The effects of haloperidol on cocaine-induced conditioned taste aversions

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Although the mechanism underlying the rewarding effects of cocaine has been well characterized, little is known about the mechanism underlying its aversive effects. Several reports have indicated a possible role of dopamine (DA) in the aversive effects; however, several procedural issues limit any conclusions regarding its specific role. In order to investigate a possible dopaminergic role in cocaine-induced CTAs using procedures that circumvented these possible issues, the present series of investigations assessed the aversive effects of the DA antagonist haloperidol alone (Experiment 1) and in combination with cocaine (Experiment 2). Haloperidol, at doses that were determined to be non-aversive, yet behaviorally active in a locomotor assessment, attenuated cocaine-induced taste aversions, suggesting that cocaine’s aversive effects are mediated in part by dopaminergic activity. These findings were discussed in consideration with other evidence implicating DA and other neurotransmitter systems in cocaine-induced CTAs.

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1. General introduction

Cocaine, like other drugs of abuse, has been shown to have both rewarding [1–3] and aversive [4–6] effects with the balance of these effects determining its abuse potential [see 7–9]. The rewarding effects of cocaine are well characterized and appear to be mediated by its inhibition of the dopamine transporter [10–13]. The mechanism underlying its aversive effects is less understood, although dopamine (DA) has been implicated here as well. The evidence for a role of DA in cocaine’s aversive effects comes from a variety of sources. By virtue of its ability to block the reuptake of DA, cocaine results in an increase in synaptic DA levels. It is interesting in this context that a variety of DA agonists (e.g., SKF38393, quinpirole) induce conditioned taste aversions (CTAs) on their own [14]. Further, other compounds that increase DA levels, e.g., amphetamine, induce taste aversions that are blocked by the DA antagonist pimozide [see 15].

The results from direct assessments of the role of DA in cocaine’s aversive effects, however, have been somewhat equivocal [see 16,17]. For example, Gale [17] attempted to block cocaine-induced taste aversions by the dopamine antagonist pimozide. In this report, rats were given a novel saccharin solution to drink followed by an injection of cocaine. A subset of these subjects was injected with either pimozide (1 mg/kg, intraperitoneal; IP) or saline after saccharin but prior to cocaine. Animals injected with saline prior to cocaine acquired a robust aversion to the saccharine-associated solution. Interestingly, animals injected with pimozide prior to cocaine did not differ from those treated with saline, i.e., pimozide had no effect on the acquisition of the cocaine-induced aversions, although it has been reported to be behaviorally active for up to 24 h and clearly overlapped the effects of cocaine (see [18]). These results suggest that DA is not involved in cocaine’s aversive effects; however, the dose of cocaine used during conditioning was very large [160 mg/kg; see 5,19] and delivered in a single bolus subcutaneously at a high concentration (400 mg/ml). The large dose coupled with the high concentration may have resulted in a prolonged drug effect that was responsible for the near complete suppression of consumption (a mean of 80% suppression) after only two conditioning trials [see 20,21 for a discussion on the relation of duration of drug effects and CTAs; though see 22]. Under such conditions, it is likely that some animals displayed complete suppression. Although cocaine may have been acting through DA, the antagonist effects of pimozide may have been masked by such a large drug effect. Further, only a single dose of cocaine was administered in the Gale report, precluding identification of doses that produced intermediate suppression possibly more subject to modulation by pimozide.

Hunt and colleagues [16] also assessed the effects of pimozide on cocaine-induced taste aversions, but reported that such aversions were attenuated by the DA antagonist. In their design, animals were injected with 1 mg/kg pimozide (IP) prior to saccharin access which was subsequently followed by four spaced IP injections of cocaine (9 mg/kg; every 15 min) or saline, a procedure reported to extend the duration of action of cocaine (see [23]). As noted, pimozide attenuated the cocaine-induced taste aversion. Although suggestive of a role for DA in cocaine’s aversive effects, under this procedure pimozide unconditionally suppressed saccharin consumption prior to the pairing of saccharin with cocaine, introducing a potential confound of amount consumed as a factor in the...
differential acquisition of aversions [compare to saline-pretreated subjects who drank at high levels at the outset of conditioning; see 24,25, but see also 26, see 27 for a discussion]. Further, pimozide may have affected sensory processes that could have impacted the acquisition of the aversion independent of any antagonism of cocaine’s specific aversive effects [28–30].

