Available online at www.sciencedirect.com

SCIENCE DIRECT

Pharmacology, Biochemistry and Behavior 80 (2005) 281–288

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

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

Kevin B. Freeman[a,*], Monika I. Konaklieva[b], Anthony L. Riley[a]

[a]*Psychopharmacology Laboratory, Department of Psychology, American University, Washington, DC 20016, United States*
[b]*Organic Synthesis Laboratory, Department of Chemistry, American University, Washington, DC 20016, United States*

Received 13 August 2004; received in revised form 16 November 2004; accepted 23 November 2004
Available online 19 December 2004

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

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

0091-3057/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2004.11.009

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

was repeated as needed with additional cocaine free base to produce the necessary supply of cocaine methiodide for the study.

Saccharin (0.1% sodium saccharin, Sigma) was prepared as a 1 g/l solution in tap water.

2.4. Procedure

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.

Phase II. Conditioning: On Day 1 of this phase, all 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 10 groups (n=8 per group) such that each group was comparable in consumption. Approximately 20 min after saccharin access, each subject was removed from its home cage, taken to a separate room and injected subcutaneously (SC) with cocaine (18, 32 or 50 mg/kg), cocaine methiodide (23.6, 41.9 or 65.5 mg/kg) or procaine (18, 32 or 50 mg/kg). The doses used for cocaine methiodide were the molar equivalents (mol eq.) of the three doses used for cocaine. The use of equimolar doses for cocaine methiodide was employed to remove the influence of the relatively heavy Iodine ion (I^-) from the drug weight, thus ensuring that cocaine and cocaine methiodide were matched molecule for molecule. Because the salt forms of procaine and cocaine were both developed with the same acid (HCl), no molar adjustment was made for these two compounds. A final group of animals was injected with the drug vehicle (distilled water) equivolume to the highest cocaine methiodide dose. Following the injection, each animal was returned to its respective home cage. This treatment resulted in the following groups: Groups Coc Low, Coc Med, Coc High, Met Low, Met Med, Met High, Pro Low, Pro Med, Pro High and Veh. The first variable in each group designation refers to the drug administered, i.e., cocaine (Coc), cocaine methiodide (Met) and procaine (Pro). The second variable refers to the dose, i.e., Low (18 mg/kg or mol eq.), Medium (32 mg/kg or mol eq.) and High (50 mg/kg or mol eq.). The control group received vehicle (Veh). On the following 3 water-recovery days, all animals 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 four complete cycles. On the day following the final water-recovery session, all subjects were given 20-min access to saccharin in a one-bottle test of the aversion to saccharin (Aversion Test). No injections were given following the test. Fluid was available only during the 20-min access period on conditioning and recovery days.

2.5. Statistical analysis

Differences in mean saccharin consumption were analyzed using a 10×5 Repeated Measures Analysis of Variance (ANOVA) with the between-subjects variable of Group (Coc Low, Coc Med, Coc High, Met low, Met Med, Met High, Pro Low, Pro Med, Pro High and Veh) and the within-subjects variable of Trial (Trials 1–4 and the Aversion Test). One-way ANOVAs were used to analyze mean saccharin consumption for Trials 1–4 and the Aversion Test with the between-subjects variable of Group. Fisher's PLSD post hoc tests were used to make pairwise comparisons between groups on Trials 1–4 and on the Aversion Test. All significance levels were set at $p \leq .05$.

3. Results

A 10×5 repeated-measures ANOVA revealed significant main effects for Group ($F(9,70)=18.01$, $p \leq .0009$) and Trial ($F(4,280)=66.48$, $p \leq .0009$) as well as a significant Group×Trial interaction ($F(36,280)=8.39$, $p \leq .0009$). On Trial 1, a one-way ANOVA revealed no significant main effect for Group ($F(9,80)=.028$, $p \geq .999$). However, subsequent one-way ANOVAs conducted on Trials 2–4 and the Aversion Test revealed significant main effects for Group, all F's$(9,80) \geq 14.50$, p's$\leq .0009$.

