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Assessment of monoamine transporter inhibition in the mediation of cocaine-induced conditioned taste aversion

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Abstract

Although the mechanisms of cocaine reward have been well characterized, the pharmacological basis of cocaine's aversive effects is less understood. Using the conditioned taste aversion (CTA) preparation, the present study examined the role of monoamine uptake inhibition in cocaine's aversive effects by comparing cocaine to three reuptake inhibitors with relative specificity for the transporters of dopamine (DAT; GBR 12909), norepinephrine (NET; desipramine) and serotonin (SERT; clomipramine). Specifically, 104 male Sprague–Dawley rats were given 20-min access to a novel saccharin solution followed immediately by a subcutaneous injection of cocaine, GBR 12909, desipramine, clomipramine (each at 18, 32 or 50 mg/kg; 12 groups) or drug vehicle (equivolume to the highest cocaine dose). Over trials, cocaine and desipramine each dose-dependently suppressed saccharin consumption and did so in an equivalent manner when matched by dose. However, both GBR 12909 and clomipramine conditioned weaker aversions than cocaine at the two lowest doses (18 and 32 mg/kg). At the highest dose (50 mg/kg), GBR 12909 produced equivalent suppression of saccharin consumption to cocaine while clomipramine's conditioned suppression remained relatively weak at this dose. These results suggest that cocaine's adrenergic actions resulting from NET inhibition may play a more significant role in the mediation of its aversive effects than its actions at DAT and SERT.

Keywords: Cocaine; Conditioned taste aversion; Monoamine transporter inhibition; GBR 12909; Desipramine; Clomipramine; Dopamine; Norepinephrine; Serotonin

1. Introduction

Cocaine, like a number of other drugs of abuse, has been shown to possess both rewarding (Nomikos and Spyraki, 1988; Wise et al., 1992) and aversive (Ettenberg, 2004; Ferrari et al., 1991; Koob et al., 1997) properties. Although its rewarding effects appear to be mediated by monoamine transporter inhibition in the central nervous system (CNS; Ritz et al., 1987; Rocha, 2003), the basis for the aversive effects of cocaine is less well understood. Interest in the aversive properties of abused drugs stems from the notion that the acceptability and abuse potential of the drug may depend on a balance of its rewarding and aversive effects (Riley and Simpson, 2001). Understanding the physiological bases of cocaine's aversive effects as well as the conditions under which they occur may provide insight into a key vulnerability factor mediating the abuse potential of cocaine.

In the investigation of cocaine's behavioral effects, one area that has received considerable attention is its action on monoaminergic systems. Cocaine affects monoamine activity by acting as an indirect agonist for the three monoamine neurotransmitters dopamine (DA), norepinephrine (NE) and serotonin (5-HT) via its blockade of their respective transporter proteins (Taylor and Ho, 1978; Woolverton and Johnson, 1992). To understand the relative roles of cocaine's actions on each of these monoamine systems in the expression of various behaviors (e.g., self-administration [SA], drug discrimination [DD]), researchers have employed pharmacological probes that act with relative specificity on each of the monoamine transporters and have compared the effects of these drugs to those of cocaine (Baker et al., 1993; Cunningham and Callahan, 1991; Tella, 1995). Although these assessments have provided insight into the rewarding (Tella, 1995) and discriminative stimulus (Baker et al., 1993; Cunningham and Callahan,

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1991) effects of cocaine, this methodology has yet to be used to examine cocaine's aversive effects. There is some evidence that 5-HT transporter (SERT) inhibition with fluoxetine can induce a CTA (Berendsen and Broekkamp, 1994; Prendergrast et al., 1996), although no comparison was made to cocaine in these assessments. In addition, there appears to be a dopaminergic contribution to cocaine-induced CTAs as the DA receptor antagonist pimozide has been shown to attenuate a cocaine-induced CTA (Hunt et al., 1985). However, this demonstration did not assess the direct effect of DA transporter (DAT) inhibition on the induction of a CTA.