The present studies attempted to address the role of DA in the aversive effects of cocaine directly by examining the effects of the DA antagonist haloperidol on cocaine-induced taste aversions using procedures that circumvented the abovementioned possible effect of near maximal suppression [17] and the intrusion of any possible confounds of the DA antagonist [16]. Given that haloperidol, although typically referred to as a D2 antagonist, is a nonspecific DA antagonist with binding affinity for several other DA receptor subtypes, including D1, D3, D4 and D5 [see 34], this assessment should provide an initial investigation of DA’s involvement (if any) in this phenomenon.

2. General methods

2.2. Method

2.2.1. Apparatus

All subjects were individually housed in hanging wire-mesh cages on the front of which graduated Nalgene tubes could be placed for fluid presentation. Subjects were maintained on a 12:12 light–dark cycle (lights on at 0800 h) and at an ambient temperature of 23 °C. Except where noted, food and water were available ad libitum. Locomotor assessments were conducted using a three-chamber automated apparatus (San Diego Instruments Place Preference system, San Diego, CA) modified to assess locomotor activity. Specifically, all flooring and panels were identical such that the three-chamber apparatus was converted to an open field apparatus 70 cm wide × 21 cm deep × 34.5 cm high. White LED lights provided constant illumination throughout the apparatus. A total of eight identical apparatuses were used. Each apparatus featured photobeam arrays for recording gross locomotor activity (consecutive beam breaks) and fine motor activity (repeated breaks of the same beam). The room in which the locomotor assessments were made was illuminated by an 85-watt red light mounted to the ceiling in the center of the room, and background noise was masked by a white noise generator located in the front of the room.

2.2.2. Subjects

The subjects were 92 experimentally naïve, male Sprague–Dawley rats (Harlan Sprague–Dawley, Indianapolis, Indiana) approximately 75 days old and between 250 and 350 g at the start of the experiment. Procedures recommended by the National Institutes of Health Guide for the Care and Use of Laboratory Animals (1985) the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (2003) and the Institutional Animal Care and Use Committee at American University were followed at all times. Animals were handled daily approximately 2 weeks prior to the initiation of the study to limit the effects of handling stress during conditioning and testing.

2.2.3. Drugs and solutions

Haloperidol (VWR) was prepared in acetic acid (0.4% of total volume) then added to distilled water and brought to a pH of approximately 5 at a concentration of 1 mg/ml. Cocaine hydrochloride (generously provided by the National Institute on Drug Abuse) was dissolved in distilled water at a concentration of 10 mg/ml and administered subcutaneously (SC). Cocaine doses are expressed as the salt. Saccharin (sodium saccharin, Sigma) was prepared as a 1 g/l (0.1%) solution in tap water.

2.2.4. Procedure

2.2.4.1. Habituation. Following 24 h water deprivation, subjects were given 20-min access to tap water daily. This daily access was repeated until consumption stabilized, i.e., subjects approached and drank from the tube within 2 s of its presentation and water consumption was within 2 ml of the previous day for a minimum of 4 consecutive days with no consistent increase or decrease. Throughout the study, fluid was presented in graduated 50-ml Nalgene tubes and measured to the nearest 0.5 ml by subtracting the difference between the pre- and post-consumption volumes.

2.2.4.2. Conditioning. Conditioning began 4 days following the final habituation session. On Day 1 of conditioning, all subjects were given 20-min access to the novel saccharin solution. Immediately following this presentation, animals were ranked based on saccharin consumption and assigned to treatment groups (n = 8/9 per group), such that overall consumption was comparable among groups.

2.2.4.2.1. Experiment 1. Following habituation and initial saccharin exposure, 32 subjects were assigned as described above into four groups and were injected intraperitoneally (IP) with 0, 0.25, 0.50 and 1.0 mg/kg haloperidol, yielding Groups 0, 0.25, 0.50 and 1.0. The vehicle group (Group 0) was matched in volume to the group receiving the high dose of haloperidol (Group 1.0). The 3 days following this initial saccharin presentation were water-recovery days during which animals were given 20-min access to tap water (no injections followed this access). This alternating procedure of conditioning and water recovery was repeated for a total of four complete cycles. Following the last water-recovery session after the fourth conditioning trial, animals were given 20-min access to saccharin in a final aversion test. No injections followed this access. Following this test, subjects were maintained on 20-min access to water for 2 weeks during which time no saccharin or injections were given. This period was introduced to limit any residual effects of haloperidol. After this period, subjects were administered a vehicle injection (IP: matched in volume to the dose of haloperidol with which they were initially conditioned) and placed into locomotor chambers for 60 min (baseline). The following day, subjects were administered an IP injection of haloperidol or vehicle (matched to the dose given during conditioning) and placed back into the locomotor chambers for 60 min (test).

