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Possible role of norepinephrine in cocaine-induced conditioned taste aversions

Katherine M. Serafine *, Anthony L. Riley

Psychopharmacology Laboratory, Department of Psychology, American University, Washington, DC 20016, USA

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ABSTRACT

Although cocaine readily induces taste aversions, little is known about the mechanisms underlying this effect. The present series of studies used the cross-drug preexposure design to determine if desipramine (DMI), a selective NE transporter (NET) inhibitor, and cocaine (a nonselective monoamine transport inhibitor) induce aversions by a common mechanism, specifically increases in NE activity. Male Sprague-Dawley rats were exposed to DMI prior to aversion conditioning with cocaine (Experiment 1) and with cocaine prior to aversion conditioning with DMI (Experiment 2). All drugs were administered subcutaneously at 18 mg/kg. Preexposure to DMI attenuated aversions induced by cocaine. However, preexposure to cocaine did not weaken DMI-induced aversions and, in fact, potentiated aversions induced by DMI on several trials. The asymmetrical results are discussed in terms of the possible role NE might play in the mediation of aversions induced by cocaine. Additionally, serial use of these compounds is discussed in terms of clinical implications.

1. Introduction

In an attempt to assess the neurochemical mediation of the aversive effects of cocaine, Freeman et al. (2005) recently compared cocaine-induced conditioned taste aversions (CTAs) with those induced by three monoamine transporter inhibitors with relative specificity for NE, DA or 5-HT, i.e., desipramine (NE transporter [NET] inhibitor), GBR 12909 (DA transporter [DAT] inhibitor), and clomipramine (5-HT transporter [SERT] inhibitor). Aversions induced by desipramine (DMI) most closely resembled the strength and acquisition of those induced by cocaine. Aversions induced by GBR 12909 only matched those of cocaine at the highest dose tested (50 mg/kg), while those induced by the SERT inhibitor clomipramine were never comparable to those induced by cocaine. Given that the relatively selective NET inhibitor DMI induced aversions comparable to those induced by the relatively nonselective monoamine transporter inhibitor cocaine, Freeman et al. concluded that NE activity may be mediating the aversions induced by both compounds. It should be noted, however, that such evidence is quite indirect, i.e., although comparable aversions may indicate a common mechanism, such effects could be produced by different systems (LeBlanc and Cappell, 1974; Ton and Amit, 1983).

Another assay that may be useful in assessing the role of NE in cocaine's aversive effects is the cross-drug preexposure preparation. This preparation is a variation of a well-established procedure (the US preexposure design) used in assessing the effects of drug history in taste aversion learning. In this latter design, animals are given exposure to a drug prior to taste aversion conditioning with that same drug. Typically, such preexposure attenuates the acquisition of the taste aversion, an attenuation generally explained to be a function of adaptation or tolerance to the drug's aversive effects during preexposure (Berman and Cannon, 1974; Dacanay et al., 1984; LeBlanc and Cappell, 1974; Riley et al., 1984; for reviews including alternative interpretations, see Cappell and LeBlanc, 1977; Randich and LoLordo, 1979; Riley and Simpson, 2001). Such attenuating effects have also been reported when the preexposure and conditioning drugs are different, i.e., the cross-drug preexposure effect (Braveman, 1975; De Beun et al., 1996; Goudie and Thornton, 1975), although this effect is not always symmetrical (Goudie and Thornton, 1975; Rabin et al., 1988; Switzman et al., 1981). In cross-drug preexposure preparations, it is generally assumed that drugs that are working by a similar mechanism will produce attenuated aversions due to cross tolerance to their aversive effects (Berendsen and Broekkamp, 1994; Gommans et al., 1998). Such a suggestion is supported by the fact that the cross-drug preexposure effect is often reported with drugs from the same class (e.g., see De Beun et al., 1993; Gommans et al., 1998; although see Brown et al., 1979; Cappell and LeBlanc, 1977; Ton and Amit, 1985 for examples in which cross-drug preexposure occurs between drugs of different classes). Given that such effects are widely reported and the design is used to investigate the underlying mediation of aversion learning (De Beun et al., 1993; Olivier et al., 1999), the present series of studies used this preparation to assess the role of NE in cocaine-induced taste aversions. Specifically, different groups of subjects were exposed to cocaine (or DMI) prior to taste aversion conditioning with DMI (or cocaine). If NE was involved in cocaine-induced aversions, it would be expected that preexposure to cocaine would attenuate

