Food dependence in rats selectively bred for low versus high saccharin intake: Implications for “food addiction.”

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Available at: https://works.bepress.com/nancy_dess/10/
Introduction

Criteria for drug dependence, such as bingeing and withdrawal, are increasingly being applied to nutritive substances (Blumenthal & Gold, 2010; Corwin & Grigson, 2009; Gearhardt, Corbin, & Brownell, 2009). Laboratory rats, long used to study basic biobehavioral mechanisms of drug dependence, now are being used to study food dependence. Rats display rapid, escalating overconsumption over a course of periodic access to calorie-rich foods and, during abstinence, behaviors such as chattering and shaking; aspects of these phenomena resemble drug bingeing and withdrawal (Avena, Rada, & Hoebel, 2008; Hoebel, Avena, Bocarsly, & Rada, 2009). Such research represents an important bridge between humans and other animals: All animals eat, and consuming biochemically complex food, like using drugs, creates an allostatic load to which reward and other systems respond (Woods, 2002). Moreover, psychoactive drugs ingested by other animals are consumed mostly in food, such as ethanol in fermenting fruit (Dudley, 2002). Eating (dys)regulation has comparative validity, especially for social omnivores such as humans and rats, as a tool for studying the use and abuse of diverse substances.

How far the parallel between food and drugs of abuse should be taken – whether there is such a thing as “food addiction” – is controversial (e.g. Avena, 2010; Benton, 2010; Corsica and Pelchat, 2010; Epstein & Shaham, 2010; Hughes, 2007; Wilson, 2010). The present study contributes to the discussion by reporting effects of periodic sugar and/or fat access in rats selectively bred on an ingestive phenotype who respond differently to drugs of abuse. Relative to Occidental low-saccharin-consuming rats (LoS), Occidental high-saccharin-consuming rats (HiS) overconsume sapid solutions (Dess, 2000), acquire and escalate cocaine self-administration faster, regulate food and cocaine intake less tightly, and are more impulsive (Carroll, Morgan, Anker, Perry, & Dess, 2008). Consistent with other evidence that rat lines more prone to voluntary ethanol intake are less vulnerable to withdrawal (Chester, Blose, & Froehlich, 2003), HiS rats show higher voluntary ethanol intake (Dess, Badia-Elder, Thiele, Kiefer, & Blizard, 1998) and less withdrawal than do LoS rats after 14 days of comparable, forced-choice ethanol intake (Dess, O’Neill, & Chapman, 2005). If food dependence is a form of drug dependence, the lines should differentially overconsume and/or withdraw from foods.

Three experiments examined LoS and HiS rats’ behavior in two leading food-dependence protocols, at the core of which is periodic access to calorie-rich substances. Sugar solution (Experiments 1 and 2; Colantuoni et al., 2002) and high-fat foods high or low in sugar (Experiment 3; Corwin, 2006; Corwin & Wojnicki, 2006: Chapter 9) were used, as they may differentially activate addiction-related mechanisms (Avena, Rada, & Hoebel (2009)). Because periodic access to putatively addictive food can increase ethanol intake – a finding interpretable as drug cross-sensitization (Avena, Carrillo, Needham, Leibowitz, & Hoebel, 2004) – Experiment 3 included two ethanol-intake probe tests. The key issue here is not the robustness of overall effects. It is whether lines distinguished...
by an ingestive phenotype with drug-related correlates would yield evidence of being differentially impacted in established food-dependence regimes. Such results would constitute novel evidence linking food and drug dependence.

Methods and materials

Rats

Experimentally naïve female LoS and HiS rats from our colony (generations 33–36), approximately 60–90 days old and averaging 260 g, were used. Post-experimental testing confirmed the phenotype (saccharin intake relative to a water baseline and bodyweight: mean ± SEM for LoS 4 ± 1Δ%, HiS 47 ± 2Δ%; see Carroll et al., 2008). Group sizes ranged from 8 (Experiments 2 and 3) to 13–15 (Experiment 1). Littermates (10–14 litters/line in Experiments 1 and 2, 3–4 litters/line in Experiment 3) were balanced across experimental groups. Rats were housed individually on a 12:12 light:dark schedule with water freely available.