Recent work examining factors outside of cocaine's monoaminergic activity highlight the possibility that monoamine transporter inhibition may be mediating its aversive effects. Specifically, a report by Freeman et al. (2005) comparing the aversive effects of cocaine to the analogs procaine and cocaine methiodide in the conditioned taste aversion (CTA) preparation demonstrated that the full expression of cocaine's aversive effects do not appear to be singularly mediated by either sodium channel inhibition or activity in the peripheral nervous system (PNS). That is, neither the inhibition of sodium channels with procaine nor the cocaine-like actions in the PNS induced by peripherally administered cocaine methiodide produced aversions comparable in magnitude to cocaine when matched by dose, although each analog did induce some degree of aversion by itself. Given that neither of these compounds specifically allowed for an assessment of the contribution of monoamine transporter inhibition, there remains the possibility that one or more of the monoamine systems may be participating in the mediation of cocaine's aversive effects.

In order to make a systematic assessment of monoamine transport inhibition as a mediator of cocaine-induced CTA, the present study compared cocaine to three reuptake inhibitors, each of which possesses relative specificity for one of the three monoamine transporters, in their ability to induce a CTA. Specifically, rats were given access to a novel saccharin solution and injected with either cocaine, GBR 12909 (DAT inhibitor; Andersen, 1989), desipramine (NE transporter [NET] inhibitor; Tatsumi et al., 1997) or clomipramine (SERT inhibitor; Thomas and Jones, 1977) at one of three doses (18, 32 and 50 mg/kg).

2. Method

2.1. Subjects

The subjects were 104 male Sprague–Dawley rats, approximately 150 days of age and 300–400 g at the beginning of the experiment. The specific study described was approved by the Institutional Animal Care and Use Committee at American University and was conducted under the procedures recommended by the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996) and the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council, 2003). Food and water consumption were monitored daily to assess the health of the subjects.

2.2. Apparatus

Subjects were housed in individual stainless-steel, wire-mesh cages on the front of which graduated Nalgene tubes could be placed for the presentation of either water or saccharin. Subjects were maintained on a 12 L/12 D cycle, with lights on at 0800 h, and at an ambient temperature of 23 °C for the duration of the experiment. Food was available ad libitum.

2.3. Drugs and solutions

Cocaine hydrochloride (cocaine–HCl), GBR 12909-2HCl, desipramine–HCl and clomipramine–HCl were each prepared as 10 mg/ml solutions in distilled water and injected subcutaneously (SC) at one of three doses (18, 32 and 50 mg/kg). The doses and route of administration for cocaine were based on previous work showing these parameters to be the most effective for producing CTAs with cocaine (Busse et al., 2005; Ferrari et al., 1991). Because there is no previous research using GBR 12909, desipramine or clomipramine in the CTA preparation, these compounds were matched with cocaine on dose and route of administration in order to make the most systematic comparison with cocaine. All drug doses are expressed as the salt. Cocaine was generously provided by the National Institute on Drug Abuse (NIDA). GBR 12909, desipramine and clomipramine were provided by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Saccharin (0.1% sodium saccharin, Sigma) was prepared as a 1 g/l solution in tap water.

2.4. Procedure

2.4.1. Phase I: habituation

Following 23-h water deprivation, subjects were given 20-min access to water. This procedure was repeated daily until all subjects were approaching and drinking from the tube within 2 s of its presentation.

2.4.2. Phase II: conditioning

On Day 1 of this phase, subjects were given 20-min access to a novel saccharin solution. Immediately following access to saccharin, the subjects were ranked according to saccharin consumption and assigned to 13 groups ($n=8$ per group) such that each group was comparable in consumption. Approximately 20 min after saccharin access, the animals were removed from their home cages and injected subcutaneously (SC) in an adjacent room with cocaine (18, 32 or 50 mg/kg), GBR 12909 (18, 32 or 50 mg/kg), desipramine (18, 32 or 50 mg/kg) or clomipramine (18, 32 or 50 mg/kg). A final group of animals was injected with the drug vehicle (distilled water) equivolume to the highest cocaine dose. Each animal was placed back in its respective home cage following the injection. This treatment resulted in the following groups: Groups Coc-18, Coc-32, Coc-50, GBR-18, GBR-32, GBR-50, Des-18, Des-32, Des-50, Clm-18, Clm-32, Clm-50 and Veh. The first variable in each group designation refers to the drug

administered, i.e., cocaine (Coc), GBR 12909 (GBR), desipramine (Des) and clomipramine (Clm). The second variable refers to the dose, i.e., 18 (18 mg/kg), 32 (32 mg/kg) and 50 (50 mg/kg). The control group received drug vehicle (Veh). On the following 3 water-recovery days, all animals were given 20-min access to water. No injections were given following water access on these days. This alternating procedure of conditioning/water recovery was repeated until all subjects received four complete cycles. On the day following the final water-recovery session, all subjects were given 20-min access to saccharin in a one-bottle test of the aversion to saccharin (Final Aversion Test). No injections were given following the test.