* Corresponding author. Psychopharmacology Laboratory, Department of Psychology, American University 4400 Mass. Ave., NW, Washington, DC 20016, USA. Tel.: +1 202 885 1721; fax: +1 202 885 1081.
E-mail address: kserafine@gmail.com (K.M. Serafine).

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aversions induced by DMI. Similarly, preexposure to the NET inhibitor DMI would be expected to attenuate cocaine-induced aversions. These predictions were tested in Experiment 1 (the effects of DMI preexposure on cocaine-induced taste aversions) and Experiment 2 (the effects of cocaine preexposure on DMI-induced taste aversions).

2. General method

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 the experiments. Procedures recommended by the National Research Council (1996), the Committee on Guidelines for the Care and Use of Animals 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 two weeks prior to the initiation of the 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. Except where noted, food and water were available ad libitum.

2.3. Procedure

Phase I: habituation. Following $23^{2/3}$ h of water deprivation, subjects were given 20-min access to tap water daily between 1000 and 1200 h. 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.

Phase II: preexposure. Water consumption for all subjects was recorded throughout Habituation. Animals were ranked on average water consumption over the last 3 days of Habituation and assigned to a preexposure condition (drug or vehicle). Five h following their regular 20-min water access (between 1500–1700 h), animals were injected subcutaneously (SC) with drug or vehicle every 4th day for a total of 5 injections (five total drug or vehicle injections). No injections were given during intervening days.

Phase III: conditioning. Conditioning began 4 days following the final preexposure injections. On Day 1 of conditioning, all subjects were given 20-min access to a novel saccharin solution. Immediately following this presentation, animals from each preexposure condition were rank ordered based on saccharin consumption and assigned to a treatment group (either vehicle or drug) such that overall consumption was comparable between groups. Subjects received a SC injection of either distilled water or drug approximately 20 min after access to saccharin. The three 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.

Phase IV: 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 Aversion Test.

2.4. Drugs and solutions

Cocaine hydrochloride (generously provided by NIDA) and desipramine 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, the differences in mean water consumption were analyzed for each experiment using a 2×20 repeated measures ANOVA with the between-subjects variable of Preexposure Drug (0 or 18 mg/kg) and the within-subjects variable of Preexposure Day (1–20). During conditioning, the differences in mean saccharin consumption were analyzed for each experiment using a 2×3×5 mixed-model ANOVA with the between-subjects variables of Preexposure Drug and Conditioning Drug and the within-subjects variable of Trial (1–4: Final Aversion Test). Where appropriate, Fisher's PLSD post-hoc analyses were used to examine mean saccharin consumption differences on individual trials. All significance levels were set at $p \leq .05$.