Apparatus and foods

Somatic signs were videotaped in a test cage. Acoustic startle was measured in an apparatus (San Diego Instruments SR-Pilot) that provides a digital amplitude score in arbitrary units (maximum: 2000). Glucose solution (Sigma–Aldrich, 25%, w/v) and ethanol (4%, v/v) were presented in glass bottles. Keebler’s Pecan Sandies and Crisco vegetable shortening were presented in acrylic dishes. Pelleted chow was Purina 5001.

Procedure

Colantuoni et al.’s (2002) 12:12 h feeding:abstinence schedule was used in Experiments 1 (8 days) and 2 (14 days). In Colantuoni et al.’s experiments, a group periodically fed chow did not differ from control groups freely fed chow and/or glucose; thus, on ethical and practical grounds, only the period-fed chow control condition was used. For 12 h daily (feeding), all rats had access to chow; half also had access to glucose solution. For the other 12 h (abstinence), only water was available. After the last feeding period, the usual 12-h abstinence period was extended by 12 h to increase the sensitivity of tests to withdrawal (Colantuoni et al., 2002, Exp. 1C), and withdrawal was assessed. Each rat was videotaped for 15 min for blind scoring of somatic signs, after which startle was measured (40-ms, 95-dB stimulus, 30 trials at 10 s intervals). Naloxone can enhance withdrawal if it is opioid mediated. Therefore, in Experiment 2, rats received either saline or naloxone (20 mg/kg i.p.; Colantuoni et al., 2002, Exp. 1B) before testing. In summary, group treatments yielded a 2 x 2 (line - × glucose access) design in Experiment 1 and a 2 x 2 × line × glucose access × naloxone/saline) design in Experiment 2.

In Experiment 3, half of the rats received cookies for 2 weeks and then shortening for 4 weeks, in a 2 h/session 3 days/week protocol used to model binge eating (Corwin, 2006; Corwin & Wojnicki, 2006: Chapter 9). Chow was available except when high-fat food was available. Controls had only continuous access to chow. All rats received a 24-h two-bottle ethanol test at the midpoint and end of the periodic access regime.

Results and discussion

Analyses of variance, Pearson’s r, and hierarchical regression were conducted. Significant test statistics (p ≤ .05) and the descriptive statistics to which they correspond are reported in the text; all nonsignificant results had p > .10. Adjusted p values (Greenhouse–Geisser for repeated measures, Bonferroni for pairwise contrasts) controlled Type 1 error.

Sugar consumption

Glucose solution intake in the first hour was greater among HiS than LoS rats (12 g versus 10 g, Experiments 1 and 2) and increased over the course of periodic access (10 g to 12 g, Experiment 1; 7 g to 13 g, Experiment 2). The increase did not differ between lines. A line x day ANOVA for each experiment yielded, respectively, main effects of line, F = 4.61 and 6.53, and day, F = 6.82 and 38.75. Total daily glucose solution intake also increased (34 g to 52 g, Experiment 1, and 31 g to 50 g, Experiment 2; main effect of day, respectively, F = 15.97 and 11.16). The lines did not differ on total daily glucose intake (as previously observed with 24% glucose, for which caloric feedback limits daily intake; Dess & Minor, 1996) or on increase in intake over days.

Somatic signs

Colantuoni et al. (2002) reported spontaneous withdrawal after eight days of periodic glucose access by three measures: forepaw tremor, teeth chatter, and head shake. Those behaviors provided no evidence of withdrawal in the present study. In Experiment 1, all three behaviors were rare. In Experiment 2, forepaw tremor occurred slightly more often but head shake and chatter were rare, and none varied as a function of glucose access, naloxone, or line.