2.2.4.2.2. Experiment 2. Following habituation and initial saccharin exposure, 60 subjects were ranked based on consumption and injected with 1.0 mg/kg haloperidol or vehicle (matched in volume to 1.0 mg/kg haloperidol). Approximately 30 min after haloperidol or vehicle injections, subjects were given a SC injection of cocaine (10, 18 or 32 mg/kg) or vehicle (matched in volume to 32 mg/kg cocaine), yielding eight experimental groups, specifically, vehicle–vehicle (V0; n = 7), vehicle–10 mg/kg cocaine (V10; n = 7), vehicle–18 mg/kg cocaine (V18; n = 7), vehicle–32 mg/kg cocaine (V32; n = 7), haloperidol–vehicle (H0 n = 8), haloperidol–10 mg/kg cocaine (H10; n = 8), haloperidol–18 mg/kg cocaine (H18; n = 8) and haloperidol–32 mg/kg cocaine (H32; n = 8). The 3 days following this initial saccharin presentation were water-recovery days, during which animals were given 20-min access to tap water (no injections followed this access). This alternating procedure of conditioning and water recovery was repeated for a total of four complete cycles. Following the last water-recovery session after the fourth conditioning trial, animals were given 20-min access to saccharin in a final aversion test. Again, no injections followed this access.

2.2.5. Statistical analysis

For Experiment 1 (haloperidol dose-response assessment), the differences in mean saccharin consumption during conditioning were analyzed using a 4 × 5 mixed ANOVA with the between-subjects variable of Group (0, 0.25, 0.50 and 1.0 mg/kg) and the within-subjects variable of Trial (1–5). Fine and gross motor activity were combined into a single measure of total activity and collapsed across all four intervals. A 2 × 4 repeated measures ANOVA was then
used to investigate differences in total activity with the between-subjects variable of Group (0, 0.25, 0.50 and 1.0 mg/kg) and the within-subjects variable of Day (baseline or test). One way ANOVAs were used to investigate the differences between doses during the baseline and test day. Differences in mean saccharin consumption during conditioning for Experiment 2 were analyzed using a 2 × 4 × 5 mixed ANOVA with the between subjects variables of Pretreatment Drug (vehicle or 1.0 mg/kg haloperidol) and Conditioning Drug (0, 10, 18, or 32 mg/kg cocaine) and the within-subjects variable of Trial (1–5). Significant interactions were investigated using Tukey post-hoc analysis to determine specific group differences where appropriate. All significance levels were set at \( p \leq 0.05 \).

3. Experiment 1

3.1. Introduction

When using pharmacological antagonists to assess mechanism in the CTA design, it is important to consider the possibility that administration of the antagonist prior to saccharin and cocaine could impact behavior, sensory and/or learning processes involved in CTA acquisition that might limit any conclusions regarding the ability of the antagonist to affect the drug’s aversive effects [see above; 16]. One way to control for this is to administer the antagonist after saccharin, rather than before. This method has been used in other assessments of the role of specific neurotransmitter systems in a variety of drug-induced taste aversions [see 31–34], including those induced by cocaine [35]. One concern with this specific procedure is that if the antagonist itself induces aversions, any interpretation of the effects of the antagonist on cocaine would be confounded. For example, the display of an aversion in the antagonist-treated animals might be interpreted as the antagonist having no effect on cocaine when in fact aversions induced by the cocaine might have been blocked. As such, it is important to determine a behaviorally active dose of the antagonist that does not induce a CTA alone prior to assessing its effect on cocaine-induced aversions. Accordingly, in Experiment 1 the ability of the D₂ antagonist, haloperidol, to induce taste aversions was assessed. Specifically, different groups of subjects were given a novel saccharin solution to drink followed by varying doses of haloperidol [see also 14]. Given that other assessments of DA antagonists have not found such compounds aversive (in the CTA design), it is also important to determine that the doses assessed are behaviorally active. As such, the doses of haloperidol examined in the CTA preparation were also examined for their ability to affect locomotor behavior.