3. Experiment 1

Following water habituation, subjects ($N=50$) were assigned to a preexposure condition and were given injections of either DMI (18 mg/kg) or vehicle (matched in volume) during the preexposure phase. During the conditioning phase, subjects were injected with either 18 mg/kg cocaine, 18 mg/kg DMI or vehicle (matched in volume), yielding six experimental groups, specifically, desipramine-desipramine (DMI-DMI; $n=9$), desipramine-cocaine (DMI-COC; $n=9$), desipramine-vehicle (DMI-VEH; $n=8$), vehicle-desipramine (VEH-DMI; $n=8$), vehicle-cocaine (VEH-COC; $n=8$), and vehicle-vehicle (VEH-VEH; $n=8$). The first designation for each group refers to the drug given during preexposure; the second refers to the drug given during conditioning. The specific choices of doses for the preexposure and conditioning drugs were based on several factors. First, given that drug preexposure could increase or decrease the ability of a second drug to induce an aversion, it was important to use a dose of cocaine during conditioning that produced intermediate aversions. Aversions induced by 18 mg/kg cocaine have been reported to be intermediate in nature (see Ferrari et al., 1991; Freeman et al., 2005) and, therefore, this dose was used for conditioning. Second, given that the effects of US preexposure are dependent in part on the dose of the preexposed drug (and its relation to the conditioning drug; see Riley and Simpson, 2001), it was important to use a dose during preexposure that produced effects (in terms of inducing aversions) comparable to that of the conditioning drug. Aversions induced by 18 mg/kg DMI match those induced by 18 mg/kg cocaine (Freeman et al., 2005), and thus, this dose was used during DMI preexposure.

4. Results

4.1. Preexposure

The 2×20 repeated measures ANOVA revealed a significant effect of Preexposure Day [$F(19, 912)=13.027$, $p<.001$] but not of Drug [$F(1, 48)=.001$, $p=.974$]. There was a significant Drug x Preexposure Day interaction [$F(19, 912)=5.470$, $p<.001$] in which Group DMI drank significantly less than Group VEH on Days 2, 6, 14, 15, 18, and 10 (all p's $<.05$; see Fig. 1). Body weight significantly increased for both groups over the preexposure phase (all p's $<.001$). There were no significant differences in this increase as a function of the preexposure injection (i.e., DMI or vehicle; $p=.970$).

4.2. Conditioning

The 2×3×5 mixed-model ANOVA revealed significant effects of Trial [$F(4, 176)=5.361$, $p<.001$], Preexposure Drug [$F(1, 44)=15.855$, $p<.001$] and Conditioning Drug [$F(2, 44)=11.446$, $p<.001$] and

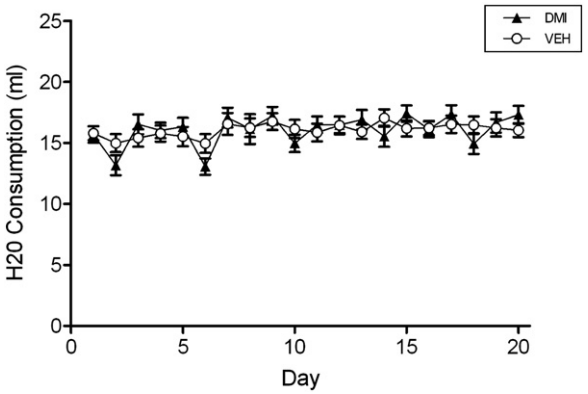

Fig. 1. Mean (±SEM) water consumption (ml) for all subjects in groups preexposed to DMI or vehicle. There was a significant effect of preexposure day and a significant drug by day interaction (all *p*'s<.001).

significant Trial x Conditioning Drug [F (8, 176)=7.695, p<.001], Trial×Preexposure Drug [F (4, 176)=8.833, p<.001] and Trial×Preexposure Drug×Conditioning Drug [F (8, 176)=2.127, p<.036] interactions. On Trial 1, there were no significant differences in consumption between any groups. On Trial 2, Groups VEH–COC and VEH–DMI drank significantly less saccharin than Group VEH–VEH (both *p*'s<.002) as well as significantly less than Group DMI–VEH (both *p*'s<.02). Group DMI–DMI drank significantly more saccharin than Group VEH–DMI (p<.001), but did not differ from Group DMI–VEH. Group DMI–COC drank significantly more than Group VEH–COC (p=.015), but did not differ from Group DMI–VEH. These patterns of significance between comparisons of interest were maintained on Trials 3 (all *p*'s<.003) and 4 (all *p*'s<.04). However, on the Final Aversion Test Group DMI–COC drank significantly less than Group DMI–VEH (p=.003). Groups DMI–VEH and VEH–VEH did not differ on any trial or on the Final Aversion Test (see Fig. 2). As during preexposure, body weight increased over conditioning (*p*'s<.001) with no significant differences among groups (p=649).

