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Preexposure to cocaine attenuates aversions induced by both cocaine and fluoxetine: Implications for the basis of cocaine-induced conditioned taste aversions

Katherine M. Serafine *, Anthony L. Riley

Psychopharmacology Laboratory, Department of Psychology, American University 4400 Mass. Ave., NW, Washington, DC 20016, United States

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ABSTRACT

Although cocaine-induced conditioned taste aversions (CTA) are well documented, little is known about the basis for cocaine's aversive effects. To address the role of serotonin (5-HT) in cocaine-induced aversions, the present experiments used the cross-drug preexposure design in which the effects of exposure to fluoxetine, a selective 5-HT reuptake inhibitor (SSRI) with 5-HT transporter (SERT) inhibitory properties, were examined on aversions induced by cocaine (a nonselective monoamine transport inhibitor) and the effects of cocaine preexposure were examined on fluoxetine-induced aversions. Prior to these assessments, a fluoxetine dose–response function (3.2, 5.6, 10, and 18 mg/kg) was established in male Sprague–Dawley rats to determine a dose of fluoxetine that would induce intermediate aversions that were comparable to those induced by 18 mg/kg cocaine (Experiment 1). Other groups of rats were then exposed to fluoxetine prior to aversion conditioning with cocaine (Experiment 2) and with cocaine prior to aversion conditioning with fluoxetine (Experiment 3). All drugs were administered subcutaneously (cocaine 18 mg/kg; fluoxetine 10 mg/kg). Although there was no effect of fluoxetine preexposure on either cocaine- or fluoxetine-induced aversions, preexposure to cocaine significantly attenuated aversions induced by itself and by fluoxetine. These results were discussed in terms of the possible role 5-HT might play in the mediation of aversions induced by cocaine.

1. Introduction

Similar to other drugs of abuse, cocaine has both rewarding (Wise et al., 1992) and aversive (Ettenberg, 2004; Ferrari et al., 1991) effects. Although the rewarding effects of cocaine appear to be mediated by its actions as a monoaminergic reuptake inhibitor (De Wit and Wise, 1977; Hall et al., 2004; Ritz et al., 1987; Sora et al., 2001; Tilley et al., 2009), the biochemical mediation of the aversive effects of cocaine is less understood. In an attempt to assess the possible role of NE transport (NET) inhibition in cocaine's aversive effects, Serafine and Riley (2009) used the cross-drug preexposure preparation (De Beun et al., 1996; Gommans et al., 1998) to examine common stimulus effects between cocaine and the NET inhibitor desipramine. Specifically, they exposed rats to desipramine prior to taste aversion conditioning with cocaine and found that such preexposure attenuated the acquisition of cocaine-induced taste aversions. Given that such attenuation is generally interpreted as being due to cross-tolerance between the aversion-inducing effects of both compounds (De Beun et al., 1996; Kayir et al., 2008; Kunin et al., 1999; Olivier et al., 1999, for reviews and alternative interpretations, see Cappell and LeBlanc, 1977; Randich and LoLordo., 1979; Riley and Simpson, 2001), these results suggested that the aversive effects of cocaine may be mediated by its action as a NET inhibitor.

Although these results suggest that NET inhibition may be mediating cocaine-induced CTAs, it is important to note that cocaine inhibits transporters for all three monoamines (Taylor and Ho, 1978; Woolverton and Johnson, 1992). Further, although desipramine has the highest affinity for NET, it also binds to the serotonin (5-HT) transporter (SERT; Richelson and Pfenning, 1984; Tatsumi et al., 1997). Accordingly, it is possible that SERT inhibition may play some secondary role in cocaine-induced CTAs. Administration of a selective SERT inhibitor and cocaine in the cross-drug preexposure preparation may help to identify such an involvement. Specifically, if SERT inhibition is involved in aversions induced by cocaine, it might be expected that preexposure to a selective 5-HT reuptake inhibitor (SSRI), e.g., fluoxetine which has SERT inhibitory properties, would attenuate aversions induced by both itself and cocaine. Similarly, preexposure to cocaine might be expected to attenuate aversions induced by itself and fluoxetine. These predictions were tested in the following experiments in which the effects of fluoxetine preexposure on cocaine-induced aversions (Experiment 2) and cocaine preexposure on fluoxetine-induced aversions (Experiment 3) were assessed. Prior to the assessment of the effects of preexposure to fluoxetine or cocaine on aversions induced by these two compounds, dose–response determinations were made to establish doses of fluoxetine that produced aversions comparable to those produced by cocaine (see Ferrari et al., 1991; Freeman et al., 2005; for similar analyses with fluoxetine, see Ervin et al., 1995; Prendergast et al., 1996).