3.2. Results

3.2.1. Dose response assessment

The doses of haloperidol used failed to induce a significant CTA, suggesting that the particular doses chosen had no aversive effects on their own. The 4 × 5 mixed ANOVA on consumption during conditioning revealed a significant effect of Trial \( F(4, 120) = 26.640, p = 0.001 \) but no effect of Group \( F(3, 30) = 0.772, p = 0.519 \) and no significant Trial × Group interaction \( F(12, 120) = 1.060, p = 0.400 \). In relation to the Trial effect, all groups increased consumption across conditioning, indicating that no significant CTA was induced by any of the doses of haloperidol (see Fig. 1).

3.2.2. Locomotor assessment

Although all subjects with a history of haloperidol increased activity at baseline, when injected with haloperidol (at all three doses tested) these subjects decreased locomotor activity within 30 min of the assessment. The 2 × 4 repeated measures ANOVA for total locomotor activity (collapsed across intervals) revealed a significant effect of Day \( F(1, 30) = 156.221, p < 0.001 \) as well as a significant Day × Group \( F(3, 30) = 14.741, p = 0.001 \) interaction. Given this interaction, one way ANOVAs were run for each day (baseline and test). This analysis revealed that at baseline (Fig. 2) subjects with a history of 0.25 mg/kg haloperidol displayed significantly more locomotor activity than subjects in the vehicle group \( (p = 0.013) \). One way ANOVAs for the test day (Fig. 2) revealed that all subjects injected with haloperidol (regardless of dose) significantly decreased locomotor activity relative to vehicle-injected controls \( (all \ p's < 0.05) \). Subjects injected with 0.50 mg/kg did not differ from subjects injected with 1.0 mg/kg haloperidol. All subjects decreased in activity on the test day within the first 30 min of the locomotor assessment (data not shown).

3.3. Discussion

Haloperidol (0.25, 0.50 and 1.0 mg/kg) was tested for its ability to induce CTAs. As noted, all doses tested failed to induce CTAs. Subjects with a history of haloperidol (administered during taste aversion conditioning) demonstrated increased locomotor activity at baseline (when no drug was administered). This is consistent with several reports demonstrating that animals with a history of antipsychotics (ranging in number of exposures) show enhanced stimulant-induced locomotor activity, indicating a change in DA receptor expression (see 36–40). Although this increase in locomotor activity was only significant for subjects injected with the lowest dose of haloperidol (0.25 mg/kg), all groups injected with haloperidol displayed more locomotor activity than animals injected with vehicle on baseline day (see Fig. 2). When haloperidol was administered on the test day, this effect was reversed and animals injected with 0.50 and 1.0 mg/kg haloperidol displayed...
significant decreases in motor activity within 30 min of administration (and did not differ from each other). Since there was no difference between 0.50 and 1.0 mg/kg, the highest dose tested was used in the assessment of the effects of haloperidol on cocaine-induced CTAs (see Experiment 2) to optimize the likelihood of detecting antagonism.

4. Experiment 2

4.1. Introduction

The aversive effects of haloperidol were tested in Experiment 1 to establish a dose of the antagonist that could be administered following saccharin consumption (and prior to cocaine) without the likelihood of inducing an aversion on its own which could confound any interpretation of its antagonist effects on cocaine (see above). Such a procedure has previously been used in an assessment of the role of DA in cocaine-induced aversions [see 17]; however, the dose of cocaine and its high concentration may have limited the ability to see antagonism. To circumvent this problem, in Experiment 2 animals were injected with cocaine at doses that produce graded aversions that ranged from little to intermediate to near complete suppression [see 5,19]. Such a dose range provides behavioral effects that are subject to modulation. Specifically, animals in Experiment 2 were given a novel saccharin solution to drink followed by an injection of 1.0 mg/kg haloperidol. Thirty min following this injection, different groups of animals were injected with 10, 18, and 32 mg/kg cocaine. Previous studies in our laboratory have demonstrated necrosis following subcutaneous injections of cocaine at this dose range; however, such effects were not related to degree of aversions and no significant distress in these animals was observed.