Acoustic startle

In Experiment 1, LoS rats startled more overall than did HiS rats (marginal means of 415 versus 301), replicating prior findings (Dess et al., 2000; Gonzales, Garrett, Chapman, & Dess, 2008). Mean startle did not differ between chow-glucose and chow-only groups, and startle amplitude habituated over successive two-trial blocks at a similar rate in all groups. A line x glucose access x trial block ANOVA yielded only main effects of line, F(1, 52) = 5.46, and trial block, F(14, 728) = 8.67. Inspection of within-group variance reveals a line difference in impacts of the periodic feeding regime that are not apparent at the group-aggregated level. Early-course and late-course glucose intake were distinguished by averaging the first three versus the last three access periods, to minimize effects of novelty and/or estrus. Among LoS rats, higher late-course glucose intake predicted higher mean startle, r(12) = 0.63; this relationship remained significant after controlling for bodyweight. F(3, 11) = 6.84. Early-course glucose intake did not predict startle. Among HiS rats, neither early- nor late-course glucose intake predicted startle.

In Experiment 2, with one exception explained below, all findings were replicated. A line x glucose access x naloxone/saline x trial block ANOVA indicated that startle habituated at a similar rate in all groups [trial block main effect only, F(14, 784) = 6.49], and marginal group means did not differ as a function of glucose access. Among LoS rats, higher late-course glucose intake predicted higher startle, r(14) = 0.50, to a similar degree among naloxone- and saline-treated rats [r(6) = 0.56 and 0.54]. The correlation remained significant after controlling for bodyweight and naloxone treatment, F(3, 12) = 4.81. Early-course glucose intake did not predict startle. Among HiS rats, neither early- nor late-course glucose intake predicted startle. In both experiments, all nonsignificant rs ≤ 0.20. The presence or absence of correlations is not an artifact of more or less variance in glucose intake, as withingroup variance was relatively homogenous over the course of periodic access and between lines in both experiments.

The finding in Experiment 1 that was not observed in Experiment 2 was the main effect of line on startle. In prior
studies yielding a line difference (Experiment 1; Dess et al., 2000; Gonzales et al., 2008), rats were freely fed. A followup experiment was conducted in which naive rats were fed chow freely or periodically for 14 days: the usual line difference was obtained for freely fed groups [LoS 527 versus HiS 290; \( t(58) = 3.16 \)]; periodic feeding reduced LoS rats’ startle such that the lines did not differ (LoS 371 versus HiS 275, n.s.). This result comports with findings in several paradigms of greater sensitivity to feeding status in LoS rats, including modulation of methylphenidate effects (McLaughlin, Dess, & Chapman, 2011).

One other finding in Experiment 2 is noteworthy. The lines were differentially affected by naloxone [line × naloxone interaction, \( F(1, 56) = 4.07 \)]; contrasts showed that naloxone reduced startle in HiS rats (from a marginal mean of 395 to 270) but had no significant effect on LoS rats (respectively, 326 versus 381). This line difference was independent of glucose access. Little is known about neurochemical mediation of behavioral HiS/LoS line differences, and endogenous opioids merit further attention.

Glucose effects were not as robust as reported by others using the same parameters. Whereas Colantuoni et al. (2002) observed gross motor signs of withdrawal, we obtained evidence of subler effects within the LoS line using elevated startle as a measure. Hyperstartling is reasonably interpreted as a withdrawal symptom here, as in previous studies with ethanol (Dess et al., 2005), morphine (Mansbach, Gold, & Harris, 1992), and intermittent access to sugar solution (De Jonghe, Di Martino, Hajnal, & Covasa, 2005). The direct effect on startle of concurrent access to sugar solution (Martin-Iverson & Stevenson, 2005) or of conditioned signals for sugar (Schmid, Koch, & Schnitzler, 1995) is exactly the opposite – i.e., attenuation – as is typical of hedonically positive stimuli. Finally, there is no a priori reason other than dose-dependent withdrawal to expect a positive correlation between glucose intake and startle. In fact, if one were to presume that glucose intake is causally unrelated to startle, serving at most as a marker for startle-modulating processes, the best guess would be of a negative, not a positive, correlation (Chester et al., 2003; Dess et al., 2005).

