

Sugar-dependent rats show enhanced intake of unsweetened ethanol

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Abstract

Rats show signs of dependence on sugar when it is available intermittently, including bingeing, withdrawal, and cross-sensitization with amphetamine. In the current study, we sought to determine whether sugar-dependent rats would show increased intake of unsweetened ethanol and, conversely, whether intermittent access to ethanol would augment sugar consumption. In Experiment 1, with intermittent versus ad libitum access to ethanol, Sprague–Dawley rats were given escalating concentrations of ethanol (1%, 2%, 4%, 7%, and 9%) over the course of 20 days. Rats in the intermittent ethanol access group, with 12-h daily access, consumed more 4%, 7%, and 9% ethanol during the first hour of access, and more 9% ethanol daily, than did rats in the ad libitum ethanol access group. In Experiment 2, with ethanol as a gateway to sugar intake, the rats from Experiment 1 were switched to 10% sucrose with 12-h daily access for 1 week. Rats in the intermittent ethanol access group consumed significantly more sugar than was consumed by rats in a control group with no prior ethanol experience. In Experiment 3, with sugar as a gateway to ethanol to determine whether sugar dependence leads to increased ethanol intake, four groups were maintained for 21 days according to the following designations: intermittent access to sugar and chow, ad libitum access to sugar and chow, intermittent access to chow, or ad libitum access to chow. Four days later, all groups were switched to intermittent ethanol access, as described in Experiment 1. The group with intermittent access to sugar and chow consumed the most 9% ethanol, supporting the suggestion that sugar dependence alters a rat's proclivity to drink ethanol. These results may relate to the co-morbidity between binge-eating disorders and alcohol intake and the tendency of people abstaining from alcohol to consume excessive amounts of sugar. In conclusion, bingeing on either ethanol or sugar fosters intake of the other. © 2005 Elsevier Inc. All rights reserved.

Keywords: Alcohol; Sucrose; Cross-sensitization; Binge-eating; Bulimia nervosa

1. Introduction

Findings of both clinical research and studies with animals indicate that a correlation exists between the consumption of sweets and ethanol. Randomly bred rats consume more ethanol after having been exposed to saccharin (Bell et al., 1994; Gosnell & Krahn, 1992; Kampov-Polevoy et al., 1995), and animals that prefer sweets are predisposed to drinking ethanol (Sinclair et al., 1992). In a similar manner, in comparison with ethanol-nonpreferring animals, ethanol-preferring animals consume much larger quantities of saccharin (Bachmanov et al., 1996; Belknap et al., 1993; Forgie et al., 1988; Ramirez & Sprott, 1978) and drink saccharin in excess of their normal daily fluid intake (Kampov-Polevoy et al., 1995). Results from studies with human beings indicate that sweet-liking is more prevalent in alcoholic men than in

nonalcoholic men, and that preference for sweets is a marker for inherited paternal alcoholism (Kampov-Polevoy et al., 1997, 2001).

The main question we sought to answer in the current study was whether learning to binge on sugar, to a degree that causes signs of dependence, alters subsequent alcohol intake. Investigators in our laboratory have developed an animal model of sugar dependence, in which rats maintained on a diet of intermittent access to sucrose show behavioral and neurochemical signs of substance abuse. These rats, given 12-h/day access to sugar solution plus chow, binge on the sugar in the first hour of daily access (Colantuoni et al., 2001). They exhibit somatic signs of spontaneous withdrawal when they are food deprived, display both behavioral and neurochemical signs of naloxone-precipitated opioid withdrawal (Colantuoni et al., 2002), and show cross-sensitization with amphetamine after a week of abstinence (Avena & Hoebel, 2003). They also release a large amount of dopamine in the nucleus accumbens and continue to release dopamine each day in response to bingeing on sugar even

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after 21 days of access (unpublished observation, P. V. Rada, N. M. Avena, N. Moise, and B. G. Hoebel, 2004). These rats also show increased mu-opioid and D₁ receptor binding, increased D₃ mRNA, and decreased preproenkephalin mRNA in the nucleus accumbens (Colantuoni et al., 2001; Spangler et al., 2004). These similarities to the effects of drugs of abuse support the idea that such rats have become dependent on sugar.

The current study comprised three experiments. In Experiment 1, we tested a 12-h limited-access paradigm to determine whether such a schedule can enhance intake of unsweetened ethanol. In Experiments 2 and 3, this paradigm was used to test the hypothesis that (1) ethanol bingeing produces a subsequent increase in consumption of sugar and (2) learning to binge on sugar leads to greater intake of ethanol, respectively.