Fig. 1 illustrates the mean consumption of saccharin (±S.E.M.) for subjects injected with vehicle (Group Veh) and subjects injected with the low drug dose (Groups Coc Low, Met Low and Pro Low) on Trials 1–5. On Trial 1, post hoc analyses using Fisher's PLSD revealed no differences in saccharin consumption among groups (all p's$\geq .7126$). Significant differences in saccharin consumption did emerge on Trial 2 as subjects in Group Coc Low consumed significantly less saccharin than those in Groups Veh, Met Low and Pro Low (all p's$\leq .0066$). There were no significant differences in consumption between Group Veh and Groups Pro Low and Met Low or between Groups Met Low and Pro Low on this trial (all p's$\geq .1660$). These patterns were repeated on the remaining conditioning trials with the exception of Group Pro Low consuming significantly less saccharin than Group Veh on Trials 3 and 4 (all p's$\leq .0071$).

Fig. 2 illustrates the mean consumption of saccharin (±S.E.M.) for Groups Coc Med, Met Med, Pro Med and Veh for Trials 1–5. On Trial 1, there were no significant differences in saccharin consumption among groups (all p's$\geq .7126$). On Trial 2, Groups Coc Med, Met Med and Pro Med each consumed significantly less saccharin than Group Veh (all p's$\leq .0445$). Furthermore, Group Coc Med consumed significantly less saccharin than Groups Met Med and Pro Med (all p's$\leq .0002$). Groups Met Med and Pro Med did not differ (p=.1885). Over trials, these patterns were repeated with the exception of Group Met Med consuming

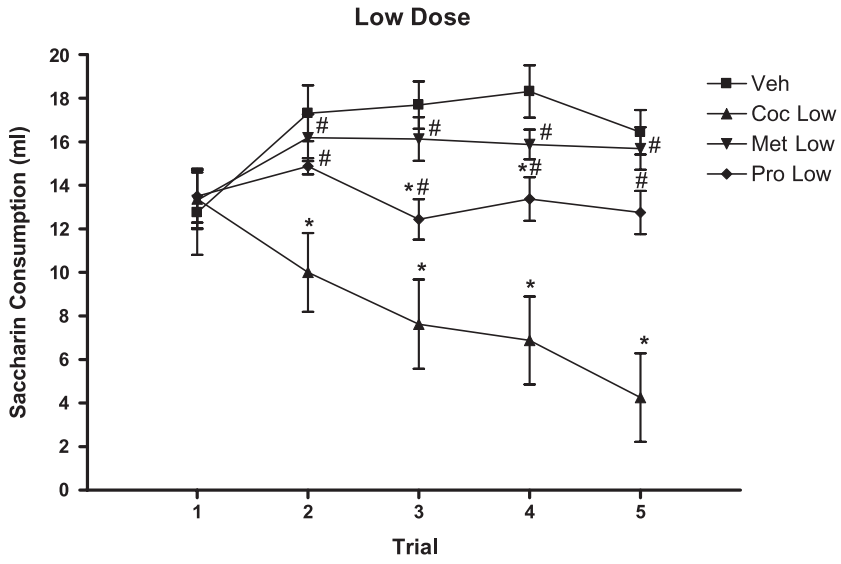

Fig. 1. Mean saccharin consumption (ml) for subjects in Groups Veh, Coc Low, Met Low and Pro Low (n=8 per group) on each of five conditioning trials. Bars above and below each point represent S.E.M. *Significantly different from Group Veh. #Significantly different from Group Coc Low.

significantly less saccharin than Group Pro Med on Trial 5 (p=.0192).