2.5. Statistical analysis

Differences in mean saccharin consumption were analyzed using a 13×5 Repeated Measures Analysis of Variance (ANOVA) with the between-subjects variable of Group (Coc-18, Coc-32, Coc-50, GBR-18, GBR-32, GBR-50, Des-18, Des-32, Des-50, Clm-18, Clm-32, Clm-50 and Veh) and the within-subjects variable of Trial (Trials 1–4 and the Final Aversion Test). One-way ANOVAs were used to analyze mean saccharin consumption for Trials 1–4 and the Final Aversion Test with the between-subjects variable of Group. Fisher's PLSD post-hoc tests were used to make pairwise comparisons between groups on Trials 1–4 and on the Final Aversion Test. All significance levels were set at $p \leq .05$.

3. Results

A 13×5 Repeated Measures ANOVA revealed significant main effects for Group ($F(12,91)=23.898$, $p \leq .0001$) and Trial ($F(4,364)=81.315$, $p \leq .0001$) as well as a significant Group × Trial interaction ($F(48,364)=9.573$, $p \leq .0001$). On Trial 1, a one-way ANOVA revealed no significant main effect for Group ($F(12,91)=.103$, $p \geq .9999$). However, subsequent one-way ANOVAs conducted on Trials 2–4 and on the Final Aversion Test revealed significant main effects for Group (all F's$(12,91) \geq 10.913$, all p's$\leq .0001$).

Fig. 1 illustrates the mean consumption of saccharin (±S.E.M.) for subjects injected with vehicle (Veh) and subjects injected with 18 mg/kg cocaine (Coc-18), GBR 12909 (GBR-18), desipramine (Des-18) and clomipramine (Clm-18) on Trials 1–4 and on the Final Aversion Test. On Trial 1, post-hoc analyses using Fisher's PLSD revealed no significant differences in saccharin consumption among groups (all p's$\geq .5435$). However, differences emerged on Trial 2 with all drug-injected groups (with the exception of Group Clm-18, $p=.1575$) consuming significantly less saccharin than Group Veh (all p's$\leq .0269$). Furthermore, Group Coc-18 consumed significantly less than all other groups (all p's$\leq .0269$) with the exception of Group Des-18 ($p=.5916$). Although Group Des-18 did not differ in consumption from Group GBR-18 ($p=.1167$), subjects in Group Des-18 did consume significantly less saccharin than those in Group Clm-18 ($p=.0181$) which did not differ in consumption from Group GBR-18 ($p=.4124$). On Trial 3, all groups consumed significantly less saccharin than Group Veh (all p's$\leq .0150$). In addition, Groups Coc-18 and Des-18 each consumed less than all other groups (all p's$\leq .0001$), although they did not differ from each other ($p \geq .9999$). Furthermore, Group GBR-18 consumed significantly less saccharin than Group Clm-18 ($p=.0399$). These patterns were maintained for the remaining of conditioning with the exception that Group GBR-18 did not consume a significantly different amount of saccharin than Group Clm-18 on Trial 4 and on the Final Aversion Test (all p's$\geq .1296$) and Group Clm-18 did not differ from Group Veh on the Final Aversion Test ($p=.0623$).

Fig. 2 illustrates the mean consumption of saccharin (±S.E.M.) for Groups Veh, Coc-32, GBR-32, Des-32 and Clm-32 on Trials 1–4 and on the Final Aversion Test. On Trial