* Corresponding author. Tel.: +1 202 885 1721; fax: +1 202 885 1081.
E-mail address: kserafine@gmail.com (K.M. Serafine).

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2. General methods

2.1. Subjects

The subjects were experimentally naïve male Sprague–Dawley rats, approximately 75 days old and weighing between 250 and 350 g at the start of each experiment. All procedures were approved by the Institutional Animal Care and Use Committee at American University and consistent with the guidelines recommended by the National Research Council (1996) and the Committee on Guidelines for the Care and Use of Animals in Neuroscience and Behavioral Research (2003). Animals were handled daily two weeks prior to the initiation of each study to limit the effects of handling stress during conditioning and testing.

2.2. 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 for the duration of the study. Except where noted, food and water were available ad libitum.

2.3. Procedure

2.3.1. Phase I: habituation

Following $23^{2/3}$-h water deprivation, subjects were given 20-min access to tap water. This procedure 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. Throughout each 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.

2.3.2. Phase II: conditioning

Following water habituation, all subjects were given 20-min access to a novel saccharin solution. Immediately following this presentation, animals were rank ordered based on saccharin consumption and assigned to a treatment group (either vehicle or drug for each experiment) such that overall consumption was comparable among groups. Approximately 20 min after access to the saccharin solution, subjects received a subcutaneous (SC) injection of either drug or vehicle. 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.

2.3.3. Phase III: final aversion test

Following the last water-recovery session of the fourth conditioning cycle, all subjects were given access to the saccharin solution for 20 min in a final test of the aversion to saccharin.

2.3.4. Experimental designs

The three experiments all utilized the abovementioned procedure with the following exceptions. In Experiment 1, during conditioning subjects were injected with either 3.2, 5.6, 10 or 18 mg/kg fluoxetine, cocaine (18 mg/kg) or the distilled water vehicle, yielding Groups Flu-3.2 ($n=8$), Flu-5.6 ($n=8$), Flu-10 ($n=9$), Flu-18 ($n=9$), Cocaine-18 ($n=8$) and Vehicle ($n=8$). In Experiment 2, subjects were injected with fluoxetine (10 mg/kg) or vehicle 5 h following 20-min water access every 4th day for a total of five injections prior to taste aversion conditioning with either fluoxetine, cocaine or vehicle, yielding Groups fluoxetine–fluoxetine (FLU–FLU; $n=8$), fluoxetine–cocaine (FLU–COC; $n=9$), fluoxetine–vehicle (FLU–VEH; $n=8$), vehicle–vehicle (VEH–VEH; $n=8$), vehicle–cocaine (VEH–COC; $n=9$) and vehicle–fluoxetine (VEH–FLU; $n=8$). In Experiment 3, the procedure was identical to that in Experiment 2 with the exception that rats in this experiment were injected with cocaine (18 mg/kg) or vehicle (matched in volume) prior to taste aversion conditioning with cocaine, fluoxetine or vehicle, yielding Groups cocaine–cocaine (COC–COC; $n=9$), cocaine–fluoxetine (COC–FLU; $n=9$), cocaine–vehicle (COC–VEH; $n=8$), vehicle–vehicle (VEH–VEH; $n=8$), vehicle–fluoxetine (VEH–FLU; $n=8$) and vehicle–cocaine (VEH–COC; $n=8$).

2.4. Drugs and solutions

Cocaine hydrochloride (generously provided by NIDA) and fluoxetine hydrochloride (Sigma) were each dissolved in distilled water at a concentration of 10 mg/ml. All drug doses are expressed as the salt. Saccharin (sodium saccharin, Sigma) was prepared as a 1 g/l (0.1%) solution in tap water.

