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Compared with DBA/2J mice, C57BL/6J mice demonstrate greater preference for saccharin and less avoidance of a cocaine-paired saccharin cue

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Abstract

Rats avoid intake of a saccharin cue when paired with a drug of abuse. While this is true for most subjects, the degree of avoidance of the drug-paired cue depends upon many factors including an individual rat's preference for rewards. That said, the direction of this effect is complex. For example, reward-preferring Lewis rats exhibit greater cocaine-induced avoidance of a saccharin cue relative to Fischer 344 rats; while reward-preferring mice that over express Δ FosB (NSE-tTA x TetOp- Δ FosB) exhibit less avoidance of the drug-paired taste cue compared to controls. The aim here was to use two strains of commonly used mice, C57BL/6J and DBA/2J, to determine whether known differences in sensitivity to rewards will facilitate or attenuate drug-induced suppression of intake of a drug-paired taste cue. The results of Experiment 1 demonstrate that C57BL/6J mice, compared with DBA/2J mice, exhibit attenuated suppression of saccharin intake when it is paired with cocaine. The results of Experiment 2 demonstrate that strain differences in impulsivity are not likely to account for these differences. It is proposed that, while the C57BL/6J mice typically are more responsive to drug, they also are more responsive to natural rewards (in this case saccharin), and the stronger preference for saccharin serves to militate against drug.

Keywords

addiction; drug abuse; impulsivity; natural rewards; reward comparison

Introduction

In our standard paradigm, two groups of rats receive access to a palatable saccharin cue for 5 minutes. Five minutes later, one group of rats receives an injection of saline while the other is injected with (or self-administers) a drug of abuse such as cocaine. There are a number of such taste-drug pairings and, over trials, the group that receives saline continues to drink saccharin while the group that receives cocaine comes to avoid intake of the taste cue (Grigson, 1997, 2008; Grigson & Twining, 2002). This suppressive effect has been demonstrated with all drugs of abuse tested (Cappell, LeBlanc, & Endrenyi, 1973; Castane, Soria, Ledent, Maldonado, & Valverde, 2006; Glowa, Shaw, & Riley, 1994; Lester, Nachman, & Le Magnen, 1970; Sherman, Pickman, Rice, Liebeskind, & Holman, 1980) and we have hypothesized that rats avoid intake of the taste cue, at least in part, because its relative value decreases when compared with the potent drug of abuse expected in the near future (Grigson, 1997, 2000, 2002, 2008; Grigson, Twining, Freet, Wheeler, & Geddes, 2009). In accordance, the suppressive effects of drugs of abuse have been aligned most closely with the suppressive effects of a highly rewarding sucrose solution as opposed to

that of the aversive illness-inducing agent, LiCl (Geddes, Han, Baldwin, Norgren, & Grigson, 2008; Grigson, 1997; Grigson & Freet, 2000; Grigson, Lyuboslavsky, & Tanase, 2000; Grigson, Lyuboslavsky, Tanase, & Wheeler, 1999).

Along with drug-induced devaluation of the sweet cue, recent evidence suggests that avoidance of the drug-paired cue also reflects the development of a conditioned aversive state involving, possibly, cue-induced withdrawal (see Grigson *et al.*, 2009). In support, avoidance of a drug-paired taste cue is associated with an elevation in circulating corticosterone (Gomez, Leo, & Grigson, 2000), blunted accumbens dopamine (Grigson & Hajnal, 2007; Wheeler *et al.*, 2011), naloxone-precipitated loss in body weight (Nyland & Grigson, 2013), and the onset of frank aversive taste reactivity following the intraoral delivery of the drug-paired cue (Wheeler *et al.*, 2008). Importantly, onset of this aversive conditioned state occurs, not merely because the cue predicts drug, but because the cue predicts that the rat will need to wait for drug (Wheeler *et al.*, 2011). As such, this paradigm serves as a potential animal model for the devaluation of natural rewards observed with drug use in humans (Goldstein *et al.*, 2006; Goldstein *et al.*, 2008; S.J. Wilson *et al.*, *in review*; S. J. Wilson, Sayette, Delgado, & Fiez, 2008) and as a model for the study of cue-induced craving and withdrawal.

