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Pharmacology, Biochemistry and Behavior 82 (2005) 583 – 589
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

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

Kevin B. Freeman [a,*], Kenner C. Rice [b], Anthony L. Riley [a]

[a] *Psychopharmacology Laboratory, Department of Psychology, American University, Washington, DC 20016, United States*
[b] *Laboratory of Medicinal Chemistry, NIDDK, National Institutes of Health, Bethesda, MD 20892, United States*

Received 4 June 2005; received in revised form 14 September 2005; accepted 26 October 2005

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,

* Corresponding author. Tel.: +1 202 302 4514; fax: +1 202 885 1081.
E-mail address: kf6802a@american.edu (K.B. Freeman).

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doi:10.1016/j.pbb.2005.10.014

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