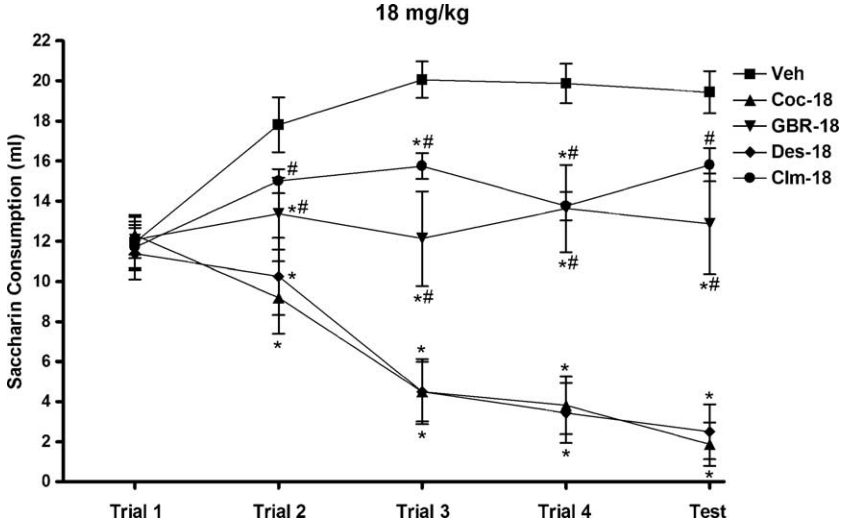

Fig. 1. Illustrates mean saccharin consumption (ml) for subjects in Groups Veh, Coc-18, GBR-18, Des-18 and Clm-18 ($n=8$ per group) on Conditioning Trials 1–4 and the Final Aversion Test. Bars above and below each point represent S.E.M. *Significantly different from Group Veh. #Treatment groups significantly different from Group Coc-18.

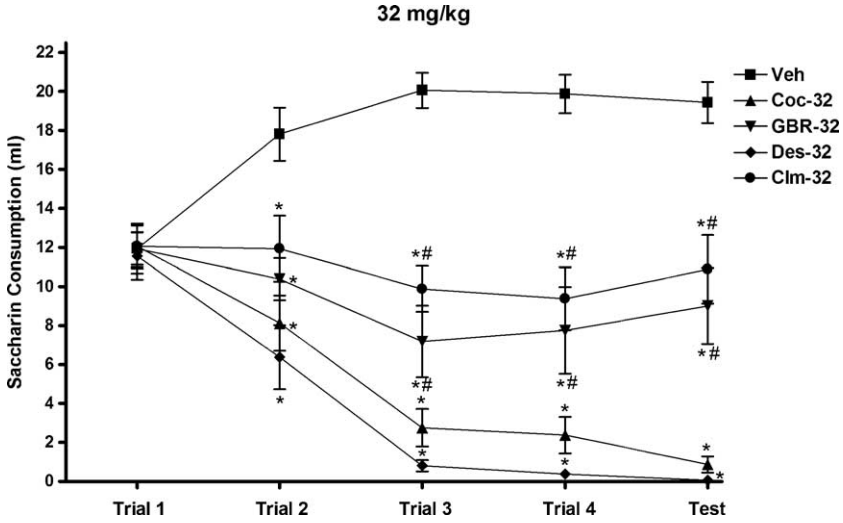

Fig. 2. Illustrates mean saccharin consumption (ml) for subjects in Groups Veh, Coc-32, GBR-32, Des-32 and Clm-32 ($n=8$ per group) on Conditioning Trials 1–4 and the Final Aversion Test. Bars above and below each point represent S.E.M. *Significantly different from Group Veh. #Treatment groups significantly different from Group Coc-32.

1, there were no significant differences in saccharin consumption among groups (all p's $\geq .7458$). However, on Trials 2–4 and on the Final Aversion Test, all groups drank significantly less saccharin than Group Veh (all p's $\leq .0037$) with Groups Coc-32 and Des-32 not differing in consumption (all p's $\geq .2642$). On Trial 2, Group Coc-32 did not differ in consumption from Groups GBR-32 and Clm-32 (all p's $\geq .0565$) but did consume significantly less than these groups for the remainder of conditioning (all p's $\leq .0124$). Finally, Group Des-32 consumed significantly less saccharin than Groups GBR-32 and Clm-32 on Trials 2–4 and on the Final Aversion Test (all p's $\leq .0456$).