Avoidance of the drug-paired taste cue is affected by many factors including the nature of the taste cue (Bevins, Delzer, & Bardo, 1996; Grigson, 1997), the need state of the animal (Gomez & Grigson, 1999; Grigson *et al.*, 1999), and by the perceived value of the taste cue and the drug reward (Grigson & Freet, 2000). Regarding the perceived value of the taste cue, for example, Lewis rats often are characterized as addiction-prone or reward-preferring compared with Fischer 344 rats. In accordance, Lewis rats demonstrate increased responsiveness to drugs of abuse in a number of measures including self-administration (George & Goldberg, 1989; Guitart *et al.*, 1993; Kosten *et al.*, 1997; Li & Lumeng, 1984; Suzuki, George, & Meisch, 1988), progressive ratio (Martin *et al.*, 1999), conditioned place preference (Guitart, Beitner-Johnson, Marby, Kosten, & Nestler, 1992; Horan, Smith, Gardner, Lepore, & Ashby, 1997; Kosten, Miserendino, Chi, & Nestler, 1994), and drug-induced reinstatement (Kruzich & Xi, 2006a, 2006b). This increased responsiveness for drug, which is likely the result of numerous strain differences in the neurochemistry of the mesolimbic dopamine system (Beitner-Johnson, Guitart, & Nestler, 1991; Guitart *et al.*, 1993; Haile, Hiroi, Nestler, & Kosten, 2001), also is accompanied by greater avoidance of a saccharin cue when paired with cocaine (Glowa *et al.*, 1994; Grigson & Freet, 2000). An opposite pattern has been found in Lewis and Fischer rats with morphine and heroin (Davis, Rice, & Riley, 2009; Freet, Wheeler, Leuenberger, Sublette, & Grigson, *in review*; Lancellotti, Bayer, Glowa, Houghtling, & Riley, 2001), but these effects appear to be related to differential sensitivity to agonist action at the kappa receptor (Freet *et al.*, *in review*; Liu & Grigson, 2005).

Although the majority of research evaluating drug-induced suppression of intake of a natural reward cue has been conducted in rats, similar suppressive effects have been observed in mice following taste-drug pairings (Castane *et al.*, 2006; Risinger & Boyce, 2002). Interestingly, in our hands, an increased preference for rewards in mouse strains is associated with reduced, rather than accentuated, avoidance of a drug-paired cue. For example, similar to Lewis rats, transgenic NSE-tTA x TetOp- Δ FosB mice with selective over expression of the transcription factor Δ FosB, demonstrate an increase in the perceived rewarding value of drugs of abuse (Nestler, Barrot, & Self, 2001; Nestler, Kelz, & Chen, 1999). However, unlike Lewis rats, cocaine-induced suppression of intake of a saccharin cue is attenuated compared with controls (Freet, Steffen, Nestler, & Grigson, 2009). These mice also exhibit an increased preference for sweets and for a running wheel (Freet *et al.*, 2009; Werme *et al.*, 2002). Thus, we have hypothesized that, a general increased preference for all

rewards in these mice, as opposed to a specific increased preference for drugs serves to attenuate the suppressive effect of the drug on intake of the saccharin cue. Interestingly, female Sprague-Dawley rats also are known to be more responsive to rewards (Fuchs, Evans, Mehta, Case, & See, 2005; Kippin *et al.*, 2005; Lynch & Taylor, 2004; Roth & Carroll, 2004) and they also exhibit attenuated drug-induced suppression of intake of a saccharin cue compared with male Sprague-Dawley rats (Cason & Grigson, *submitted*). Lewis rats' general preference for natural rewards is unclear (for example Christensen, Kohut, Handler, Silberberg, & Riley, 2009; Goodwin & Amit, 2000; Grigson & Freet, 2000; Werme *et al.*, 2002).

The aim of the current manuscript, then, is to evaluate two commonly used strains of mice with differential preference for rewards, C57BL/6J and DBA/2J mice, in the reward comparison paradigm. C57BL/6J mice demonstrate increased preference for many rewards compared with DBA/2J mice. For example, C57BL/6J mice demonstrate increased oral consumption of a number of drugs of abuse including alcohol (Belknap, Crabbe, & Young, 1993; Meliska, Bartke, McGlacken, & Jensen, 1995; Misra & Pandey, 2003), morphine (Berrettini, Alexander, Ferraro, & Vogel, 1994), and amphetamine (Meliska *et al.*, 1995). Similarly, C57BL/6J mice consume more of a natural reward such as saccharin or sucrose compared with a range of mouse strains (Bachmanov, Tordoff, & Beauchamp, 2001; Belknap *et al.*, 1992; Fuller, 1974; Lewis *et al.*, 2005). In addition, C57BL/6J mice also demonstrate greater conditioned place preference effects to morphine and cocaine (Orsini, Bonito-Oliva, Conversi, & Cabib, 2005) and greater cocaine self-administration compared with DBA/2J mice (Carney, Landrum, Cheng, & Seale, 1991; Kuzmin & Johansson, 2000). It is predicted that, even though C57BL/6J mice may have a greater preference for drug, an increased preference for natural rewards will work to attenuate drug-induced suppression when the gustatory cue is a natural reward. Experiment 1 was conducted to test this prediction.