5. Experiment 2

Following water habituation, subjects (N=50) were assigned to a preexposure condition and were given injections of either cocaine (18 mg/kg) or vehicle (matched in volume) during the preexposure phase. During conditioning, rats were injected with either 18 mg/kg cocaine, 18 mg/kg DMI or vehicle (matched in volume), yielding six experimental groups, specifically, cocaine-cocaine (COC-COC; n=9), cocaine-desipramine (COC-DMI; n=8), cocaine-vehicle (COC-VEH; n=8), vehicle-cocaine (VEH-COC; n=9), vehicle-desipramine (VEH-DMI; n=8), and vehicle-vehicle (VEH-VEH; n=8). The specific dose of DMI (18 mg/kg) was based on its ability to induce intermediate aversions; the dose of cocaine (18 mg/kg) was based on its ability to produce aversions comparable to the training dose of DMI (see Experiment 1).

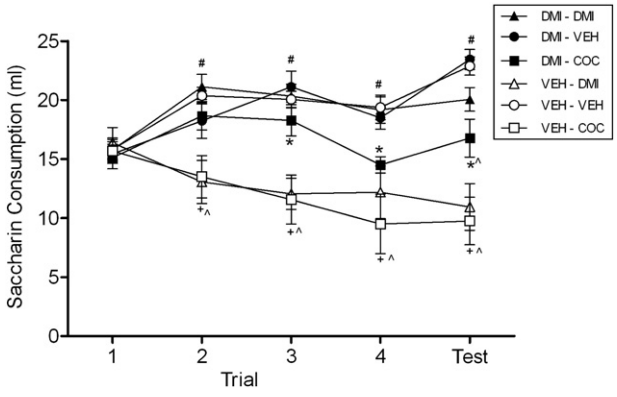

Fig. 2. Mean (±SEM) saccharin consumption (ml) for all subjects in groups preexposed with DMI or vehicle and conditioned with cocaine, DMI or vehicle. Groups VEH–DMI and VEH–COC drank significantly less saccharin than Group VEH–VEH (significant on four trials). Preexposure to DMI attenuated aversions induced by cocaine (on three trials) and DMI (on four trials). Group DMI–COC drank significantly less than Group DMI–VEH only on the final aversion test. *Significantly different from Group VEH–DMI; #Significantly different from Group VEH–COC; +Significantly different from Group VEH–VEH. ^Significantly different from Group DMI–VEH. All *p*'s<.05.

6. Results

6.1. Preexposure

The 2×20 repeated measures ANOVA revealed a significant effect of Preexposure Day [F (19, 912)=4.077, p<.001] and a significant Drug x Preexposure Day interaction [F (19, 912)=3.368, p<.001]. There was no significant effect of Drug [F (1, 48)=1.545, p=.220]. Overall, consumption increased for the cocaine-preexposed group over this phase, but remained stable for animals in the vehicle-preexposed group (see Fig. 3). Body weight significantly increased for both groups over the preexposure phase (all *p*'s<.001). There were no significant differences in this increase as a function of the preexposure injection (i.e., cocaine or vehicle) (p=.157).