2.5. Statistical analysis

During drug preexposure (Experiments 2 and 3), differences in mean water consumption were analyzed using a 2×20 repeated measures ANOVA with the between-subjects variable of Preexposure Drug (vehicle or drug) and the within-subjects variable of Preexposure Day (1–20).

During conditioning for Experiment 1, the differences in mean saccharin consumption were analyzed using a 6×5 repeated measures ANOVA with the between-subject variable of Conditioning Drug (Flu-3.2, Flu-5.6, Flu-10, Flu-18, Cocaine-18 or vehicle) and the within-subjects variable of Trial (1–4: Final Aversion Test). During conditioning in Experiments 2 and 3, differences in mean saccharin consumption were analyzed using a $2\times3\times5$ mixed-model ANOVA with the between-subjects variables of Preexposure Drug (vehicle or drug) and Conditioning Drug (cocaine, fluoxetine or vehicle) and the within-subjects variable of Trial (1–4: Final Aversion Test). For all three experiments, Fisher LSD post-hoc analyses were used to examine mean saccharin consumption differences on each individual trial following demonstration of significant interaction and main effects. All significance levels were set at $p<0.05$.

3. Results

3.1. Experiment I

3.1.1. Conditioning

Fluoxetine induced dose-dependent aversions (see Fig. 1). The 6×5 repeated measures ANOVA revealed significant effects of Trial

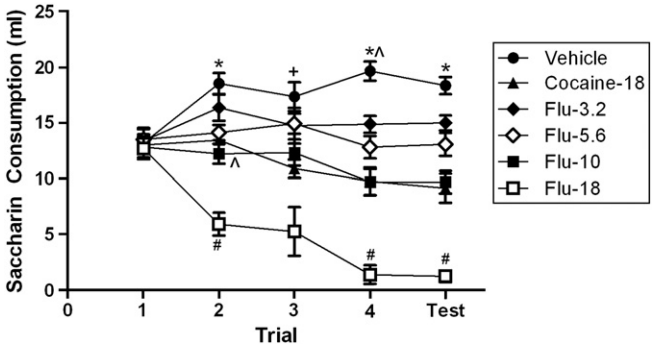

Fig. 1. Mean (±SEM) saccharin consumption (ml) for all subjects in groups conditioned with cocaine (18 mg/kg), fluoxetine (18, 10, 5.6, and 3.2 mg/kg) or vehicle. *Significantly different from Groups Flu-5.6, Flu-10, Flu-18 and Cocaine-18; #Significantly different from all other groups; ^Significantly different from Group Flu-3.2; +Significantly different from Groups Flu-18 and Cocaine-18.

[F (4, 176) = 7.936, p<.001] and Conditioning Drug [F (4, 44) = 32.758, p<.001] and a significant Trial × Conditioning Drug interaction [F (8, 176) = 7.252, p<.001]. Since there was a significant interaction of Trial × Conditioning Drug, Fisher LSD post-hoc analyses were run on individual trials. On Trial 1, there were no significant differences in consumption between any groups. On Trial 2, animals in Groups Flu-5.6, Flu-10, Flu-18 and Cocaine-18 drank significantly less saccharin than subjects in Group Vehicle (all p's<.02), indicating the acquisition of cocaine- and fluoxetine-induced aversions. Animals in Group Flu-18 drank significantly less saccharin than subjects in all other groups (all ps<.001). Group Flu-10 drank significantly less than animals in Group Flu-3.2 (p = .032). On Trial 3, only Groups Flu-18 and Cocaine-18 drank significantly less than Group Vehicle (both ps<.04). On Trial 4, all drug-injected groups drank significantly less than Group Vehicle (all ps<.029). Group Flu-18 drank significantly less than every other group (all ps<.001). On the Final Aversion Test, all drug-injected groups again drank significantly less than vehicle (all ps<.005), with the exception of Group Flu-3.2. All other comparisons that were significant on Trial 4 were maintained on the Final Aversion Test.