Fig. 3 illustrates the mean consumption of saccharin (±S.E.M.) for Groups Veh, Coc-50, GBR-50, Des-50 and Clm-50 on Trials 1–4 and on the Final Aversion Test. On Trial 1, there were no significant differences in saccharin consumption among groups (all p's $\geq .4662$). However, on Trials 2–4 and on the Final Aversion Test all groups drank significantly less saccharin than Group Veh (all p's $\leq .0154$). Groups Coc-50, GBR-50 and Des-50 did not differ in saccharin consumption after the first conditioning trial (all p's $\geq .2317$) but consumed significantly less saccharin than Group Clm-50 on Trials 2–4 and on the Final Aversion Test (all p's $\leq .0002$).

Fig. 4 illustrates the mean saccharin consumption for all groups (Veh, Coc-18, -32 and -50, GBR-18, -32 and -50, Des-18, -32 and -50 and Clm-18, -32 and -50) on the Final Aversion Test to facilitate comparisons across all drugs and doses tested. On this test, all groups with the exception of Group Clm-18 ($p=.0623$) drank significantly less saccharin than Group Veh (all p's $\leq .0009$). There were no significant differences in consumption on this test among Groups GBR-50, Coc-18, Coc-32, Coc-50, Des-18, Des-32 and Des-50 (all p's $\geq .1963$), although each group did consume significantly less than the remaining groups (all p's $\leq .0012$). Furthermore, Group Clm-

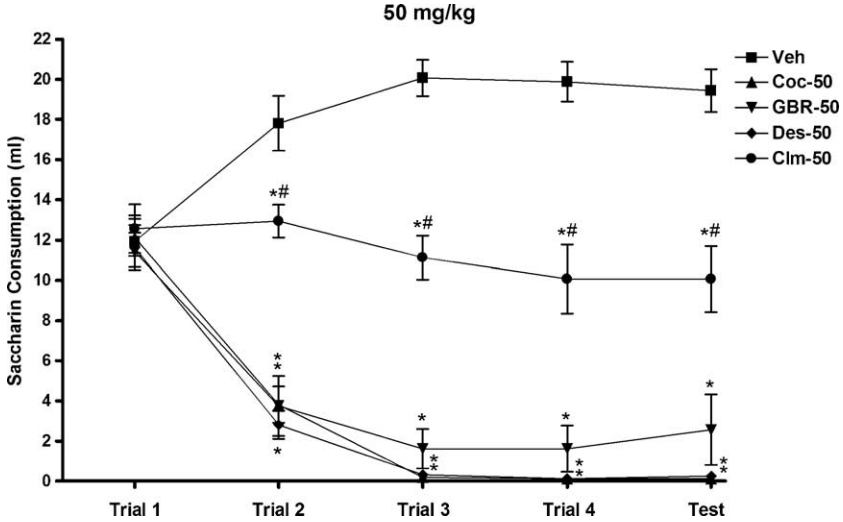

Fig. 3. Illustrates mean saccharin consumption (ml) for subjects in Groups Veh, Coc-50, GBR-50, Des-50 and Clm-50 ($n=8$ per group) on Conditioning Trials 1–4 and the Final Aversion Test. Bars above and below each point represent S.E.M. *Significantly different from Group Veh. #Treatment groups significantly different from Group Coc-50.