Fig. 3 illustrates the mean consumption of saccharin (±S.E.M.) for Groups Coc High, Met High, Pro High and Veh for Trials 1–5. On Trial 1, there were no significant differences in saccharin consumption among groups (all p's≥.7126). On Trial 2, Groups Coc High, Met High and Pro High consumed significantly less saccharin than Group Veh (all p's≤.0012). Also, Group Coc High consumed significantly less saccharin than Groups Met High and Pro High (all p's≤.0125), although the latter two groups did not differ (p=.3184). Over trials, this pattern was maintained with an exception on Trial 5 where Groups Coc High, Met High and Pro High did not differ (all p's≥.3184).

The data for the Aversion Test are presented here in order to facilitate comparisons across all drugs and doses tested. Fig. 4 illustrates the mean saccharin consumption for all groups (Veh, Coc Low, Coc Med, Coc High, Met Low, Met Med, Met High, Pro Low, Pro Med and Pro High) on this test. All treatment groups with the exception of Group Met Low (p=.1753) consumed significantly less saccharin than Group Veh (all p's≤.0071). Groups Coc High and Coc Med did not differ significantly in consumption (p=.4221) but did each consume significantly less than Group Coc Low (all p's≤.0035) with Group Coc High consuming less than all other groups (all p's≤.0125). Group Coc Med did not differ significantly from Groups Met High or Pro High (all p's≥.0670) but did consume significantly less than the

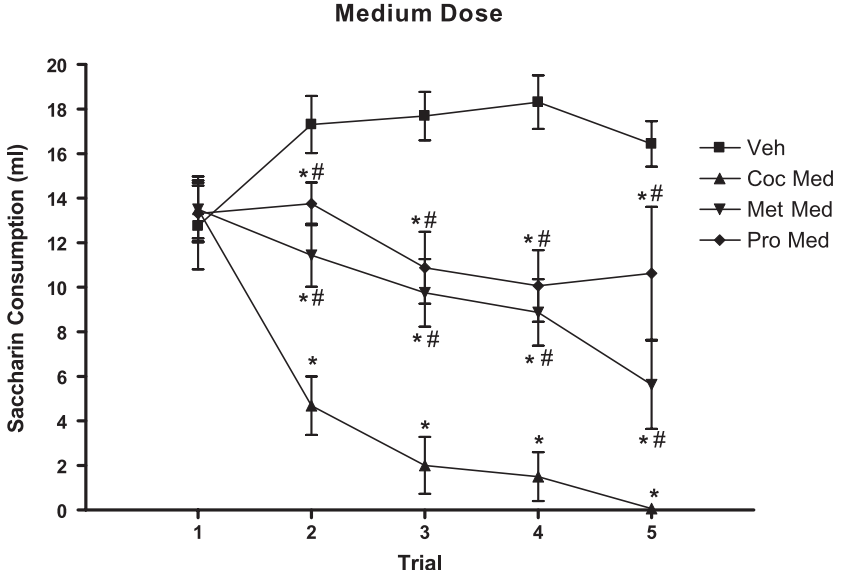

Fig. 2. Mean saccharin consumption (ml) for subjects in Groups Veh, Coc Med, Met Med and Pro Med (n=8 per group) on each of five conditioning trials. Bars above and below each point represent S.E.M. *Significantly different from Group Veh. #Significantly different from Group Coc Med.