2. Materials and methods

2.1. General methods

Male, Sprague–Dawley rats were obtained from the Princeton University vivarium from a stock originating from Taconic Farms (Germantown, NY). The rats were housed individually on a reversed 12-h light:12-h dark cycle, with ad libitum access to water and LabDiet rodent chow, unless otherwise specified. Voluntary access to both ethanol and water was given by means of two graduated cylinders fitted with 4-inch curved drinking tubes with tip valves (steel balls) to prevent leakage (Lab Products Inc., Seaford, DE). The cylinders were rinsed and refilled each day, and the right–left position was reversed daily to prevent place preference. Solutions were diluted from 95% ethanol (David Sherman Corp., St. Louis, MO; Experiments 1 and 2) or 200-Proof ethanol (AAPER Alcohol, Shelbyville, KY; Experiment 3). The ethanol concentration was increased stepwise every 4 days over the course of 20 days in the following manner: 1%, 2%, 4%, 7%, and 9% (volume/volume). The care and use of, as well as all procedures involving, animals were in accordance with the Institutional Animal Care and Use Committee regulations at Princeton University.

2.2. Method for Experiment 1: rapidly induced ethanol intake without the use of sweeteners

Before we tested for consummatory cross-sensitization between ethanol and sugar intake, it was necessary to establish a method for promoting ethanol intake that did not include added sweeteners, which would confound the results. For consistency, the daily intermittent access schedule that induces signs of sugar dependence was adapted to determine whether it also enhances consumption of ethanol. This intermittent paradigm was slightly different than that normally used in the alcohol literature. As is typical, ethanol was available for a part of the day, every day, but ethanol was available for 12 h with a 4-h delay in access after the

onset of the dark cycle. This was designed to induce daily bingeing on ethanol at a time when the animals are most active with ample time to consume more ethanol. Forty rats, each weighing between 250 and 350 g, were randomly assigned to one of two groups. The group designated as Intermittent Ethanol ($n = 20$) had access to the ethanol solutions for 12 h/day, starting 4 h into the dark phase, with ad libitum access to water and chow. Intake of ethanol and water was recorded during the first hour of access (fourth hour of the dark phase) and after 12-h access. The group designated as Ad libitum Ethanol ($n = 20$), in contrast, had constant access to ethanol solutions, water, and chow for 20 days in the same stepwise manner, as described above. In these rats, measurements of ethanol and water intake were recorded during the first and fourth hours of the dark phase as well as after 24 h. Body weights were recorded every 4 days (last day of each ethanol concentration).

2.3. Method for Experiment 2: the effect of drinking ethanol on sugar intake

In Experiment 2, we tested whether intermittent versus ad libitum access to ethanol results in differences in subsequent sugar intake. Rats from Experiment 1, plus a naive control group with no prior experience with ethanol ($n = 10$ rats per group), were used. After the two ethanol groups were drinking 9% ethanol, all groups were switched for 7 days to daily 12-h food deprivation, followed by 12-h access to 10% sucrose and chow. Sugar intake was recorded each day after 1 h and 12 h of access.

2.4. Method for Experiment 3: daily sugar bingeing as a gateway to ethanol intake

In Experiment 3, we tested whether sugar-dependent rats would display alterations in subsequent ethanol consumption. Four groups of animals ($n = 10$ rats per group; each rat weighing between 350 and 450 g) were tested. To induce sugar dependence, the group designated as Intermittent Sugar & Chow had 12-h deprivation, followed by 12-h access to 10% sucrose and chow starting 4 h into the dark phase. Rats exposed to this protocol have shown signs of sugar dependence in other studies (Avena & Hoebel, 2003; Colantuoni et al., 2001, 2002; Spangler et al., 2004). To control for limited food access without sugar, a group designated as Intermittent Chow had 12-h deprivation, followed by 12-h access to chow with the same 4-h delay. A group designated as Ad libitum Sugar & Chow had free access to both 10% sucrose and chow, and this group was included as a control for intermittent versus ad libitum access to sugar. There was also a group designated as Ad libitum Chow. After 21 days of receiving their respective diets, all animals were subsequently maintained on chow ad libitum for 3 days, after which they were given daily 12-h access to increasing concentrations of ethanol (i.e., 1%, 2%, 4%, 7%, and 9%), as described in Experiment 1. Intakes were recorded daily, and body weights were recorded every 4 days.