4.2. Results

4.2.1. Antagonism assessment

Haloperidol (1.0 mg/kg) significantly attenuated cocaine-induced CTAs at 18 and 32 mg/kg. The 2 × 4 × 5 mixed ANOVA revealed significant effects of Trial [F (4, 208) = 5.943, p < 0.001], Pretreatment Drug [F (1, 52) = 9.224, p = 0.004] and Conditioning Drug [F (3, 52) = 51.530, p < 0.001] as well as significant Trial × Pretreatment Drug [F (4, 208) = 8.785, p < 0.001], Trial × Conditioning Drug [F (12, 208) = 29.158, p < 0.001] and Trial × Pretreatment Drug × Conditioning Drug [F (12, 208) = 3.108, p < 0.001] interactions. In relation to the significant three-way interaction, Tukey post-hoc analysis revealed the following significant differences among groups for each trial. On Trial 1, there were no significant differences among groups. On Trial 2, subjects injected with the high dose of cocaine (Groups V32 and H32) drank significantly less than subjects injected with vehicle (Groups V0 and H0) (all p’s < 0.05), indicating a significant cocaine CTA at 32 mg/kg for both cocaine-injected groups. Subjects in Group V32 drank significantly less than subjects in all other groups (all p’s < 0.05) except Group H32. Group H32 drank significantly less than all other groups (all p’s < 0.05) except Group V18 and Group V32. On Trial 3, these differences were maintained. Additionally, subjects in Group V18 drank significantly less than all other groups (except Group H32) and significantly more than subjects in V32 (all p’s < 0.05). That Group H18 drank more than Group V18 indicates a significant attenuation of CTAs by haloperidol. All of these differences were maintained on Trial 4, with the addition of a significant difference between H32 and V32 (p = 0.036), indicating a significant attenuation of CTAs by haloperidol. Trial 5 was identical to Trial 3 (all p’s < 0.05; see Fig. 3).

4.3. Discussion

To examine a role for DA receptor activation in the induction of cocaine’s aversive effects, haloperidol was administered following saccharin access (but prior to a range of cocaine doses) in a CTA procedure. As described, the effects of cocaine were dose-dependent with aversions induced by 18 and 32 mg/kg [see 5,35]. Further, aversions at these two doses were attenuated by haloperidol (1.0 mg/kg) with the attenuation greater and more consistent at the intermediate (18 mg/kg) dose. These results replicate those of Hunt and colleagues [16] using a design that allows for an assessment of the ability of a D2 antagonist to block cocaine-induced aversions without the possible confounds of an effect of haloperidol on fluid consumption or sensory processes. The present data also suggest that the failure by Gale [17] to block cocaine by pimozide may have been a function of the dose and concentration of cocaine used in her assessment (see above). From this and other work, cocaine-induced CTAs appear mediated in part by cocaine’s ability to increase DA activity at the D2 receptor.

5. General discussion

As described, a nonaversive, but behaviorally active, dose of haloperidol (1.0 mg/kg) attenuated cocaine-induced aversions at 18 and 32 mg/kg. The effects of haloperidol were dependent upon the dose of cocaine. Specifically, aversions induced by 18 mg/kg were intermediate and were significantly attenuated by haloperidol on three conditioning trials. On the other hand, aversions induced by 32 mg/kg resulted in near complete suppression and were attenuated by haloperidol only on one trial. It is certainly possible that had a higher dose of haloperidol been assessed that cocaine-induced aversions even at 32 mg/kg would have been attenuated. The fact that haloperidol produced significant attenuation of cocaine-induced aversions at 18 mg/kg is consistent with the early work by Hunt and colleagues [16] who reported that pimozide, another D2 antagonist, attenuated aversions induced by cocaine. The fact that haloperidol was minimally effective at 32 mg/kg is consistent with the report by Gale [17] in which pimozide did not attenuate aversions induced by 160 mg/kg cocaine and suggests that such assessments need a full dose range to assay the effects of receptor mediation via antagonist pretreatment. Together with the initial assessments of D2 antagonist on cocaine-induced aversions, the present data indicate that DA activity induced by cocaine, as a DA transporter (DAT) inhibitor, may mediate its aversive effects at least as measured in the conditioned taste aversion preparation.