Experiment 1. Saccharin-cocaine pairings in C57BL/6J & DBA/2J mice

The aim of Experiment 1 was to determine whether drug-induced suppression of intake of a saccharin cue in the reward preferring C57BL/6J mice aligned more closely with that observed in general rewarding preferring NSE-tTA x TetOp- Δ FosB mice (Freet *et al.*, 2009) or the drug-specific reward preferring Lewis rats (Grigson & Freet, 2000). That is, does the differential preference for rewards in C57BL/6J mice (compared with DBA/2J mice) result in an attenuation or facilitation of the suppressive effect of drugs of abuse on the intake of a natural reward cue? Experiment 1 was designed to address this question.

Methods

Subjects—Subjects were 29 naïve male C57BL/6J mice and 30 naïve DBA/2J mice obtained from Jackson Laboratories. Mice weighed between 17.9 and 27.5 grams (mean C57BL/6J: 24.0 grams; mean DBA/2J: 22.5 grams) at the beginning of the experiment. All subjects were housed individually in standard, clear plastic pan cages in a temperature-controlled (21 °C) animal care facility with a 12:12 hour light:dark cycle (lights on at 7:00 am) and all experimental manipulations were conducted 2 hours into the light phase of the cycle. Mice were maintained with free access to dry Harlan Teklad rodent diet (W) 8604 and water except where otherwise noted.

Apparatus—All experimental manipulations were conducted in the home cages. Modified serological pipettes (Fisher Scientific; 07-200-574) were used to provide dH₂O and saccharin access. Pipettes were converted to plastic cylinders by removing the tapered ends. A stainless steel spout (Girton Manufacturing Co., Inc.; ST300C) was then placed in the

bottom of the cylinder while a silicon stopper (Fisher Scientific; 09-704-1D) sealed the top of the cylinder. Intake of dH₂O and saccharin was recorded in 1/10 milliliters.

Procedure

Saccharin-cocaine pairings: All subjects were weighed once a day throughout the study. For baseline measurements, all mice were placed on a water restriction schedule which consisted of access to dH₂O for 1 hour in the morning and 2 hours in the afternoon. Baseline intake and body weight were recorded for 1 week. Mice remained on a water restriction schedule as described above for the duration of the study. On each taste-drug pairing (which occurred every 48 hours), all mice received 1 hour access to 0.15% saccharin (instead of dH₂O) followed by an i.p. injection of either saline (n=7, C57BL/6J; n=8, DBA/2J), 10 mg/kg cocaine (n=7, C57BL/6J; n=6, DBA/2J), 20 mg/kg cocaine (n=7, C57BL/6J; n=10, DBA/2J), or 30 mg/kg cocaine (n=8, C57BL/6J; n=6, DBA/2J). Taste-drug pairings occurred in the morning (2 hours into the light phase) for 5 trials. A sixth trial was conducted with CS only access (no injection). The saccharin solution was presented at room temperature and cocaine HCl was provided by the National Institute on Drug Abuse.

Two-bottle intake test: All mice were returned to ad lib water for four days following the last CS only trial. Mice were then water deprived overnight and tested for saccharin preference using a two-bottle intake test. All mice simultaneously received a bottle of 0.15% saccharin and a bottle of dH₂O for 1 hour. The left/right position of bottles was counter-balanced across groups.

Results

CS Intake—Intake was analyzed using a $2 \times 4 \times 6$ mixed factorial analyses of variance (ANOVA) varying strain (C57BL/6J or DBA/2J), drug (saline, 10, 20, or 30 mg/kg cocaine), and trials (1–6). Post hoc tests were conducted, where appropriate, using Newman-Keuls tests with $\alpha = .05$. Observation of Figure 1 shows that while DBA/2J mice demonstrate dose-dependent suppression of saccharin intake (right panel), suppression is significantly attenuated in the C57BL/6J mice (left panel). Support for this observation was provided by post hoc analysis of a significant strain $\times$ drug $\times$ trials interaction, $F(15,255)=2.21$, $p<.01$. Specifically, while cocaine was effective in reducing CS intake in DBA/2J mice at 10 mg/kg (Trial 6, $p<.02$), 20 mg/kg (Trials 4–6, $ps<.0001$), and 30 mg/kg (Trials 2–6, $ps<.0001$), C57BL/6J mice only suppressed intake of saccharin when paired with the 30 mg/kg dose of cocaine (Trials 4–6, $p<.05$). Although saccharin intake did not differ between the strains when paired with saline or 10 mg/kg cocaine ($ps>.05$), suppression of saccharin intake was greater in DBA/2J mice compared with C57BL/6J mice when the taste cue was paired with the 20 mg/kg (Trials 4 and 6, $ps<.02$) or 30 mg/kg (Trials 3–6, $ps<.001$) dose of cocaine. The main effects of strain, $F(1,51)=6.25$, $p<.02$, and drug, $F(3,51)=13.03$, $p<.0001$, also were significant.