2.5. Data analysis

Ethanol intake, recorded to the nearest milliliter, was converted to grams per kilogram of body weight. For Experiments 1 and 3, ethanol intake data were averaged over the 4 days at each concentration. Data were analyzed by two-way repeated-measures analysis of variance (ANOVA), with post hoc Fisher least significance difference tests when justified.

3. Results

3.1. Twelve-hour intermittent access to ethanol produces bingeing and enhances voluntary consumption of 9% ethanol in 20 days

In Experiment 1, we compared 12-h daily access to ethanol with ad libitum access. Rats that were given ethanol intermittently drank copiously in the first hour of access. Comparison of intake between the first hour of the dark phase for the Ad libitum Ethanol group and first hour of access for the Intermittent Ethanol group revealed a significant difference [$F(4, 152) = 7.17, P < .01$], with the Intermittent Ethanol group drinking significantly more at the 4%, 7%, and 9% concentrations ($P < .05$). A significant group \times concentration interaction for 1-h intake during the fourth hour of the dark phase [$F(4, 152) = 2.48, P < .05$; Fig. 1A] also showed a significant difference at 9%. A similar result was obtained for total ethanol intake [$F(4, 148) = 2.82, P < .03$; Fig. 1B], with the Intermittent Ethanol group drinking significantly more per day at the 9% concentration (1.4 vs. 0.7 g/kg/day, respectively; $P < .05$). There were no differences in water intake across time or between these groups, nor were there differences between the groups in terms of body weight.

3.2. Rats that drink ethanol intermittently later consume more sugar than consumed by control rats

In Experiment 2, we tested whether daily bingeing on ethanol, as established in Experiment 1, enhances subsequent sugar intake. Rats with a history of intermittent ethanol access consumed more sugar than did control rats during the first hour of access, with significant differences on days 1 to 3 [$F(12, 162) = 3.28, P < .01$; Fig. 2A]. The Intermittent Ethanol group also drank more sugar during the 12-h interval than did the Ad libitum group in the entire day, again with significant differences on days 1 to 3 [$F(12, 162) = 5.9, P < .01$; Fig. 2B].

3.3. Sugar-dependent rats consume more of the higher concentrations of ethanol

In Experiment 3, we tested whether daily ethanol consumption varies as a function of previous experience with (1) intermittent access to sugar and chow, (2) intermittent access to chow, (3) ad libitum access to sugar and chow, or

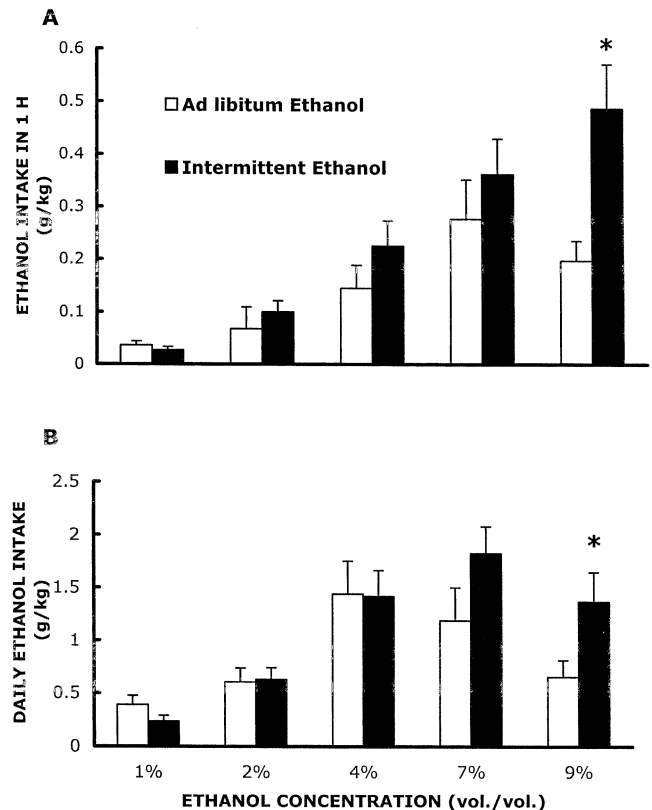


Fig. 1. A. Rats in the group designated as Intermittent Ethanol drank more ethanol in the first hour of access (fourth hour of the dark phase) than did rats in the group designated as Ad libitum Ethanol during the same hour. B. Rats in the Intermittent Ethanol group also consumed more 9% ethanol daily. * $P < .05$. Intake data were averaged over the 4 days of access to each concentration.