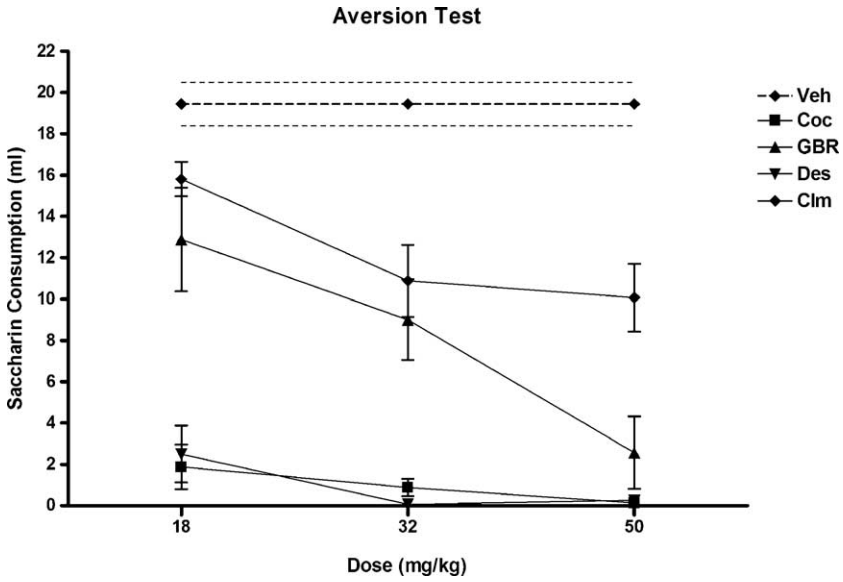

Fig. 4. Illustrates mean saccharin consumption (ml) for subjects in Groups Veh, Coc-18, Coc-32, Coc-50, GBR-18, GBR-32, GBR-50, Des-18, Des-32 and Des-50, Clm-18, Clm-32 and Clm-50 ($n=8$ per group) on the Final Aversion Test. Bars above and below each point represent S.E.M for the treatment groups. The dashed lines above and below the prominent dashed line represent S.E.M. for Group Veh.

18 did not differ in consumption from Group GBR-18 ($p=.1296$) but did consume significantly more than all other treatment groups (all p's $\leq .0012$). Although Group GBR-18 consumed significantly more saccharin than Group GBR-32 ($p=.0466$), which itself did not differ from Groups Clm-32 or Clm-50 (all p's $\geq .3315$), there were no significant differences in saccharin consumption among Groups GBR-18, Clm-32 and Clm-50 (all p's $\geq .1465$).

4. Discussion

Cocaine acts as an indirect agonist on the three monoamine neurotransmitter systems (DA, NE and 5-HT) by binding to their cognate transporter proteins. Although the rewarding and discriminative stimulus properties of cocaine appear to be mediated largely by the dopaminergic system (Baker et al., 1993; Cunningham and Callahan, 1991; Kleven et al., 1990; Tella, 1995), it is unclear to what extent cocaine's actions on these three monoamine systems participate in its aversive effects. To assess this issue, the current study used transporter inhibitors with relative specificity for DAT (GBR 12909), NET (desipramine) and SERT (clomipramine) in a CTA design and compared the results of these drug treatments to aversions induced by matched doses of cocaine (18, 32 and 50 mg/kg). As described, aversions induced by the NET inhibitor desipramine were comparable to those induced by cocaine at all doses tested. However, the DAT inhibitor GBR 12909 and the SERT inhibitor clomipramine did not induce aversions equivalent to cocaine at the two lowest doses. At the highest dose tested, GBR 12909 induced aversions equivalent to cocaine and desipramine, but clomipramine at this dose still induced significantly weaker aversions.

The fact that desipramine produced a suppression pattern very similar to cocaine when matched by dose suggests that the adrenergic system (or at least cocaine's blockade of NET) may play a significant role in the aversive properties of cocaine as indexed in the CTA design. In accordance with blocking NET, cocaine causes increases in plasma NE levels (Sofuoglu et al., 2001). One possible origin of the adrenergic contribution to the aversiveness of cocaine may occur through an enhancement of sympathetic outflow. Cocaine administration often causes significant increases in blood pressure (pressor response) and heart rate (tachycardia; Schindler et al., 1995). Furthermore, these effects appear to be mediated through adrenergic mechanisms as the pressor response can be diminished by pretreatment with the α_1 antagonist prazosin (Mo et al., 1999) while the tachycardiac effects are similarly attenuated by pretreatment with the β_1 receptor antagonist atenolol (Schindler et al., 1995). Further supporting the role of NE in these effects, humans maintained on a desipramine regimen exhibit significant increases in heart rate and blood pressure under conditions of cocaine self-administration that are greater than the increases seen with cocaine alone (Fischman et al., 1990), presumably due to the elevated baseline levels of norepinephrine resulting from desipramine treatment. It should be noted, however, that low doses of desipramine (0.03–1.0 mg/kg, intravenous [IV]), when given alone, do not induce pressor responses or tachycardia comparable to cocaine at matched doses (Tella et al., 1993). However, at a 5 mg/kg dose (IV), desipramine has been shown to significantly increase NE plasma levels as well as heart rate and blood pressure (Carson et al., 2002). Given that the doses in the present study were relatively high (18, 32 and 50 mg/kg), it is possible that such increases in blood pressure and heart rate may have occurred (although no such assessment was made).