6.2. Conditioning

The 2×3×5 mixed-model ANOVA revealed a significant effect of Trial [F (4, 176)=8.369, p<.001] and Conditioning Drug [F (2, 44)= 57.060, p<.001] (but not Preexposure Drug) and significant Trial× Conditioning Drug [F (8, 176)=20.968, p<.0001], Trial×Preexposure Drug [F (4, 176)=3.438, p=.010] and Trial×Preexposure Drug×Conditioning Drug [F (8,176)=4.537, p<.001] interactions. On Trial 1, there were no significant differences in consumption between any groups. On Trial 2, Groups VEH–COC and VEH–DMI drank significantly less saccharin than Group VEH–VEH (both *p*'s<.0001). Group COC–COC drank significantly more saccharin than Group VEH–COC (p=.0005) but did not differ from Group COC–VEH. Interestingly, Group COC–DMI drank significantly less than Group COC–VEH (p<.0001) and did not differ from Group VEH–DMI. These patterns were maintained on Trial 3. The only difference on this trial was that Group COC–DMI drank significantly less than Group VEH–DMI (all *p*'s<.02). The effects on Trial 4 (all *p*'s<.02) paralleled those of Trial 2. On the Final Aversion Test, Group COC–DMI again drank significantly less than Group VEH–DMI (all *p*'s<.03). Groups COC–VEH and VEH–VEH did not differ on any trial or on the Final Aversion Test (see Fig. 4). As during preexposure, body weight

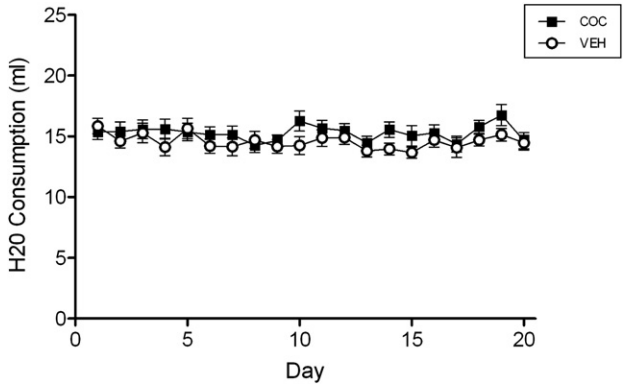

Fig. 3. Mean (±SEM) water consumption (ml) for all subjects in groups preexposed to cocaine or vehicle. There was a significant effect of preexposure day and a significant drug by day interaction (all *p*'s<.001).

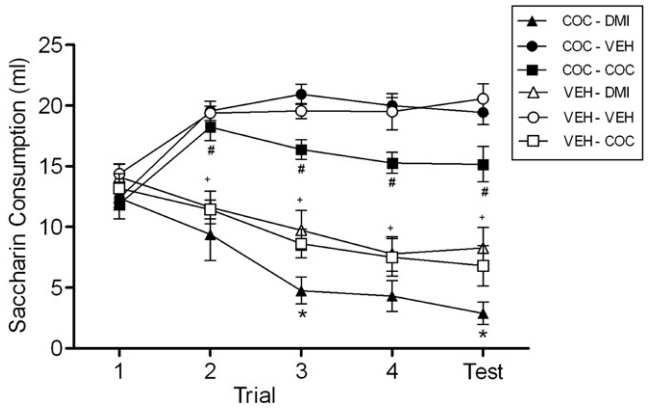

Fig. 4. Mean (±SEM) saccharin consumption (ml) for all subjects in groups preexposed with cocaine or vehicle and conditioned with DMI, cocaine or vehicle. Groups VEH–DMI and VEH–COC drank significantly less saccharin than Group VEH–VEH (significant on four trials). Preexposure to cocaine attenuated aversions induced by cocaine (on four trials), but did not attenuate aversions induced by DMI (on any trial). Group COC–DMI drank significantly less than Group VEH–DMI on Trial 3 and the Final Aversion Test. *Significantly different from Group VEH-DMI; #Significantly different from Group VEH-COC; +Significantly different from Group VEH-VEH. All *p*'s <.05.

increased over conditioning (*p*'s<.001) with no significant differences among groups (*p*=.177).