(4) ad libitum access to chow. Rats with sugar experience drank more ethanol [$F(12, 132) = 4.08, P < .01$]. At the 7% concentration, the Ad libitum Sugar & Chow group consumed more ethanol than was consumed by either the Intermittent Sugar & Chow group or the Intermittent Chow group ($P < .05$). At the 9% concentration, the Intermittent Sugar & Chow group consumed significantly more than was consumed by the Ad libitum Sugar & Chow and the Ad libitum Chow groups ($P < .05$; Fig. 3). At this concentration, the Intermittent Chow group consumed more ethanol than was consumed by the Ad libitum Chow group ($P < .05$). There were no significant differences between the groups in body weight.

4. Discussion

Results of the current study, which are consistent with findings in the published literature (Bell et al., 1994; Gosnell & Krahn, 1992; Kampov-Polevoy et al., 1995), demonstrate a clear relation between sugar intake and voluntary ethanol consumption. By adapting the paradigm that induces sugar dependence (Avena & Hoebel, 2003; Colantuoni et al., 2001,

2002; Spangler et al., 2004), rats in Experiment 1 were induced to consume unsweetened ethanol voluntarily by using daily 12-h limited access that caused a binge during the first hour of access. In Experiment 2, these animals with intermittent ethanol access consumed more sugar than was consumed by rats with a prior history of ad libitum access to ethanol. Conversely, in Experiment 3, rats with a history of dependence on sugar (i.e., those in the Intermittent Sugar & Chow group) consumed more 9% ethanol than was consumed by animals with ad libitum experience with sugar. These findings indicate that the manner in which sugar is provided (i.e., 12-h intermittent access) is important in fostering this increased consummatory cross-sensitization. Together, these results show a positive relation in which bingeing on either ethanol or sugar fosters intake of the other.

The relation between sugar dependence and ethanol intake may be important for understanding the classic sucrose-fading paradigm. In this paradigm, ethanol is flavored

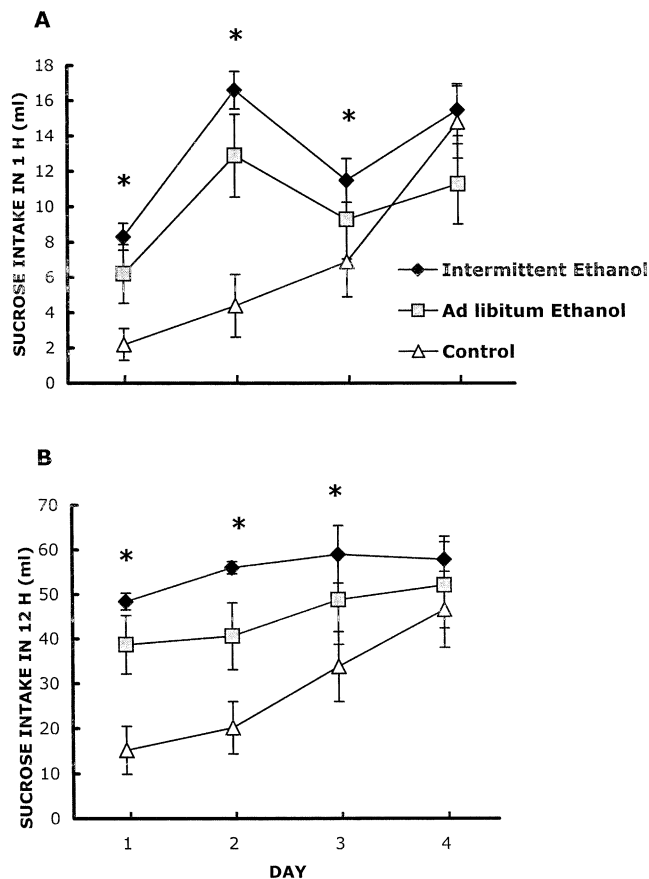


Fig. 2. A. Rats that had been drinking ethanol intermittently (i.e., those in the group designated as Intermittent Ethanol) later consumed more sugar in the first hour of daily 12-h access than was consumed by naive Control rats. This effect was not observed between Control and Ad libitum Ethanol groups. B. In comparison with naive Control rats, rats in the Intermittent Ethanol group also consumed more sugar in 12 h of access. Again, this effect was not observed with rats that had been consuming ethanol ad libitum. * $P < .05$, differences between Intermittent Ethanol and Control groups.