Although the emphasis of the present discussion has been on the role of norepinephrine in the aversive stimulus properties of cocaine, it should be noted that GBR 12909 did induce some degree of aversion at each dose tested, suggesting that DAT inhibition plays some role in the induction of CTAs

with cocaine. Although this is the first study to directly assess DAT inhibition in CTA, a role for DA in cocaine-induced CTA has been implicated by previous work (Hunt et al., 1985). It should also be noted that GBR 12909 has a molecular weight that is approximately 54% greater than cocaine's (ratio of salt forms), meaning that matched doses of these two drugs results in a greater number of available cocaine molecules relative to GBR 12909 upon initial administration. As such, the weaker effects of GBR 12909 relative to cocaine may be a function of lower drug availability. However, consideration should also be given to the fact that GBR 12909 has a much higher affinity for and a slower dissociation rate from DAT than cocaine (Andersen, 1987; Reith et al., 1981; Rothman et al., 1991), meaning that molar matching between the two drugs would result in a greater number of occupied transporters in addition to a longer duration of action with GBR 12909 relative to cocaine. The results with clomipramine in the current study were consistent with those using fluoxetine in previous assessments of CTA (Berendsen and Broekkamp, 1994; Prendergrast et al., 1996), confirming that SERT inhibition can induce CTAs. However, the weakness of the aversions with clomipramine relative to cocaine suggests that SERT inhibition, while playing some role in cocaine-induced CTAs, may not be a major factor mediating its aversive effects.

The current results are an interesting contrast to the findings of previous reports showing that GBR 12909 fully substitutes for cocaine in DD tasks, whereas desipramine and the NET inhibitor nisoxetine exhibit either partial or no substitution for cocaine (Baker et al., 1993; Cunningham and Callahan, 1991; Kleven et al., 1990; Spealman, 1995). Consistent with the findings from these DD studies, pretreatment with GBR 12909 causes a dose-dependent reduction in cocaine SA with only a marginal reduction occurring with desipramine and nisoxetine pretreatment (Tella, 1995). Furthermore, neither desipramine nor nisoxetine is effective in maintaining responding in animals trained to SA cocaine (Wee and Woolverton, 2004; Woolverton, 1987), whereas GBR 12909 maintains responding in cocaine-trained animals and produces a comparable breakpoint with cocaine in a progressive-ratio schedule of reinforcement (Roberts, 1993). Taken together, this evidence argues that the DD and SA assays are more sensitive to cocaine's actions at DAT and less so at NET and SERT while the CTA assay may be most sensitive to cocaine's actions at NET. Given the challenges in cocaine research that arise from its diverse pharmacology, it is of interest that the CTA assay may show differential sensitivity to a pharmacological component of cocaine's actions that is less indexed in the DD and SA assays.

Although the aim of this study was to better characterize the pharmacological basis of cocaine's aversive effects, it should be noted that there are alternative interpretations regarding the subjective nature of cocaine-induced CTAs (see Parker, 2003 for a full review of this issue). Of particular interest is the reward-comparison hypothesis (see Grigson, 1997) which posits that palatable taste solutions that are paired with SA compounds such as cocaine are devalued as a function of their contingent presentation with the more rewarding SA compound through a process known as anticipatory contrast (see Flaherty et al., 1994). That is, the more rewarding drug cue overshadows the less rewarding taste cue, thus leading to avoidance of the taste cue on subsequent presentations by animals anticipating the arrival of the more rewarding drug state. As such, the CTA assay in this case would function as an index of drug reward rather than aversion and would most likely be mediated by the mesolimbic dopaminergic system. Although the current results do not discount this hypothesis, the fact that aversions can be induced by desipramine, a non-SA NET inhibitor (see above), suggests that cocaine, also a NET inhibitor, may induce CTAs through processes separate from the neurochemical system thought to mediate its rewarding effects, i.e., NET vs. DAT inhibition, respectively.

To further explore the contribution of adrenergic activity in the induction of cocaine-induced CTAs, the aversive properties of cocaine and desipramine (or perhaps nisoxetine) should be compared under conditions of pretreatment with various adrenergic receptor agonists and antagonists. If, indeed, the adrenergic system is playing a significant role in cocaine's aversive effects, characterizing the specific mechanisms by which this system interacts with cocaine will ultimately lead to a better understanding of a key vulnerability factor affecting the acceptability of this drug of abuse.

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