fosters alcohol intake (Sections 4.4 and 4.5) may be related to the comorbidity between bulimia and substance abuse (Holderness et al., 1994).

The overall similarities in behavior and brain adaptations with sugar bingeing and drug intake described above support the theory that some eating disorders, such as bulimia, may have properties of an "addiction" in certain individuals (Davis and Claridge, 1998; Gillman and Lichtigfeld, 1986; Heubner, 1993; Marrazzi and Luby, 1986, 1990; Mercer and Holder, 1997; Riva et al., 2006).

6.2. Obesity

6.2.1. Sugar and obesity

Obesity is one of the leading preventable causes of death in the USA (Mokdad et al., 2004). Several studies have correlated the rise in the incidence of obesity with an increase in sugar consumption (Bray et al., 1992; Elliott et al., 2002; Howard and Wylie-Rosett, 2002; Ludwig et al., 2001). The US Department of Agriculture has reported that per capita soft-drink consumption has increased by almost 500% in the past 50 years (Putnam and Allhouse, 1999). Sugar intake may lead to an increased number of and/or affinity for opioid receptors, which in turn leads to further ingestion of sugar and may contribute to obesity (Fullerton et al., 1985). Indeed, rats maintained on the diet of intermittent sugar access show opioid receptor changes (Section 5.1); however, after 1 month on the diet using 10% sucrose or 25% glucose, these animals do not become overweight (Colantuoni et al., 2001; Avena and Hoebel, 2003b), although others have reported a metabolic syndrome (Toida et al., 1996), a loss of fuel efficiency (Levine et al., 2003) and an increase in body weight in rats fed sucrose (Bock et al., 1995; Kawasaki et al., 2005) or glucose (Wideman et al., 2005). Most studies of sugar intake and body weight do not use a binge-inducing diet, and the translation to human obesity is complex (Levine et al., 2003). As described in Section 4.1, it appears that rats in our model compensate for sucrose or glucose calories by decreasing chow intake. They gain weight at a normal rate. This may not be true of all sugars.

Fructose is a unique sweetener that has different metabolic effects on the body than glucose or sucrose. Fructose is absorbed further down the intestine, and whereas circulating glucose releases insulin from the pancreas (Sato et al., 1996; Vilsboll et al., 2003), fructose stimulates insulin synthesis but does not release it (Curry, 1989; Le and Tappy, 2006; Sato et al., 1996). Insulin modifies food intake by inhibiting eating (Schwartz et al.,

2000) and by increasing leptin release (Saad et al., 1998), which also can inhibit food intake. Meals of high-fructose corn syrup can reduce circulating insulin and leptin levels (Teff et al., 2004), contributing to increased body weight. Thus, fructose intake might not result in the degree of satiety that would normally ensue with an equally caloric meal of glucose or sucrose. Since high-fructose corn syrup has become a major constituent in the American diet (Bray et al., 2004) and lacks some effects on insulin and leptin, it may be a potential agent for producing obesity when given intermittently to rats. Whether or not signs of dependency on fructose are apparent when it is offered intermittently has yet to be determined. However, based on our results showing that sweet taste is sufficient to elicit the repeated release of DA in the NAc (see Section 5.3), we hypothesize that any sweet taste consumed in a binge-like manner is a candidate for producing signs of dependence.

6.2.2. Fat and obesity

While we have chosen to focus on sugar, the question arises as to whether non-sweet, palatable foods could produce signs of dependence. The evidence is mixed. It appears that some signs of dependence are apparent with fat, while others have not been shown. Fat bingeing in rats has been modeled using intermittent access to pure fat (vegetable shortening), sweet-fat cookies (Boggiano et al., 2005; Corwin, 2006), or sweet-fat chow (Berner et al., unpublished). Repeated, intermittent access to oil releases DA in the NAc (Liang et al., 2006). Like sugar, bingeing on a fat-rich diet is known to affect the opioid system in the accumbens by decreasing enkephalin mRNA, an effect that is not observed with acute access (Kelley et al., 2003). Also, treatment with baclofen (GABA-B agonist), which reduces drug intake, also reduces binge eating of fat (Buda-Levin et al., 2005).

This all implies that fat dependency is a possibility, but withdrawal signs following fat-bingeing are not as apparent as with sugar. Le Magnen (1990) reported that naloxone could precipitate opiate-like withdrawal in rats on a cafeteria-style diet, which contains a variety of fat- and sugar-rich foods (e.g., cheese, cookies, chocolate chips). However, we have not observed signs of opiate-like withdrawal following naloxone administration or fasting in rats fed pure fat (vegetable shortening) or a sugar-fat combination. Further studies are needed to fully understand the differences between sugar and fat bingeing and their subsequent effects on behavior. Just as different classes of drugs (e.g., DA agonists vs. opiates) have specific behavioral and physiological withdrawal signs, it may be that different macronutrients also produce specific behavior alterations. Since "craving" of fat or cross-sensitization between fat intake and drugs of abuse has yet to be documented in laboratory animals, sugar is currently the only palatable substance for which bingeing, withdrawal signs, abstinence-induced enhanced motivation and cross-sensitization have all been demonstrated (Sections 4 and 5).

6.2.3. Brain imaging

Recent findings using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) in humans have supported the idea that aberrant eating behaviors, including those observed in obesity, may have similarities to drug dependence. Craving-related changes in fMRI signal have been identified in response to palatable foods, similar to drug craving. This overlap occurred in the hippocampus, insula, and caudate (Pelchat et al., 2004). Similarly, PET scans reveal that obese subjects show a reduction in striatal D_2 receptor availability that is associated with the body weight of the subject (Wang et al., 2004b). This decrease in D_2 receptors in obese subjects is similar in magnitude to the reductions reported in drug-dependent subjects (Wang et al., 2001). The involvement of the DA system in reward and reinforcement has led to the hypothesis, that alterations in DA activity in obese subjects disposes them to excessive use of food. Exposure to especially palatable foods, such as cake and ice cream, activates several brain regions including the anterior insula and right orbitofrontal cortex (Wang et al., 2004a), which may underlie the motivation to procure food (Rolls, 2006). Although binge eating was not directly addresses in these imaging studies, it may nonetheless be a factor since some obese individuals engage in binge-eating behavior (Stunkard, 1959).

7. Conclusion

From an evolutionary perspective, it is in the best interest of humans to have an inherent desire for food for survival. However, this desire may go awry, and certain people, including some obese and bulimic patients in particular, may develop an unhealthy dependence on palatable food that interferes with well-being. The concept of "food addiction" materialized in the diet industry on the basis of subjective reports, clinical accounts and case studies described in self-help books. The rise in obesity, coupled with the emergence of scientific findings of parallels between drugs of abuse and palatable foods has given credibility to this idea. The reviewed evidence supports the theory that, in some circumstances, intermittent access to sugar can lead to behavioral and neurochemical changes that resemble the effects of a substance of abuse. Sugar "dependency" was operationally defined by tests for bingeing, withdrawal signs, craving and cross-sensitization to amphetamine and alcohol. The correspondence to some people with binge-eating disorder or bulimia is notable, but whether or not it is a good idea to call this a "food addiction" in people is both a scientific and societal question that has yet to be answered. What this review demonstrates is that rats with intermittent access to a sugar solution can show both a constellation of behaviors and parallel brain changes that are characteristic of rats that voluntarily self-administer addictive drugs. In conclusion, this is evidence that under some circumstances sugar can be addictive.

Acknowledgments

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