3.2. Experiment 2

3.2.1. Preexposure

There was a slight increase in water consumption during this phase regardless of preexposure compound. The 2×20 repeated measures ANOVA revealed a significant main effect of Preexposure Day [F (19, 912) = 8.991, p<.01] and a Preexposure Day × Preexposure Drug interaction [F (19, 912) = 1.778, p = .02] (see Fig. 2). Although there was a significant Preexposure Day × Preexposure Drug interaction, one way ANOVAs run for each day revealed no significant differences in water consumption between groups preexposed with vehicle or fluoxetine.

3.2.2. Conditioning

Fluoxetine preexposure had no effect on aversions induced by either cocaine or fluoxetine. The 2×3×5 mixed-model ANOVA revealed a significant main effect of Trial [F (4, 176) = 12.691, p<.001] and Conditioning Drug [F (2, 44) = 42.217, p<.001] as well as Trial × Preexposure Drug [F (4, 176) = 7.336, p<.001] and Trial × Conditioning Drug [F (8, 176) = 7.399, p<.001] interactions. Although aversions were induced by both cocaine and fluoxetine over trials, there was no effect of fluoxetine preexposure on conditioning (i.e., there was no main effect of Preexposure or any other significant interaction with Preexposure as a term). In the absence of these significant interactions, post-hoc analyses were not conducted (see Fig. 3).

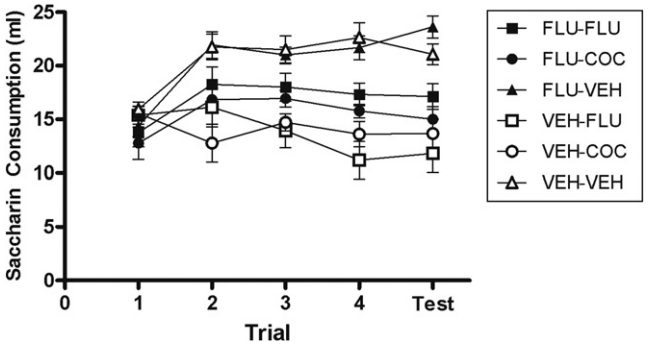

Fig. 3. Mean (±SEM) saccharin consumption (ml) for all subjects in groups preexposed to fluoxetine or vehicle and conditioned with cocaine (18 mg/kg), fluoxetine (10 mg/kg) or vehicle. Since there were no significant interaction effects, post-hoc analyses for individual trials were not run.

3.3. Experiment 3

3.3.1. Preexposure

Both groups slightly increased water consumption over this phase, regardless of the preexposure compound. The 2×20 repeated measures ANOVA revealed a significant main effect of Preexposure Day [F (19, 912) = 4.839, p<.001], but no significant effect of Preexposure Drug and no significant Preexposure Day × Preexposure Drug interaction (see Fig. 4).

3.3.2. Conditioning

Cocaine preexposure attenuated aversions induced by both cocaine and fluoxetine. The 2×3×5 mixed-model ANOVA revealed a significant main effect of Trial [F (4, 176) = 11.973, p<.001], Preexposure Drug [F (1, 44) = 17.387, p<.001] and Conditioning Drug [F (2, 44) = 19.307, p<.001]. Additionally, there were significant interactions of Trial × Preexposure Drug [F (4, 176) = 10.199, p<.001], Trial × Conditioning Drug [F (8, 176) = 9.531, p<.001] and Trial × Preexposure Drug × Conditioning Drug [F (8, 176) = 16.884, p<.001]. Given the significant three-way interaction, Fisher LSD post-hoc analyses were run to examine differences between groups on individual trials. On Trial 1, there were no significant differences between any groups. On Trial 2, Group VEH–COC, subjects preexposed to vehicle and injected with cocaine during conditioning, drank significantly less than both Groups VEH–VEH and COC–COC (all ps<.05). Group VEH–FLU drank significantly less than Groups VEH–VEH and COC–FLU (p = .049). Group COC–VEH drank significantly more than Groups COC–FLU (p = .025). On Trials 3 and 4, the abovementioned comparisons remained significant; however, on Trial 3 Groups COC–VEH and COC–FLU were no longer different. Also, Group VEH–VEH drank significantly