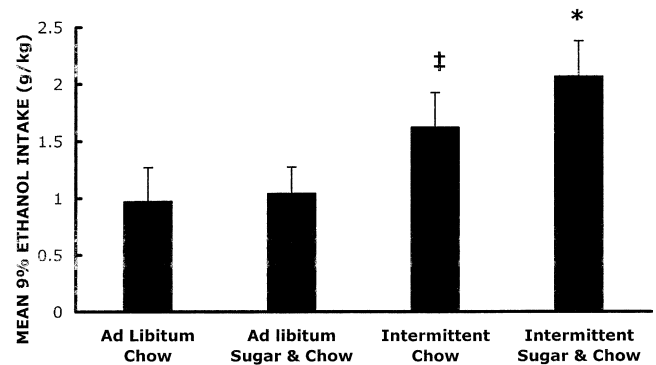


Fig. 3. Rats with a history of 12-h daily access to sugar and chow (Intermittent Sugar & Chow) consumed more ethanol at 9% than was consumed by rats in either the Ad libitum Sugar & Chow group or the Ad libitum Chow group (* $P < .05$). In comparison with rats in the Ad libitum Chow group, rats in the Intermittent Chow group also consumed more ([‡] $P < .05$).

with a sweetener to make it palatable, and when intake reaches acceptable levels for research purposes, the sweetener is gradually eliminated (Samson, 1986). Many researchers have used this model successfully to induce ethanol intake in rats (Brown et al., 1998; Clark et al., 2001; Gauvin & Holloway, 1992; Roberts et al., 1999; Samson, 1986; Shoemaker et al., 2002; Tolliver et al., 1988; Vacca et al., 2002; van Erp & Miczek, 1997). Because rats can become dependent on sugar, animals in the classic version of the sucrose-fading paradigm may be partially dependent on the sucrose. This, in addition to the taste factor, could facilitate ethanol intake. Ethanol may help alleviate withdrawal from sugar, and intermittent sugar access may cross-sensitize with ethanol. Although this can be an advantage in some experiments, it could create a possible confound or auxiliary factor that complicates the interpretation of the results of other experiments, such as in the current study, in which the goal was to determine whether repeated bingeing on one substance enhances subsequent intake of the other.

Ad libitum access to ethanol without added sweeteners has been used successfully to lead randomly bred rats to consume large quantities, although it often takes months to do so (Hölter et al., 1998; Lancaster et al., 1987; Marcucella et al., 1984; Spanagel & Hölter, 1999; Wolffgramm & Heyne, 1995). Limited access also induces rats to drink ethanol, but in daily binges such as 1 h/day (Cicelli & Lewis, 2002; Kunin et al., 2000; MacDonall & Marcucella, 1979; Marcucella & Munro, 1987; Poulos et al., 1998; Smith et al., 1999). These limited-access paradigms incorporate periodic deprivation, which is important in facilitating dependence on drugs of abuse, including ethanol (Koob, 2003). In the model described in Experiment 1, we compared intermittent and ad libitum access, and the results support the conclusion that limited access is superior in eliciting moderate ethanol intake within 20 days. The use of a 12-h period of access, in contrast to a shorter 1-h access, allows for comparison of intake at different times of the dark phase.

There are many models and definitions of bingeing, and these differ between animal and human research. Several investigators have studied bingeing on alcohol in rats (Callaci et al., 2004; Carmiel-Haggai et al., 2003; Crews & Braun, 2003; Hunt & Phillips, 2004; Nixon & Crews, 2002; Popović et al., 2004), where the binge is generally considered a large proportion of ethanol intake in a short time. In the current study, the animals clearly binge, because they ingested 33% of their daily ethanol intake in the first hour of access, even though there was no time pressure. Having consumed both sugar and ethanol on the same 12-h intermittent access schedule may also facilitate the increased intake of sugar or ethanol, as observed in Experiments 2 and 3.

Our means of relating sweet taste and ethanol intake in the current study is different from prior studies (Bell et al., 1994; Gosnell & Krahn, 1992; Kampov-Polevoy et al., 1995; Sinclair et al., 1992) in that the animals were made dependent on sugar, as described above. Intermittent periods of total deprivation were followed by 12-h access to sugar and chow before the animals were tested with ethanol. Food deprivation is known to enhance ethanol intake (Deems et al., 1986; Söderpalm & Hansen, 1999; Stiglick & Woodworth, 1984); however, food restriction during ethanol access abolishes the enhanced intake normally observed in saccharin-preferring rats (Gosnell & Krahn, 1992). Therefore, in the current study, limited ethanol access was given with ad libitum access to food, which also ensured that the rats were not drinking ethanol to replenish calories.