Body weight—Body weight was analyzed using a $2 \times 4 \times 19$ mixed factorial analyses of variance (ANOVA) varying strain (C57BL/6J or DBA/2J), drug (saline, 10, 20, or 30 mg/kg cocaine), and trials (1–19). Drug exposure did not significantly alter body weight (data not shown). This conclusion was supported by a non-significant 3-way interaction, $F<1$, and main effect of drug, $F<1$. The main effect of trials was significant, $F(18,918)=52.42$, $p<.0001$, indicating that body weight increased over successive trials for all mice. The main effect of strain also was significant, $F(1,51)=7.38$, $p<.01$, confirming that C57BL/6J mice were significantly heavier than DBA/2J mice overall, (mean C57BL/6J: 24.5 g; mean DBA/2J: 22.9 g).

AM water intake—Morning intake of dH₂O (ml/hr) on the days between conditioning trials (Trials W1–W5) is presented in Figure 2 (top left and right panels). A $2 \times 4 \times 5$ mixed factorial ANOVA revealed that drug exposure did not significantly alter morning dH₂O intake as a function of strain as indicated by a non-significant strain $\times$ drug $\times$ trials interaction, $F(12,204)=1.18$, $p=.30$. In addition, the main effect of strain was not statistically significant, $F(1,51)=2.17$, $p=.15$. The main effects of drug, $F(5,51)=2.94$, $p<.05$, and trials, $F(4,204)=9.05$, $p<.001$, however, were statistically significant. Post hoc test on the main effect of drug revealed that, overall, morning water intake was dose-dependently reduced between conditioning trials, $ps < .05$. As evidenced by the figure, this effect was carried by the DBA/2J mice, suggesting a degree of non-specific suppression of intake in this strain.

PM water intake—Intake of dH₂O for the 2 hour access period in the afternoon for all trials is presented in Figure 2 (bottom left and right panels). Although a $2 \times 4 \times 9$ mixed factorial ANOVA did not reveal a significant 3-way interaction, $F<1$, the main effects of strain, $F(1,51)=36.82$, $p<.001$, drug, $F(3,51)=4.25$, $p<.01$, and trial, $F(8,408)=10.08$, $p<.001$, as well as interactions between strain $\times$ drug, $F(3,51)=2.86$, $p<.05$, strain $\times$ trials, $F(8,24)=2.12$, $p<.03$, and drug $\times$ trials, $F(8,24)=1.62$, $p<.03$, did attain statistical significance. The significant main effect of strain shows that the DBA/2J mice drank more water during the afternoon session than did the C57BL/6J mice overall. Further, the significant main effect of drug suggests that afternoon water intake is increased to compensate for lower intake in the drug-treated groups. Again, this effect appears to be carried largely by the behavior of the DBA/2J mice.

Two-bottle intake test—The results of the two-bottle intake test for saccharin against dH₂O in C57BL/6J and DBA/2J mice are presented in Figure 3. Preference for saccharin was analyzed using t-tests with $\alpha = .05$ for each cell. C57BL/6J mice (left panel) significantly preferred saccharin over dH₂O ($ps<.05$), with the exception of the group with a history of saccharin pairings with the 30 mg/kg dose of cocaine ($p>.05$). In contrast, DBA/2J mice did not demonstrate a significant preference for saccharin in the saline and 10 mg/kg cocaine groups ($ps>.05$). In addition, DBA/2J mice preferred dH₂O over saccharin in the 20 mg/kg and 30 mg/kg cocaine groups ($ps<.05$). The data also were analyzed using a $2 \times 4 \times 2$ strain $\times$ drug $\times$ solution ANOVA; results were identical to that found with the t-test analysis, with the exception that intake of water vs. saccharin did not differ significantly for the C57BL/6J with a history of saccharin-20 mg/kg cocaine pairings ($p=.07$). The advantage of the two-bottle test over the one-bottle test is that the two-bottle test provides a ready water alternative, thereby reducing the impact of need state on the data. Regardless, the results here show, unequivocally, that the “more reward-preferring” C57BL/6J mice exhibited less avoidance of a cocaine-paired saccharin cue than did the “less reward-sensitive” DBA/2J mice. Importantly, the C57BL/6J mice also exhibited a greater preference for saccharin than did the DBA/2J mice, as evidenced by the 2-bottle intake data in the saline treated subjects. Finally, it should be noted that this two-bottle intake data reflects saccharin preference in these strains in saccharin experienced, not saccharin naïve, rats. DBA/2J mice have been found to exhibit a preference for saccharin over water, albeit smaller than that of C57BL/6J mice, when tested naïve using longer 24 h tests (Belknap et al., 1992; Fuller, 1974).