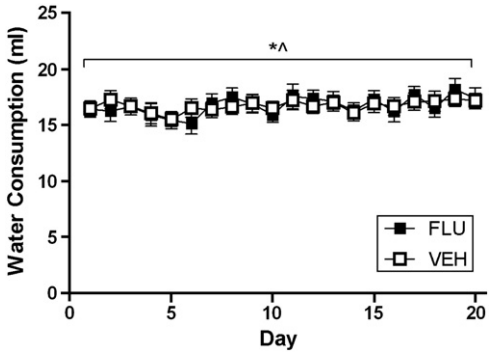

Fig. 2. Mean (±SEM) water consumption (ml) for all subjects in groups preexposed to fluoxetine or vehicle. *Significant effect of preexposure day; ^Significant preexposure drug by preeexposure day interaction.

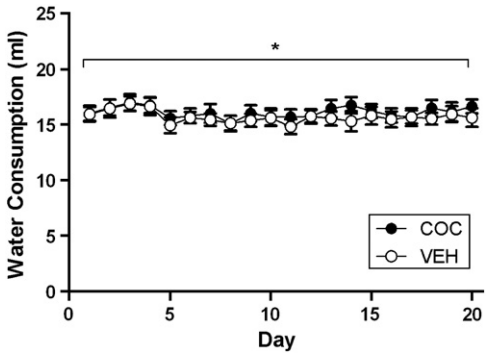

Fig. 4. Mean (±SEM) water consumption (ml) for all subjects in groups preexposed to cocaine or vehicle. *Significant effect of preexposure day.

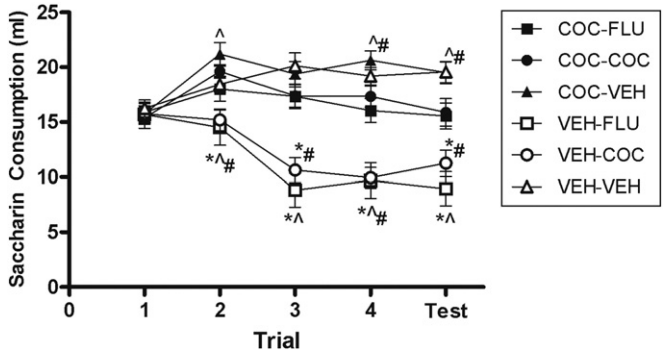

Fig. 5. Mean (±SEM) saccharin consumption (ml) for all subjects in groups preexposed to cocaine or vehicle and conditioned with cocaine (18 mg/kg), fluoxetine (10 mg/kg) or vehicle. *Significantly different from Group VEH–VEH; #Significantly different from Group COC–COC; ^Significantly different from Group COC–FLU.

more than Group COC–FLU ($p<.03$; see Fig. 5). Additionally on Trial 4, Group COC–VEH drank significantly more than Groups COC–COC and COC–FLU ($ps<.037$). These patterns were maintained on the Final Aversion Test, with the additional significant difference between Group COC–COC and Group VEH–VEH ($p=.039$).

4. Discussion

Although preexposure to fluoxetine failed to affect aversions induced by cocaine (an effect likely due to the specific doses used in the assessment; Cannon et al., 1975; De Beun et al., 1996; for a review of the US preexposure preparation, see Riley and Simpson, 2001), cocaine preexposure significantly attenuated aversions induced by fluoxetine (and cocaine). The fact that cocaine preexposure attenuated aversions induced by itself is consistent with the often reported effects of such preexposure on cocaine-induced aversions (see Davis and Riley, 2007; Riley and Simpson, 1999). The attenuation of fluoxetine-induced CTAs by cocaine preexposure is consistent with the position that these two compounds induce CTAs via a common mechanism. Since the primary action of fluoxetine is 5-HT reuptake inhibition, and cocaine also acts at SERT, these results support a role of 5-HT in the acquisition of cocaine-induced CTAs. The role of SERT inhibition in cocaine aversions has been indirectly implicated by Sora et al. (2001) in their analysis of cocaine conditioned place preferences in transgenic mice with the 5-HT transporter removed. In their work, it was reported that mice lacking the 5-HT transporter (via knock-out procedures) still displayed cocaine-induced place preferences and did so at levels greater than intact mice. Such an effect was interpreted as cocaine being aversive in wildtype mice and the removal of this aversive effect in the transgenic KO's allowed cocaine to condition greater place preferences. More direct evidence of a role of 5-HT in cocaine's aversive effects was recently reported by Jones et al. (2009) assessing the effects of fluoxetine preexposure on cocaine-induced taste aversions (also in mice). In their report, Jones et al. demonstrated that fluoxetine preexposure attenuated aversions induced by cocaine.