Intermittent access, to cause bingeing, was important in relating sugar to ethanol intake. Intermittent access to sugar, not just ad libitum access, was required to enhance intake of the highest concentration of ethanol (Experiment 3). In a similar manner, bingeing on ethanol increased subsequent sugar intake beyond that of rats with a history of ad libitum access to ethanol (Experiment 2). In that experiment, there were statistically significant differences during the first 3 days of the sucrose measurement period. This seems to be due to the formerly Intermittent Ethanol group's immediate high intake of sucrose, and by day 4, the other groups are catching up. These results indicate that intermittent bingeing on sugar or ethanol can be sufficient to cause a lasting change in the brain, leading to enhanced intake of the other substance.

In Experiment 3, we compared a group with intermittent access to chow (no sugar) to a group with ad libitum access to chow. It is interesting that the group with alternating deprivation and access to chow later consumed more 9% ethanol. This supports the idea that intermittency, even for plain chow, is important in eliciting future ethanol intake, although the effects are not as strong as those observed with intermittent access to chow and sugar. Intermittent deprivation may potentiate the release of dopamine when the diet is made available (Cadoni et al., 2003), which could, in turn, cause behavioral sensitization (Avena & Hoebel, 2003).

The relation observed in the current study between sugar and ethanol intake is suggestive of common underlying neural mechanisms. Both ethanol and palatable foods can

increase the extracellular concentration of dopamine in the nucleus accumbens (Ericson et al., 1998; Hernandez & Hoebel, 1988; Imperato & Di Chiara, 1986; Weiss et al., 1993). However, drugs of abuse such as ethanol differ from palatable foods in that they release dopamine even after repeated administration (Pothos et al., 1991; Wise et al., 1995; Yim et al., 1998; Zocchi et al., 2003), whereas palatable foods ordinarily produce blunted dopamine release after repeated access (Bassareo & Di Chiara, 1999). However, our model of sugar dependence results in a significant release of dopamine in the nucleus accumbens, day after day (unpublished observation, P. V. Rada, N. M. Avena, N. Moise, and B. G. Hoebel, 2004). This occurs during the binge after 12 h of deprivation. The combination of deprivation followed by bingeing leads to increased D₁ receptor binding and D₃ mRNA expression in the nucleus accumbens (Colantuoni et al., 2001; Spangler et al., 2004). We have shown that sugar dependence cross-sensitizes with amphetamine (Avena & Hoebel, 2003), which again indicates an important role for dopamine.

In addition, brain opioid systems are known to mediate some of the rewarding aspects of both ethanol (Djouma & Lawrence, 2002; Froehlich, 1996; Gianoulakis, 1996; Marinelli et al., 2000; McBride et al., 1998; Roberts et al., 2000) and sweet solutions (Kelley et al., 2002; Levine et al., 1985; Sclafani et al., 1982; Segato et al., 1997; Zhang & Kelley, 2002). Sugar-dependent rats show up-regulation of mu-opioid receptors in the nucleus accumbens (Colantuoni et al., 2001) and are sensitive to an opiate antagonist, naloxone, which precipitates mild withdrawal signs (Colantuoni et al., 2002). In the current study, we demonstrate consummatory cross-sensitization between sugar and ethanol, which may be due to long-lasting alterations of the dopamine and opioid systems resulting from bingeing on one substance, leading to the increased intake of the other.

Findings of the current study have clinical implications. Sugar dependence resembles the eating pattern of some patients with bulimia nervosa, which consists of daily fasting followed by bingeing, usually on a sweet food (Drewnowski et al., 1987; Gendall et al., 1997). These patients also have an increased rate of substance abuse, including alcoholism (Brewerton et al., 1995; Jonas et al., 1987; Jones et al., 1985; Mitchell et al., 1985). In a similar manner, recovering substance abusers report intense sweet cravings (Morabia et al., 1989). Results of the current study indicate that a diet comprised of intermittent access to sugar produces a state that makes rats increase their consumption of ethanol. Likewise, rats with a history of intermittent access to ethanol have an increased proclivity to drink sugar. Because this is suggestive of a relation between sugar and ethanol intake, which is enhanced by the intermittent availability of either substance, it may be important to monitor patients that have binge eating disorders for susceptibility to augmented alcohol intake. Conversely, the results may help explain why increased sugar intake may be a therapeutic tool in aiding recovery from alcoholism (Alcoholics Anonymous, 1987).

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