The consistent pattern of correlations reported here therefore points to a line difference in mechanisms sensitive to glucose access that also modulate startle. Higher startle was associated uniquely with late-course glucose intake, only among LoS rats. This temporally dynamic relationship implies an impact of the glucose access regime, with more responsive individuals ultimately consuming more glucose and startling more during abstinence. Identification of opioid or non-opioid mechanisms responsible for the relationship between glucose intake and startle requires further experimental work, ideally with parameters that produce more robust effects without homogenizing groups. Any viable explanation, however, must include dispositional differences in the startle-enhancing potential of the periodic glucose regime. The present results motivate such work by providing prima facie evidence of dose-dependent withdrawal unique to rats vulnerable to it by virtue of breeding background.

High-fat food and ethanol

HiS rats drank more ethanol than LoS rats (right panel, Fig. 1), replicating earlier results (Dess et al., 1998). In contrast to Avena et al.’s (2004) finding that periodic access to one putatively addictive food (sugar) increased ethanol intake, period-fed rats drank less ethanol than controls. All groups drank more ethanol in the first test than in the second. Thus, this protocol yielded no evidence of cross-sensitization between high-fat food and ethanol. A line × feeding condition × test ANOVA yielded only main effects of line, feeding condition, and test, \( F(1, 27) = 15.47, 18.20, \) and 11.84, respectively.

Conclusion

These results provide two parallels with line differences observed for drugs of abuse. First, evidence of vulnerability to sugar withdrawal was obtained only in LoS rats. Similarly, LoS rats, but not HiS rats, show withdrawal by the same measure – elevated startle – after 14 days of ethanol intake (Dess et al., 2005). Whereas the ethanol regime produced a significant overall difference between LoS ethanol and control groups, glucose access did not. Rather, LoS rats’ startle varied systematically with prior glucose intake – a result resembling classic drug dose dependency. Whether the difference between findings with glucose and ethanol is attributable to the substances per se or to procedural differences is unclear. LoS rats’ sugar withdrawal may have been mitigated, for instance, by the line-specific attenuation of startle by periodic chow access demonstrated in the followup study. In any case, results for both sugar and ethanol point to LoS rats being more vulnerable to withdrawal.

Second, HiS rats consumed more sugar in the first hour of access (Experiments 1 and 2) and more cookie in 2 h (Experiment 3) than LoS rats. The latter finding complements Gosnell et al.’s (2010) report of differential responding for palatable solid reinforcers in LoS and HiS rats and shows that the difference obtains in homecage intake. HiS rats overconsume palatable substances and drugs with human abuse potential, including ethanol and cocaine (Carroll et al., 2008). However, overconsumption is not synonymous with dynamic recruitment of increasingly excessive, rapid consumption. If such recruitment is regarded as a hallmark of bingeing on drugs or food – and to the extent that it is appropriate to operationally define a consummatory pattern in rats as bingeing – HiS rats do not differ from LoS rats in proneness to binge eating. The evidence is stronger that HiS rats binge more on cocaine (faster acquisition, escalation), so their binging proneness may be more substance-specific (e.g. to intense, rapid onset incentives; Hughes, 2007) than is LoS rats’ withdrawal proneness. It does not follow from cyclic binge-withdrawal models that dispositional sources of variation in

**Fig. 1.** Mean intake (g/kg bodyweight) of high-fat foods and ethanol in Experiment 3. Arrows indicate when ethanol tests occurred.
binge-eating and withdrawal are the same (George & Koob, 2010). Moreover, binge-eating and withdrawal may not both contribute positively, or for the same reasons, to drug use (Robinson & Berridge, 2003). Thus, HiS rats being more prone to binge-eating and LoS rats being more prone to withdrawal would not be paradoxical.

The nature of addiction in general and food addiction in particular will remain controversial for some time. The present results contribute to the literature by demonstrating in a novel way parallels between the selective breeding approach and research with humans on the relationship between eating disorders and drug abuse (Fortuna, 2010; Gadalla & Piran, 2007).

Attention to the strengths and limitations of comparing species and of experimental models of complex phenomena such as drug addiction and eating disorders is, of course, essential (Olmstead, 2011). Judiciously studied, selectively bred rodents can advance understanding of the links between ingestive behavior, affect, and basic biobehavioral systems that can be co-opted by drugs of abuse (Gosnell & Levine, 2009). The LoS and HiS lines are available through the Rat Resource and Research Center (www.rrrc.us).

References