



Assessment of a Noradrenergic Role in the Mediation of Cocaine-Induced Conditioned Taste Aversion



Andrey Verendeev^{1,2}, Kevin B. Freeman², and Anthony L. Riley²

¹Department of Psychology, Boğaziçi University, Istanbul, Turkey; ²Psychopharmacology Laboratory, Department of Psychology, American University, Washington D.C

Abstract

Although the physiological bases of cocaine's rewarding effects have been well characterized, the mechanisms underlying its aversive effects are less understood. Recently, Freeman et al. (2005) reported that desipramine, a selective norepinephrine transporter (NET) inhibitor, produced aversions comparable to cocaine when matched by dose (18, 32 and 50 mg/kg) in the conditioned taste aversion (CTA) preparation, while similar comparisons using transporter inhibitors for dopamine and serotonin produced much weaker aversions than cocaine. To further characterize a noradrenergic role in cocaine's aversive effects, the present study examined cocaine-induced CTAs under conditions of pretreatment with clonidine, an α_2 autoreceptor agonist capable of decreasing noradrenergic tone. In Experiment 1, multiple doses of clonidine (.01, .018 and .032 mg/kg) were injected intraperitoneally (ip) in rats following consumption of a novel NaCl solution to determine the highest possible dose that would not produce aversions on its own. In Experiment 2, rats were given a novel NaCl solution and injected ip with clonidine or its vehicle and subsequently injected subcutaneously (sc) with cocaine (20 mg/kg) or its vehicle. These manipulations were repeated for eight trials, with 3 water-recovery days between each trial. Over trials, animals treated with clonidine before cocaine displayed a weaker acquisition of cocaine-induced taste aversions than cocaine-injected animals pretreated with the clonidine vehicle. The fact that clonidine partially attenuated cocaine-induced aversions supports a possible role of norepinephrine in the mediation of cocaine's aversive effects.

Rationale & Objectives

Cocaine has been shown to produce both rewarding (Wise et al., 1992) and aversive (Ferrari et al., 1991) effects. Interest in its aversive effects stems from the notion that the acceptability and abuse liability of compounds such as cocaine may be mediated by a balance between its rewarding and aversive effects (Riley and Simpson, 2001).

Understanding the physiological bases of cocaine's aversive effects may give insight into a key vulnerability factor mediating its abuse potential.

Freeman et al. (2005) reported that desipramine, a selective NET inhibitor, produced aversions similar to those produced by cocaine.

To assess a noradrenergic contribution to cocaine-induced taste aversions, the present study assessed the ability of cocaine to induce CTAs following pretreatment with the α_2 adrenergic neurotransmitter agonist clonidine.

Method

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.

Conditioning

On Day 1 of this phase, all subjects were given 20-min access to a novel NaCl solution. Immediately following access to NaCl, the subjects were ranked according to NaCl consumption and assigned to four groups ($n = 8-9$ per group) such that each group was comparable in consumption. Approximately 20 min after NaCl access, each subject in Experiment 1 was removed from its home cage, taken to a separate room and injected ip with various doses of clonidine (.01, .018 and .032 mg/kg) or its vehicle (saline) equivalent volume to the highest clonidine dose. In Experiment 2, subjects were pretreated with clonidine (.032 mg/kg, ip) or its vehicle immediately after NaCl access and approximately 20 min after NaCl access they were injected with cocaine (20 mg/kg, sc) or its vehicle. On the following 3 water-recovery days, animals in both experiments 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 five (Experiment 1) or seven (Experiment 2) complete cycles. On the day following the final water-recovery session, all subjects were given 20-min access to NaCl in a one-bottle test of the aversion to NaCl (Test). No injections were given following this test. Fluid was available only during the 20-min access period on conditioning and recovery days.

Results

For all statistical tests, $\alpha = 0.05$

Experiment 1

A 4 x 6 repeated measures ANOVA revealed no significant main effects of Group ($F(3,145) = 34, p = .918$) or a Group x Trial interaction ($F(15,145) = 1.303, p = .207$), indicating that clonidine was not aversive on its own in this preparation.