Although the present work indicates a role of 5-HT in cocaine-induced CTAs, the fact that cocaine preexposure more completely attenuated CTAs induced by itself (rather than by fluoxetine) suggests that the compounds induce CTAs via similar, but non-identical, mechanisms. That is, while both preexposed groups displayed significantly attenuated aversions, subjects in Group COC–COC differed from the COC–VEH control group on fewer trials than did subjects in Group COC–FLU, suggesting a stronger attenuation of the aversion in the COC–COC group. The system receiving the most support in cocaine-induced aversions is norepinephrine (NE; Freeman et al., 2005; Jones et al., 2009; Serafine and Riley, 2009). Although there is substantial evidence supporting the roles of NE and 5-HT in the aversive effects of cocaine, it is important to note that not all data are supportive of their involvement in such effects. For example, Serafine and Riley (2009) reported that preexposure to cocaine potentiated aversions induced by desipramine. If NET inhibition was responsible (even partially) for the aversive effects of cocaine, it would be expected that cocaine preexposure would attenuate desipramine-induced aversions (given that aversions induced by desipramine would be mediated presumably by its inhibition of NE reuptake). More directly, Freeman et al. (2008) reported that the NE antagonists prazosin and propranolol potentiated cocaine-induced taste aversions. Given that each of these compounds blocks NE activity, yet potentiates cocaine-induced aversions, argues against a role of NE in cocaine's aversive effects. Finally, the fact that pretreatment with the NE reuptake inhibitor desipramine completely attenuates aversions induced by cocaine argues for a limited role of 5-HT in cocaine-induced aversions (Jones et al., 2009; Serafine and Riley, 2009).

The present experiments used the cross-drug preexposure design to evaluate the possible role of 5-HT in the aversive effects of cocaine. The premise underlying the use of this design is that any attenuating effects of drug history on the acquisition of aversions induced by a second compound are a function of tolerance to their common aversive effects (see Riley and Simpson, 2001). It should be noted, however, that there are a number of other interpretations, both associative (Cappell and Poulos, 1979; Peck and Ader, 1974; Willner, 1978) and nonassociative (Gamzu, 1977; Parker et al., 1973), of the effects of US preexposure. While different, each model is consistent with the position that the attenuation produced is a result of some similarity between the aversive effects of the preexposed and conditioning drug (for a discussion, see Jones et al., 2009). The specific nature of this aversive effect, however, is not yet identified. This introduces an interesting limitation to the use of the US preexposure design in assessing common mechanisms, i.e., the identification (or isolation) of the specific aversive effects mediating the aversion. This limitation arises with drugs with multiple neurochemical actions. For example, cocaine which inhibits the reuptake of 5-HT, NE and DA may be attenuating the ability of fluoxetine (that has specific activity on only one of these systems) to induce aversions not due to a similarity at the neurochemical level, but at some level more downstream, e.g., sickness, novelty, and stress. The only thing that could be implicated would be that there is a common aversive state, but not what that specific state is or how it is generated. This doesn't argue that the cross-drug preexposure design is ineffective in assessments of mechanism, only that interpretation of such results must be examined in relation to work from other designs examining the basis of aversion learning.

From the present results, it appears that 5-HT may play a role in the aversive effects of cocaine. Such a conclusion does not address the relative contribution of 5-HT to this effect or the possible role other neurotransmitters (e.g., NE and DA) may play. What is clear is that data from a range of studies are needed in these determinations. Each assessment has interpretational strengths and weaknesses, and a convergence of results may be necessary to conclude confidently the biology of cocaine's aversive effects. It also remains to be determined if such mediation parallels (neuroanatomically or neurochemically) that of other effects of cocaine, e.g., reward. An understanding of these substrates may be important to determine the nature of aversion learning with cocaine specifically or with drugs of abuse in general.

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