Experiment 2. Impulsivity in C57BL/6J & DBA/2J mice

The results in Experiment 1 demonstrated that cocaine-induced suppression of saccharin intake in C57BL/6J mice is attenuated compared with that observed in DBA/2J mice. This finding is consistent with the hypothesis that an increased preference for natural rewards in C57BL/6J mice (e.g., as evidenced for saccharin in Figure 3) may work against the suppressive effects of cocaine, resulting in less cocaine-induced suppression of saccharin intake compared with DBA/2J mice. However, an alternative explanation exists for the data

in Experiment 1 involving strain differences in impulsivity. That is, if C57BL/6J mice are generally more impulsive than DBA/2J mice, then the C57BL/6J mice may have greater difficulty suppressing intake of a gustatory cue in general, regardless of the level of preference for the cue.

Ainslie (1975) recognized two types of impulsivity: impulsivity in which consequences of a decision to obey an impulse were ignored and “true impulsivity” in which the consequences were recognized. This latter type of impulsivity has been further divided into motor impulsivity, akin to hyperactivity in which evaluation of the decision outcome is normal but overridden by a motor response, and cognitive impulsivity, in which evaluation of the decision outcome itself is affected (Brunner & Hen, 1997). Cognitive impulsivity may contribute to the data obtained in Experiment 1. It is characterized by “... an inability to wait or to consider future events and thus has the time dimension in a pivotal place” (Brunner & Hen, 1997). Although some evidence suggests against this possibility in C57BL/6J mice (Helms, Reeves, & Mitchell, 2006), Experiment 2 tested this hypothesis. The delay discounting model often is used to evaluate cognitive impulsivity, specifically impulsive choice, in rodents (Bruno *et al.*, 2007; Isles, Humby, Walters, & Wilkinson, 2004; Isles, Humby, & Wilkinson, 2003; Pine *et al.*, 2009; Wilhelm & Mitchell, 2009). Thus, naïve C57BL/6J and DBA/2J mice were evaluated for impulsive choice using a delay discounting procedure in which they were allowed to choose between immediately available dH₂O or more preferred, but increasingly delayed (0, 2, 4, 6, 8, 12 seconds) 0.15% saccharin. If C57BL/6J mice can be shown to be similarly or less impulsive than DBA/2J mice in this paradigm, then impulsivity as a possible confound can be reasonably excluded from the interpretation of the data obtained in Experiment 1.

Methods

Subjects—The subjects were 15 naïve male C57BL/6J mice and 15 naïve male DBA/2J mice obtained from Jackson Laboratories. Mice weighed between 21.0 and 28.2 grams (mean C57BL/6J: 24.6 grams; mean DBA/2J: 23.2 grams) at the beginning of the experiment. All subjects were housed individually in standard, clear plastic pan cages in a temperature-controlled (21 °C) animal care facility with a 12:12 h light:dark cycle (lights on at 7:00 am) and all experimental manipulations were conducted 1 h into the light phase of the cycle. Mice were maintained with free access to dry Harlan Teklad rodent diet (W) 8604.

Apparatus—Mice were trained and tested in one of four identical modular operant chambers (MED Associates, Inc., St. Albans, VT) measuring 30.5 × 24.0 × 29.0 cm (length x width x height). All chambers had clear Plexiglas top, front, and back walls with aluminum side walls. Grid floors consisted of nineteen 4.8-mm stainless steel rods spaced 1.6-cm apart (center to center). Each chamber was equipped with three retractable sipper tubes that could enter the chamber through 1.3-cm diameter holes spaced 16.4-cm apart (center to center). A lickometer circuit was used to monitor licking and a shaded bulb, which reflected light off the ceiling, was located to the right of the cage, opposite the sipper tubes. Each chamber was housed in a light and sound attenuated cubicle that was fitted with a ventilation fan and a white noise source that provided a background noise level of 75 dB(A). Control of events in the chamber and collection of the data were carried out on-line via computer. Programs were written in the Medstate notation language (MED Associates, Inc.).

Procedure—All subjects were weighed once a day throughout the study a half hour before experimental manipulations. For baseline measurements, all mice were placed on a water deprivation schedule which consisted of access to dH₂O for 1 hour in the morning and 2 hours in the afternoon. Baseline intake and body weight were recorded for 1 week.

Training: Each subject was taken from the home cage and placed in the modular chamber. Immediately after starting the session, a bottle containing 0.15% saccharin advanced and a corresponding cue light was turned on. Following completion of a 3-lick requirement (FR3), the saccharin bottle retracted and both the saccharin bottle and another bottle containing dH₂O advanced. The position of the saccharin and dH₂O bottles was counter-balanced across and within groups. During simultaneous presentation of the bottles, each subject could choose to lick either the 0.15% saccharin bottle or the dH₂O bottle. Choice of a particular bottle was defined by completion of an FR20 requirement on that bottle. Once a choice was established, the other bottle retracted and the subject was allowed an additional 5 seconds access to the chosen bottle. The chosen bottle then retracted and, following a 60 second intertrial interval, the procedure repeated for a total of 6 trials a day. After each daily session, the subject was removed from the box and placed back in the home cage. All mice received 2 hour access to dH₂O in the home cage each day 1 hour after training. All mice received 5 days of training (Days 1–5).