Attenuation by haloperidol indicates a dopaminergic role in cocaine aversion; however, the specific nature of this role cannot be concluded from the present results. Although haloperidol is a D2 receptor antagonist, its selectivity for D2 over other DA receptor subtypes is relatively low [see 41,42]. Specifically, in addition to
binding to the D2 receptor haloperidol has relatively high affinity for D3 and also binds to D1, D3, and D4 [41]. Therefore, it is possible that the dose chosen (1.0 mg/kg) antagonized not only D2 but other subtypes as well. Given the different roles of DA receptor subtypes in mediating cocaine reward [43–46], antagonists that are more selective for DA receptor subtypes should be investigated in the CTA procedure with cocaine in order to determine if D2 action alone mediates the aversive effects of cocaine.

Interestingly, haloperidol also has affinity for receptors other than dopamine. Specifically, haloperidol has affinity for the α1 [47] and α2 (and to a lesser extent α3) receptors [42]. Its ability to attenuate cocaine-induced CTAs could be a product of its antagonist effects at these sites, either alone or in some combination with its actions at DA receptors. Recently our laboratory has investigated the effects of α1 receptor antagonism on cocaine-induced CTAs. Specifically, when prazosin was administered prior to cocaine in a similar preparation as used in the present experiment, cocaine-induced CTAs were potentiated [35]. The fact that haloperidol attenuated (rather than potentiated) cocaine-induced CTAs suggests that the dose of haloperidol used in the present study did not cause strong α1 receptor antagonism (or at least not strong enough to negate the attenuation produced by some other action of haloperidol administration). Haloperidol is also a high affinity α2 antagonist [48–50]. In fact, haloperidol's affinity for α2 is almost as strong as its affinity for D2 [42]. Although the effects of selective α1 antagonists have not been examined in the context of cocaine-induced taste aversions, such antagonists have been shown to affect a number of other cocaine-induced behaviors including locomotor sensitization, convulsions and conditioned place preferences [see 51–53, respectively].

Although the evidence presented here suggests a dopaminergic role in cocaine-induced CTAs, other reports do not provide the same support. For example, Freeman and colleagues [19] compared the acquisition of aversions induced by various doses of cocaine and by several compounds that selectively inhibit each of the monoamine transporters. Given that compounds that work by a similar mechanism produce parallel dose response curves [see54], it would be expected that if any of the monoamine reuptake inhibitors induced aversions in a manner similar to that of cocaine, this would be reflected in the shape of their dose–response functions. When cocaine-induced aversions were compared to those induced by GBR 12909, the two curves were not parallel, suggesting different mechanisms mediating the two effects. Although suggestive of this, it should be noted that cocaine and GBR 12909 induced aversions of very different degrees [cocaine > GBR 12909; differences likely due to differences in molecular weight and affinity for DAT, see 19 for discussion] and cocaine-induced aversions were acquired very rapidly (near complete suppression) at all doses tested. These effects precluded assessments of the two drugs at low doses, limiting any direct comparisons of complete dose–response functions.

Jones and colleagues [55] examined the role of DA in cocaine-induced aversions by assessing transgenic knockout (KO) mice with gene deletions for DAT. These KO mice displayed aversions comparable to those of wild type mice, suggesting that DA played no role in cocaine’s aversive effects. However, since these animals developed into adulthood with this particular deletion, it is possible that they developed compensatory mechanism for clearing DA from the synapse [see 56–58; for reports of compensatory mechanisms developing in response to gene deletions]. Further, it may be difficult to generalize the work with mice to rats given reported species differences [for an overview of species differences see 9].

One final bit of evidence challenging the role of DA in cocaine-induced CTA involves the cross-drug preexposure effect [59]. In this design, animals are given exposure to one compound before taste conditioning with another. If attenuation is seen after this drug history, it is interpreted to be a function of cross-tolerance between some common aversion inducing mechanism shared between compounds [60–62; for a review see 59]. Using outbred mice, Jones and his colleagues investigated three selective monoamine transporter inhibitors in the cross-drug procedure with cocaine [63]. Interestingly, GBR 12909 at a dose of 50 mg/kg did not attenuate cocaine-induced CTAs, suggesting that the compounds do not induce CTAs via the same mechanism. Importantly, the dose of GBR 12909 used in this assessment was not strong enough to induce a CTA on its own in this particular species [63]. Had a larger dose been used (perhaps one comparable to cocaine in its ability to induce a CTA in mice), attenuation may have been observed [see 59 for an overview of the role of dose in the US preexposure effect]. To date, no similar investigation of a DAT inhibitor has been conducted using this procedure in rats.