7. General discussion

The present experiments used the cross-drug preexposure CTA design to assess the similarity of the aversive effects of cocaine and DMI (Berendsen and Broekkamp, 1994; Braveman, 1975; De Beun et al., 1993; Gommans et al., 1998). The fact that preexposure to the selective NET inhibitor DMI attenuated aversions induced by the nonselective monoamine transporter inhibitor cocaine suggests that NE activity may be involved in the aversive effects of the two drugs. This suggestion is based on the assumption underlying the US preexposure effect in taste aversion learning: that an attenuated taste aversion induced by Drug B following exposure to Drug A reflects some weakening of (or tolerance to) the aversive effects common to both drugs (Berendsen and Broekkamp, 1994; De Beun et al., 1993; Gommans et al., 1998; Olivier et al., 1999). Given that DMI and cocaine share a common effect of NET inhibition, the attenuating effects of preexposure to DMI on cocaine-induced aversions may be a function of changes in reactivity to NE. This attenuation, in turn, suggests that NE may be involved in the aversive effects of each of the two compounds. Although DMI and cocaine both inhibit NE reuptake, however, it is not clear that this is the mechanism mediating their aversive effects. There may be other drug-induced effects (concurrent with NET inhibition) that could be mediating the aversive effects of the two drugs. For example, NET inhibitors also have varying affinity for DAT (Bonisch and Bruss, 1994; Richelson and Pfenning, 1984; Tatsumi et al., 1997) and increase extracellular levels of both DA and NE (Shen et al., 2004). Cocaine and selective NET inhibitors have also been reported to increase extracellular DA in DAT knock-out (KO) mice, suggesting that NET might be acting as an alternative uptake site for DA in such a preparation (Carboni et al., 2001; Hall et al., 2002). Given this relative nonselectivity of DMI, it is difficult to identify which specific mechanism is being assessed in the cross-drug preexposure procedure. Interestingly, had DMI preexposure failed to attenuate cocaine-induced aversions, a role of NE in such aversions would appear less likely (see Berendsen and Broekkamp, 1994; De Beun et al., 1993; Olivier et al., 1999). Thus, their common action on NE (via NET inhibition) remains a possible mechanism underlying the preexposure effect and their ability to induce aversions. The attenuation reported here could also be a function of other drug-induced effects (mediated by or independent of NE), e.g., novelty, anxiety, sickness (for a discussion of the nature of the US in taste aversion learning, see Gamzu, 1977; Garcia and Ervin, 1968; Grigson, 1997; Parker, 2003), that could be nonspecific to the compounds examined. Assessing the effects of preexposure to drugs with no known noradrenergic actions on cocaine-induced taste aversions would allow an evaluation of such nonspecific effects (or at least effects independent of NE). The fact that alcohol preexposure has been reported to attenuate cocaine-induced taste aversions (see Grakalic and Riley, 2002; Kunin et al., 1999) clearly indicates that factors other than NET inhibition can mediate the effects of drug preexposure on cocaine-induced aversions and argues that assessments of the effects of preexposure to compounds with a myriad of neurochemical actions is necessary to more fully characterize the specific mechanism mediating the effects of preexposure to DMI on aversions induced by cocaine.

In Experiment 2, cocaine preexposure failed to attenuate aversions induced by DMI. Such a finding is somewhat surprising given the results of Experiment 1 in which DMI preexposure attenuated aversions induced by cocaine. If the abovementioned explanation for that attenuation is correct (tolerance to the aversive effects of NE activity during preexposure), one might expect that the order of drug presentation would not be important. To account for the absence of any attenuating effects of cocaine preexposure on DMI, one could posit that although there is overlap in their stimulus effects, these effects are not identical. That is, if DMI's effects on NET were greater than those of cocaine, one would expect preexposure to DMI would attenuate cocaine-induced aversions. On the other hand, preexposure to cocaine (and the resulting NE activity) might weaken DMI's aversive effects but not sufficiently enough to affect its ability to induce taste aversions. It is also possible that the asymmetry is a function of non-overlapping stimulus effects in addition to NE activation. For example, if DMI induced aversions via its actions on both NE and other neurotransmitter systems while cocaine-induced aversions were limited to NE, one might expect preexposure to DMI would attenuate cocaine-induced aversions (based on their overlapping NE activity), but preexposure to cocaine would only partially affect aversions induced by DMI (as a function of its additional stimulus properties). Such asymmetrical interactions in the preexposure effect have been reported (Braveman, 1975; Grakalic and Riley, 2002; Rabin et al., 1988; see Riley and Simpson, 2001 for an overview) and explained by such non-overlapping stimulus effects (Goudie and Thornton, 1975; Rabin et al., 1988; Switzman et al., 1981). Although possible, such mechanisms remain speculative until the biochemical bases of aversions induced by the compounds are determined and changes in these systems with drug preexposure are made.