Impulsivity Testing: Impulsivity testing was identical to training sessions with the exception of increasing delays in the advancement of the saccharin bottle during the choice phase of each trial. Immediately upon completion of the FR3 requirement on the saccharin bottle, both bottles retracted and the dH₂O bottle immediately advanced into chamber. Advancement of the 0.15% saccharin bottle was delayed depending on the interval indicated by the test day. Each delay was tested for 3 consecutive days. Consequently, advancement of the 0.15% saccharin bottle was delayed for 2 seconds on days 6–8, 4 seconds on days 9–11, 6 seconds on days 12–14, 8 seconds on days 15–17, and 12 seconds on days 18–20. As such, mice had a choice between an immediately available, less preferred water reward and a more preferred, but increasingly delayed, saccharin reward.

Results

Intake—The results of impulsivity testing in C57BL/6J and DBA/2J mice are presented in Figure 4. Intake of 0.15% saccharin and dH₂O was analyzed using a $2 \times 2 \times 20$ repeated measures ANOVA varying strain (C57BL/6J or DBA/2J), solution (saccharin or dH₂O), and trials (1–20). Newman-Keuls post hoc analysis of a significant strain $\times$ solution $\times$ trials interaction, $F(19,1064)=5.30$, $p<0.0001$, indicated that, in the C57BL/6J mice, intake of 0.15% saccharin was significantly greater than dH₂O intake for days 1–13, $ps<0.0001$, when the delay was 6 sec or less. There was no significant difference between saccharin and dH₂O intake for days 14–16, $ps>0.09$, when the delay was between 6 and 8 sec, and dH₂O intake was significantly greater than saccharin intake for days 17–20, $ps<0.002$, when the delay was increased from 8 to 12 sec. In the DBA/2J mice, saccharin intake was significantly greater than dH₂O intake for days 1–5 and 7, $ps<0.04$, when the delay was 2 sec or less. Saccharin and dH₂O intake were not significantly different for days 6, 8–12, $ps>0.34$, when the delay was between 2 and 6 sec, and dH₂O intake was significantly greater than saccharin intake for days 13–20, $ps<0.001$, when the delay was between 6 and 12 sec. In sum, the C57BL/6J mice were less impulsive than were the DBA/2J mice and were, as such, more willing to wait for access to the sweet. Whether the increased impulsivity in DBA/2J mice was a function of a reduced preference for saccharin, an innate increased sensitivity to delay, or elements of both cannot be readily determined with the data at hand. However, the data for 0 sec delay do provide additional independent evidence that DBA/2J mice can readily detect this saccharin solution, can discriminate it from water, prefer it if presented with a zero second delay, but consume it about equal to water if having to wait even 2 sec for access. The C57BL/6J mice, on the other hand, detect the saccharin solution, can discriminate saccharin from water, and greatly prefer saccharin relative to the DBA/2J mice, even when having to wait as long as 6 sec for access to the preferred stimulus.

Body weight—Body weight was analyzed using a 2×20 repeated measures analyses of variance (ANOVA) varying strain (C57BL/6J or DBA/2J) and trials (1–20). Body weight over trials (data not shown) did not significantly differ between strains as indicated by a non-significant 2-way interaction, $F < 1$. However, the main effects of trial, $F(19, 513) = 42.74$, $p < .0001$, and strain, $F(1, 27) = 11.24$, $p < .002$, were significant confirming that body weight increased over successive trials for all mice and that C57BL/6J mice were significantly heavier than DBA/2J mice overall, (mean C57BL/6J: 25.7 g; mean DBA/2J: 24.2 g).

General Discussion

The data from Experiment 1 demonstrate that C57BL/6J mice, compared with DBA/2J mice, exhibit attenuated suppression of intake of a saccharin cue when it is paired with cocaine (Figure 1). In addition, despite suppressing intake of the saccharin cue, albeit to a lesser degree, C57BL/6J mice still demonstrate a robust preference or equal preference for the same saccharin solution when presented subsequently with dH₂O in a two-bottle intake test. Conversely, DBA/2J mice exhibit no preference or preference for dH₂O following taste-drug pairings (Figure 3). Finally, the attenuated suppression observed in C57BL/6J mice in Experiment 1 is unlikely due to greater impulsivity in this mouse strain as the data from Experiment 2 demonstrate greater impulsivity in a delay discounting task in DBA/2J vs. C57BL/6J mice (Figure 4).