Experiment 2

A 4 x 8 repeated measures ANOVA revealed significant main effects of Group ($F(3,203) = 5.903, p < .003$) and Trial ($F(7,203) = 10.788, p < .001$) as well as a significant Group x Trial interaction ($F(21,203) = 3.892, p < .001$).

Subsequent one-way ANOVAs conducted for each Trial in Experiment 2 revealed no main effect of Group on Trials 1 through 3 (all $F_s(3,30) \geq .059$; all $p_s \geq .069$) but did reveal significant main effects of Group on the remaining Trials and on the Aversion Test (all $F_s(3,30) \geq 5.774$, all $p_s \leq .003$).

Fisher's PLSD post-hoc tests revealed that on Trial 6 the cocaine-treated animals pretreated with clonidine drank significantly more than cocaine-treated animals pretreated with vehicle ($p = .01$). Moreover, on the final aversion test the difference between the two groups approached statistical significance ($p = .08$).

Additionally, on the last two trials cocaine-treated animals pretreated with clonidine did not differ from control subjects administered clonidine and the cocaine vehicle (all $p_s \geq .10$). Cocaine-treated animals pretreated with the clonidine vehicle differed from their non-conditioned controls on all trials except Trials 1 and 2 (all $p_s \leq .03$). The two control groups did not differ on any trial (all $p_s \geq .19$).

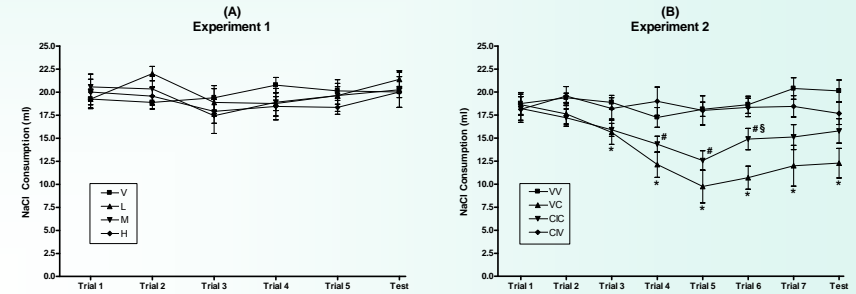


Fig. 1. (A) Mean NaCl consumption (ml) for groups receiving 0.01 (L), 0.018 (M) and 0.03 (H) mg/kg clonidine or the drug vehicle (V) on each of five conditioning trials and on the aversion test. (B) Mean NaCl consumption for groups pretreated with either vehicle (V) or clonidine (C) and subsequently injected with either vehicle (V) or cocaine (C) on each of seven conditioning trials and on the aversion test. Bars above and below each point represent S.E.M. *Significantly different from Group VV (Figure 1B). #Significantly different from Group CV (Figure 1B). §Significantly different from Group VC (Figure 1B).

Conclusions

Clonidine on its own produced no significant taste aversions even after repeated conditioning trials (Experiment 1).

Animals treated with clonidine before cocaine displayed a weaker aversion acquisition than cocaine-injected animals pretreated with the clonidine vehicle (Experiment 2).

The fact that clonidine partially attenuated cocaine-induced aversions supports a possible role of norepinephrine in the mediation of cocaine's aversive effects.

References

Ferrari CM, O'Connor DA, Riley AL. Cocaine-induced taste aversions: Effect of route of administration. *Pharmacol. Biochem. Behav.*, 1991;38:267-71.

Freeman KB, Rice KC, Riley AL. Assessment of monoamine transporter inhibition in the mediation of cocaine-induced conditioned taste aversion. *Pharmacol. Biochem. Behav.*, 2005; 82: 583-589.

Riley AL, Simpson GR. The attenuating effects of drug preexposure on taste aversion conditioning: generality, experimental parameters, underlying mechanisms, and implications for drug use and abuse. In: Mowrer RR, Klein SB, editors. *Contemporary learning theory*, 2nd edition. Hillsdale, New Jersey: Lawrence Erlbaum Associates; 2001. p. 505-59.

Wise RA, Baucu P, Carlezon WA. Self-stimulation and drug reward mechanisms. *Ann. N.Y. Acad. Sci.*, 1992; 654:192-8.