Not only did cocaine preexposure fail to attenuate DMI-induced aversions, but on at least two trials it significantly potentiated these aversions. Accounting for such potentiation requires an explanation other than a reduction in the aversive effects of NE. One possible explanation for this potentiation is that the history with cocaine changed NET's expression and affinity. For example, chronic cocaine has been reported to upregulate NET (Beveridge et al., 2004; Burchett and Bannon, 1997; Kitayama et al., 2006) or increase NET binding site densities (Macey et al, 2003; although see Arroyo et al., 2000; Benmansour et al., 1992; Karoum et al., 1990; Yeh and Desouza, 1991 for instances when cocaine exposure did not result in modulation of NET). Such increases are often thought to reflect compensatory changes in response to cocaine-induced increases in NE levels. An upregulated system could give rise to increased DMI binding, resulting in even greater increases of extracellular NE upon its administration. This excess NE could then be responsible for the strengthened DMI-induced aversions on Trials 3 and 5. Although possible, it is important to note that the preexposure phase used in the present procedures only consisted of five administrations of the drug with 3 recovery days between each administration. The studies in which chronic cocaine resulted in NET modulation used extended exposure periods (up to 100 consecutive days, see Belej et al., 1996; Beveridge et al., 2004;

Burchett and Bannon, 1997; Kitayama et al., 2006; Lanteri et al., 2008; Macey et al., 2003). Consequently, it is not clear if similar NET upregulation would occur under the conditions of the present study. Although the focus in these experiments has been on NET inhibition as the common mechanism mediating cocaine- and DMI-induced aversions, it is important to consider a possible role of DA in the reported effects, given that both cocaine and DMI also have affinity for DAT. If cross tolerance developed to cocaine's actions at DAT, the aversive effects of NET inhibition produced by DMI might seem enhanced in comparison.

Independent of the mechanism underlying the preexposure effects reported in the present studies, it is clear that the two drugs interact, albeit in a serial manner. The nature of these interactions may be important given that DMI and cocaine may be used serially in the human population as a function of the comorbidity of depression and drug use (Brown et al., 1998; Markou et al., 1998; Myers et al., 1984; Rounsaville et al., 1991). One can imagine the scenario in which depressed individuals with a history of antidepressant medication might self medicate with cocaine (Markou et al., 1998; Moss and Werner, 1992; Weiss et al., 1992). Conversely, escalated and dysregulated cocaine use may be a factor in the production of anhedonia (Koob and LeMoal, 2008) that is then treated with an antidepressant (Brown et al., 1998; Rounsaville et al., 1991). The present results may have implications for both scenarios. For example, depressed patients previously treated with DMI might have reduced aversive effects of self-administered cocaine, increasing the vulnerability to cocaine use. Further, compliance of treatment with DMI in patients with a history of cocaine might be difficult given what appears to be exacerbation of its aversive effects following cocaine use. The nature of these potential interactions and their impact on abuse liability and/or antidepressant compliance are not known. What is clear is that drug history is an important factor in both the rewarding and aversive effects of psychoactive drugs such as cocaine and DMI. Additional research investigating the serial (and concurrent) interaction of these compounds, at these and other doses, is necessary to further understand their relative impact on their use and/or effectiveness.

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