Investigations into the effect of innate, elevated preference for rewards (or experimental manipulations that elevate reward preference) on drug-induced suppression of intake of a natural reward has produced seemingly contradictory findings in the literature. Initial evaluations focused on selective rat strains with differential preference for rewards, specifically Lewis vs. Fischer rats. Lewis rats, with their innate preference for drugs of abuse compared with Fischer rats, demonstrate greater avoidance of a reward cue that has been paired with cocaine (Glowa *et al.*, 1994; Grigson & Freet, 2000) and we attributed this differential suppression to the increased preference for the drug. This logic has been reinforced by similar studies in Sprague-Dawley rats. For example, Sprague-Dawley rats with a history of chronic morphine exposure (which interestingly demonstrate many of the neurochemical features in the mesolimbic dopamine system found innately in Lewis rats; Nestler, 1992) also demonstrate increased avoidance of a saccharin cue that has been paired with cocaine compared with Sprague-Dawley rats with a history of chronic saline exposure (Grigson, Wheeler, Wheeler, & Ballard, 2001).

More recent investigations, however, have suggested that preference for the drug itself is not the only influential factor governing drug-induced suppression of CS intake. For example, although NSE-tTA x TetOp-ΔFosB mice demonstrate increased preference for drug (Nestler *et al.*, 2001; Nestler *et al.*, 1999) compared with their controls, drug-induced suppression of intake of a saccharin cue is in the opposite direction (i.e., it is attenuated rather than facilitated in these ΔFosB over expressing mice) (Freet *et al.*, 2009). Similar results were observed here for C57BL/6J mice compared with DBA/2J mice in Experiment 1 of the current manuscript. Finally, as mentioned, female Sprague-Dawley rats that demonstrate an increased responsiveness for drugs of abuse as evidenced by greater conditioned place preference (Zakharova, Wade, & Izenwasser, 2009), higher operant responding for cocaine (Fuchs *et al.*, 2005; Kippin *et al.*, 2005), greater cocaine intake during extended access (Lynch & Taylor, 2004; Roth & Carroll, 2004), and higher breakpoints on progressive ratio schedules (Carroll, Morgan, Lynch, Campbell, & Dess, 2002; Hecht, Spear, & Spear, 1999), also demonstrate attenuated suppression of intake of a cocaine-paired saccharin cue compared with male Sprague-Dawley rats (Cason & Grigson, *submitted*). Moreover, when cued by a sweet, these female rats self-administer less, not more, drug than their male

counterparts. Thus, when taken together, the data suggest that additional factors are involved in, and ultimately influence, avoidance of a drug-paired taste cue.

One possible factor is the perceived rewarding value of the cue itself. It is known that alternative rewards such as environmental enrichment or exposure to a sweet (such as sucrose or saccharin) can influence a number of drug-related behaviors including acquisition and maintenance of drug self-administration behavior (Carroll, 1985; Carroll & Lac, 1993; Carroll, Lac, & Nygaard, 1989; Comer, Lac, Wyvell, & Carroll, 1996; Lenoir, Serre, Cantin, & Ahmed, 2007; Puhl, Blum, Acosta-Torres, & Grigson, 2012; Specker, Lac, & Carroll, 1994), tolerance (D'Anci, 1999), and withdrawal (Jain, Mukherjee, & Singh, 2004). In addition, it also is known that the nature and intensity of the cue can affect the degree of suppression of intake of that cue (Gomez & Grigson, 1999; Grigson, 1997). Such data suggest an active role for the cue in taste-drug pairings and that the ability of the drug to induce suppression of CS intake in C57BL/6J mice in Experiment 1 (Figure 1), although not eliminated, may have been reduced as a function of their relative preference for saccharin. That is, greater preference for the cue in C57BL/6J mice worked against suppression of intake of that cue by the impending availability of the drug.

Why then doesn't the rewarding value of the cue always attenuate suppression induced by drugs of abuse? Specifically, why do we see facilitated suppression under some conditions and attenuated suppression under others? First, it should be recognized that additional strain specific differences may influence suppression and such possible confounds, if present, need to be incorporated into interpretation of the data. For example, and as mentioned above, Fischer rats exhibit greater avoidance of a morphine-paired saccharin cue than do Lewis rats, likely because of an increase in sensitivity to aversive kappa agonist stimulation (Freet *et al.*, *in review*). Second, while holding some of these factors more constant, one also must consider the state of the animal. In this regard, one possibility for the observed difference (i.e., attenuation versus facilitation) in models of elevated reward preference relates to differences in the state of drug use/exposure (i.e., controlled vs. compulsive). Differences in drug availability in laboratory animals (e.g. short access versus long access) have been shown to produce different states of drug use. For example, short access (< 3 hours/daily) produces stable, controlled drug use whereas extended, longer access (> 3 hours/daily) results in a pattern of escalating, compulsive drug use that is characteristic of drug addiction (for review, see Ahmed, 2005). Extended access to drugs has been shown in rats to produce greater self-administration, motivation for drug, drug seeking behavior during extinction, and drug-induced reinstatement compared with short access (Ahmed & Koob, 1998, 1999; Ahmed, Walker, & Koob, 2000; Mantsch, Yuferov, Mathieu-Kia, Ho, & Kreek, 2004; Paterson & Markou, 2003; Vanderschuren & Everitt, 2004). In addition, rats with extended access to cocaine are less sensitive to cues associated with footshock during drug extinction (Vanderschuren & Everitt, 2004). Based on the extended access data, it is possible that increases in sensitivity to alternative rewards may be able to attenuate drug-induced suppression of CS intake in the controlled state of drug use but this effect can be overridden, resulting in facilitation, in the compulsive drug state.

