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Assessment of the contributions of Na^+ channel inhibition and general peripheral action in cocaine-induced conditioned taste aversion

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Abstract

While the rewarding properties of cocaine appear to be mediated by its blockade of central monoamine uptake, the mechanisms and sites of action for cocaine's aversive effects have yet to be determined. Using the conditioned taste aversion (CTA) preparation, the present study examined the role of Na^+ channel blockade in cocaine's aversive effects by comparing cocaine to the local anesthetic procaine at three doses (18, 32 and 50 mg/kg). Furthermore, the role of cocaine's peripheral actions in its aversive effects was examined by comparing cocaine to the quaternary analog cocaine methiodide (equimolar to the three doses of cocaine) in establishing CTAs. Procaine and cocaine methiodide each dose-dependently suppressed saccharin consumption, indicating that the aversive effects of cocaine are, in part, mediated by its inhibition of Na^+ channels and via its activity in the PNS. However, the fact that the aversions induced by procaine and cocaine methiodide were weaker than those induced by cocaine at each dose tested suggests other factors are involved in its aversive effects. Possible reasons for the weaker aversions induced by procaine and cocaine methiodide relative to cocaine were discussed.

Keywords: Cocaine; Cocaine methiodide; Procaine; Conditioned taste aversion; Central effects; Peripheral effects; Local anesthetic; Na^+ channel

1. Introduction

Cocaine, like a number of other recreational drugs, produces both rewarding (Nomikos and Spyraki, 1988; Pickens and Thompson, 1968; Wise et al., 1992) and aversive (Cappell and LeBlanc, 1977; Hunt and Amit, 1987) effects. Interest in its aversive properties stems from the notion that the acceptability and abuse liability of compounds such as cocaine may be mediated by an interaction between its rewarding and aversive properties. That is, drugs with high abuse potential may possess rewarding properties that overshadow their aversive side effects. Understanding the conditions under which each of these effects occurs, how they might interact and their physiological base may give insight into the vulnerability to cocaine's use and abuse (see Riley and Simpson, 2001).

In relation to the physiological substrate of cocaine's affective properties, the neurochemical basis of cocaine reward has been well documented (Rocha, 2003; Hemby et al., 1994; Ritz et al., 1987). On the other hand, little is known about the biology of cocaine's aversive effects. One method for assessing these effects is the conditioned taste aversion (CTA) preparation (Garcia and Ervin, 1968; Revusky and Garcia, 1970), a behavioral assay of drug toxicity (Riley and Freeman, 2004; Riley and Tuck, 1985). Cocaine-induced taste aversions have been demonstrated under a variety of conditions (Gomez, 2002; Riley and Simpson, 1999; Etkind et al., 1998; Goudie et al., 1977; Heinrichs et al., 1998), across genders (Van Haaren and Hughes, 1990) and with a variety of strains (Grigson and Freet, 2000; Ferrari et al., 1991; Glowa et al., 1994). While the aversions induced by emetic agents

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such as LiCl appear to be related to nausea (Hunt and Amit, 1987; Garcia et al., 1974), much evidence indicates that aversions with recreational drugs like cocaine are often induced in the absence of malaise (Parker, 2003). As such, the research findings regarding the mechanisms of aversion with emetics cannot be generalized to cocaine.

The numerous systems and sites of cocaine action complicate the identification and isolation of the mechanisms underlying its aversive effects. Cocaine is a nonselective systemic inhibitor of the transporters for the three monoamine neurotransmitters (Taylor and Ho, 1978). Furthermore, cocaine possesses local anesthetic effects that arise from its inhibition of voltage-gated sodium (Na^+) channels in neuronal membranes (Matthews and Collins, 1983). In addition, cocaine's interaction with these systems occurs systemically, that is, in both the central nervous system (CNS) and the peripheral nervous system (PNS) (Pitts and Marwah, 1989; Woolverton and Johnson, 1992). Although cocaine's effects are well documented, their relative roles in its aversive effects, as well as the site(s) of action (CNS and/or PNS) of these effects, are unknown.

One way of assessing these roles is to use cocaine analogs that mimic certain actions of cocaine without exerting its broad range of effects (Shriver and Long, 1971). One such analog is procaine, a cocaine analog that mimics cocaine's blockade of Na^+ channels (Matthews and Collins, 1983; McNeal et al., 1985), but that lacks cocaine's high affinity for the DA transporter (Ritz et al., 1987). In addition, the PNS effects of cocaine can be assessed by the peripheral administration of cocaine methiodide, a quaternary analog of cocaine that carries a permanent positive charge on the nitrogen moiety, thus, greatly diminishing its passage across the blood brain barrier (BBB) and preventing its activity in the CNS (Brodie et al., 1960; Hemby et al., 1994).

The present study compared cocaine to cocaine methiodide and procaine in a CTA test with the aim of independently assessing the roles for Na^+ channel blockade and general peripheral activity in cocaine's aversive effects. To allow for dose comparisons, cocaine and procaine were matched on three doses (18, 32 and 50 mg/kg) with cocaine methiodide being administered at equimolar doses for each of the cocaine doses (see below). If Na^+ channel blockade (CNS and/or PNS) has a role in cocaine-induced taste aversions, then procaine should induce some degree of aversion in the CTA preparation. In addition, if the aversive properties of cocaine are in part mediated by its actions in the PNS, then peripherally administered cocaine methiodide should induce aversions, as well. However, if cocaine-induced taste aversions are mediated exclusively by central monoamine uptake inhibition, then neither procaine nor peripherally administered cocaine methiodide should induce significant aversions.

2. Method

2.1. Subjects

The subjects were 80 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. Electrospray ionization mass spectra of cocaine methiodide were recorded on a Shimadzu 2025 for chemical structure verification.

2.3. Drugs and solutions

Cocaine hydrochloride, procaine hydrochloride and cocaine methiodide were each prepared as 10 mg/ml solutions in distilled water. All drug doses are expressed as the salt. Cocaine was generously provided by the National Institute on Drug Abuse (NIDA). Procaine was purchased from Sigma Pharmaceuticals. Cocaine methiodide was synthesized from cocaine free base (also generously provided by NIDA). To effect this synthesis and determine the yield, an initial amount of cocaine free base (1.0 g cocaine, 0.0033 mol) was dissolved in acetone (40 ml) (Fisher) at room temperature. Following this, methyl iodide (0.311 ml, 0.005 mol) (Aldrich) was added. The reaction mixture was refluxed for a total of 3 h. The reaction mixture was cooled to room temperature, and the cocaine methiodide precipitate was filtered under reduced pressure. The cocaine methiodide was washed for three cycles with diethyl ether (15 ml each wash) (Fisher) and dried at room temperature. From the filtrate, an additional amount of the cocaine methiodide was obtained via the procedure described above giving 1.314 g, a 98% overall total yield of pure cocaine methiodide. The purity of the product was determined using Electrospray Ionization Mass Spectrometry (ESI-MS) on a Shimadzu 2025. The spectra obtained in the positive mode (direct injection of methanol solution of the cocaine methiodide) gave a single peak $[M]^+$=318 for the cocaine methiodide. This process