Although the present data [as well as that of Hunt and colleagues [16] support a role of DA in cocaine-induced taste aversions, such an effect does not preclude the involvement of other neurotransmitter systems in cocaine’s aversive effects. For example, our laboratory has recently reported evidence suggesting that both norepinephrine (NE) and serotonin (5-HT) may also play roles in mediating such aversions [see 19,63,55,62,64 though see also 35]. The abovementioned dose–response comparisons by Freeman and colleagues [19] demonstrated that desipramine, the selective NE transporter (NET) inhibitor, produced curves that paralleled cocaine’s at all doses examined. Using the cross-drug preexposure preparation, Serafine and Riley [62] demonstrated that this same compound administered during preexposure resulted in the complete attenuation of cocaine-induced CTAs, suggesting that cocaine-induced CTAs also depend on NET inhibition [see also 63 for a similar effect using nisoxetine with mice]. Interestingly, when serial presentation of these compounds was reversed, cocaine preexposure actually resulted in the potentiation of desipramine-induced CTAs [62]. Selective 5-HT transporter (SERT) inhibitors have provided mixed data as well in assessments of mechanism underlying cocaine-induced CTAs [see 19,63,55,64]. For example, in the cross-drug preexposure design the SERT inhibitor fluoxetine did not attenuate cocaine-induced CTAs; however, cocaine preexposure did attenuate fluoxetine-induced CTAs, suggesting at least a partial role of 5-HT in this phenomenon [64]. Transgenic mice with deletions of NET and SERT genes demonstrate attenuated aversions [with a stronger attenuation of cocaine-induced CTAs occurring in the NET KO mice; see 55].

The present series of experiments have focused on the antagonism of cocaine’s aversive effects by haloperidol. It is important to note that there is no consensus as to what these aversive effects might be, e.g., novelty, fear, sickness, anxiety (see [65,76,66], see [67] for a discussion of this issue). Interestingly, there is at least one position that argues that taste avoidance learning, especially with drugs of abuse, is not mediated by aversiveness at all, but instead by the drug’s rewarding effects. Specifically, Grigson [68] has argued that subjects avoid consuming a rewarding taste (e.g., saccharin) in anticipation of a more valued reward (e.g., cocaine). This anticipatory contrast position states that descriptions of taste avoidance as an acquired aversion do not truly capture the basis of the effect. This position has generated considerable discussion and has received various support and criticism [see 69–72]. Interestingly, if the avoidance of tastes previously associated with drugs of abuse is a function of the drug’s rewarding (and not aversive) properties, it might be expected that there the degree of a taste aversion would be directly related to the drug’s rewarding effects. Recently, Verendreev and Riley [72] demonstrated that there was no correlation between taste aversions and place preferences induced by either morphine or amphetamine in individual animals that were trained in a concurrent CTA/CPP procedure [see also 73], findings inconsistent with the predictions of the anticipatory contrast model of taste aversions. Such data are more consistent with the hypothesis that drugs of abuse have multiple effects (including reward and aversion) that can be expressed and examined in different procedures. The present experiment was not designed to address any specific mechanism thought to mediate
taste aversions. What was demonstrated was the fact that cocaine's ability to induce aversions of a specific taste can be blocked by haloperidol, implicating DA in cocaine's behavioral effect.

The present study, taken with these previous reports, indicates that the mechanisms underlying cocaine-induced CTAs are multifaceted. While previous reports have focused on NE and 5-HT, these data provide evidence of a dopaminergic contribution. Several procedures have been used to characterize cocaine's aversive effects, and given that different conclusions are often made from such analyses, future research should aim to use multiple procedures, rather than one alone, to investigate this complex phenomenon. The use of more selective compounds (at a range of doses) for each DA receptor subtype should also be examined in cocaine-induced CTAs in order to determine the specificity of DA involvement. Additionally, future research should use this neurochemical evidence in order to investigate the possible biological substrates involved in CTAs with cocaine and other drugs of abuse.

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