The taste-drug pairings conducted in C57BL/6J and DBA/2J mice in the current manuscript and in NSE-tTA x TetOp-ΔFosB mice (Freet *et al.*, 2009), as well as the data in female rats (Cason and Grigson, *manuscript submitted*), used a short access period to the drug (passive i.p. injection or 1 hour self-administration). As such, we might speculate that the subjects in these experiments are in the controlled state of drug use and may be sensitive to the presence of a non-drug reward (i.e., attenuated drug-induced suppression of CS intake). Conversely, although the Lewis rats, as well as the chronic morphine treated Sprague-Dawley rats (Grigson & Freet, 2000; Grigson *et al.*, 2001), received similar short access to drug during testing, there is reason to believe that these rats may be more like rats in the compulsive

drug state. Specifically, rats in the Grigson et al. (2001) study received chronic morphine treatment via subcutaneous pellet implantation for 5 days prior to saccharin-cocaine pairings. This route of administration provided continuous, cumulative exposure to morphine (75 mg/day) 24 hours/day for 5 days and could have produced a state more similar to compulsive than controlled drug use in which the rats then were tested. Similarly, Lewis rats have numerous neurochemical and neuroanatomical adaptations in the drug-naïve state that parallel those in animals with a history of chronic drug exposure (Beitner-Johnson *et al.*, 1991; Guitart *et al.*, 1993; Haile *et al.*, 2001). As such, naïve Lewis rats may serve as a model for, and respond similarly to, rats in a compulsive drug state. Of course, at this point in time, such a hypothesis is speculative but testable.

In conclusion, Experiment 1 demonstrated attenuated cocaine-induced suppression of intake of a saccharin cue in C57BL/6J mice compared with DBA/2J mice. This effect parallels suppression between male and female Sprague-Dawley rats and NSE-tTA x TetOp-ΔFosB mice and their controls, but is opposite to that observed in Lewis and Fischer rats (at least with cocaine) and Sprague-Dawley rats with history of chronic exposure to either morphine vs. saline. Experiment 2 demonstrated that this attenuated effect is likely not due to impulsivity as DBA/2J mice were found more impulsive than C57BL/6J mice in a delay discounting task. Given the greater preference for saccharin exhibited by the C57BL/6J mice, these data, as well as other examples in the literature, support the hypothesis that elevated preference for a non-drug reward cue may minimize suppression of intake of that cue by a drug of abuse. Drugs, then, can devalue natural rewards and natural rewards can, in turn, devalue drugs of abuse and/or militate against the impact of their potential addictive properties. Comparison, then, is a bidirectional, cross-modal phenomenon and the direction and the magnitude of the effect may, at base, be influenced by the drug state of the animal (i.e., controlled vs compulsive). Future studies will test the merits of this hypothesis.

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Experiment 1: Saccharin-Cocaine Pairings

Figure 1.

Mean ($\pm$ SEM) intake (ml/hr) of 0.15% saccharin paired with saline (open squares) or cocaine (10 mg/kg: closed circles, 20 mg/kg: closed triangles, 30 mg/kg: closed squares) in C57BL/6J (left panel) and DBA/2J (right panel) mice. Asterisks indicate significant difference compared with controls, $p < .05$.

Experiment 1: Water Intake

Figure 2.

Mean ($\pm$ SEM) intake of dH₂O in the AM (ml/hr) on trials between test trials (W1–W5, top panels) and in the PM (ml/2hr) for all trials (bottom panels) in C57BL/6J and DBA/2J mice in the saline groups (open squares) or cocaine groups (10 mg/kg: closed circles, 20 mg/kg: closed triangles, 30 mg/kg: closed squares).

Experiment 1: Two-Bottle Intake Test (following saccharin-cocaine pairings)

Figure 3.

Mean ($\pm$ SEM) intake (ml/hr) of simultaneously presented 0.15% saccharin and dH₂O 5 days after the final test trial. Asterisks indicate significant difference between saccharin and dH₂O intake, $p < .05$. C57BL/6J mice demonstrated greater preference for saccharin compared with DBA/2J mice.

Figure 4.

Mean ($\pm$ SEM) intake (licks/session) in a delayed discounting task with immediately available dH₂O and increasingly delayed 0.15% saccharin (0, 2, 4, 6, 8, and 12 sec) in C57BL/6J (top panel) and DBA/2J (bottom panel) mice. Asterisks indicate significant difference between saccharin and dH₂O intake, $p < .05$.