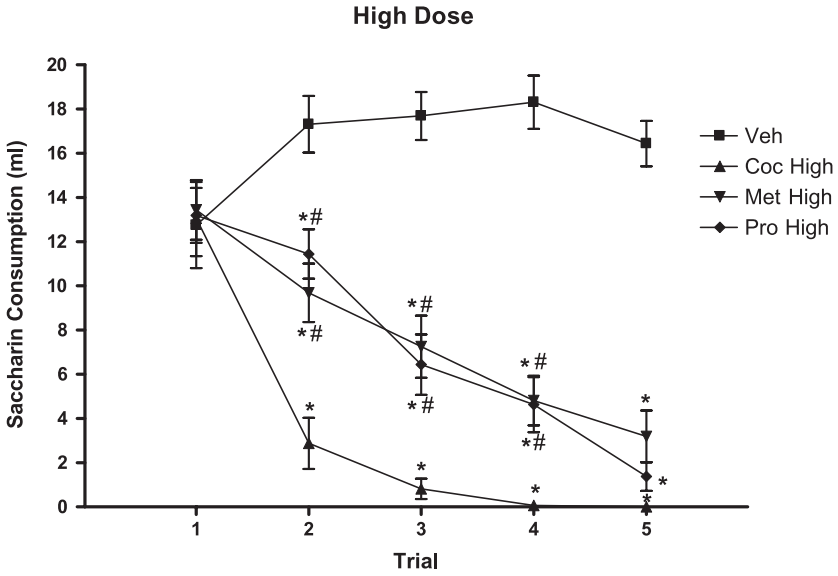

Fig. 3. Mean saccharin consumption (ml) for subjects in Groups Veh, Coc High, Met High and Pro High (n=8 per group) on each of five conditioning trials. Bars above and below each point represent S.E.M. *Significantly Different from Group Veh. #Significantly different from Group Coc High.

remaining groups outside of its drug class (all p's<.0001). Furthermore, Group Coc Low consumed significantly less than Groups Met Low and Pro Low (all p's≤.0005) but did not differ from Groups Pro High, Pro Med, Met High or Met Med (all p's≥.0777). At no point was there a significant difference in consumption between any methiodide (Met) or procaine (Pro) group within a dose category (all p's≥.1646). Groups Met High and Pro High each consumed significantly less saccharin than Groups Met Low, Pro Low, Met Med and Pro Med (all p's≤.0255). In addition, Group Met Med consumed significantly less saccharin than Groups Met Low and Pro Low (all p's≤.0137), and Group Pro Med consumed significantly less than Group Met Low (p=.0017) but did not differ in consumption from Group Pro Low (p=.0670).

The abovementioned differences in consumption were limited to days on which saccharin was presented. That is, water consumption remained high on water-recovery sessions and never differed among groups.

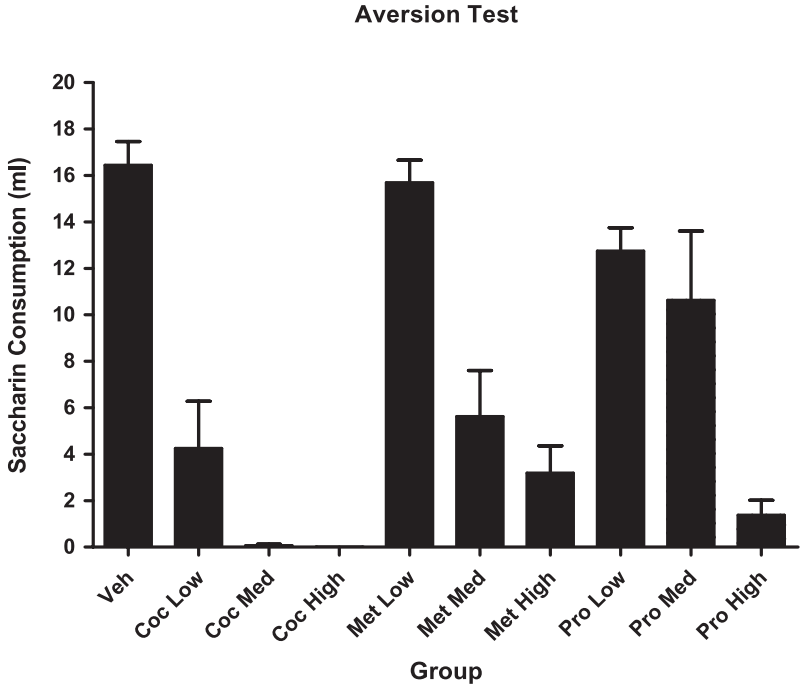

Fig. 4. Mean saccharin consumption (ml) for subjects in Groups Veh, Coc Low, Coc Med, Coc High, Met Low, Met Med, Met High, Pro Low, Pro Med and Pro High (n=8 per group) on the Aversion Test. Bars above and below each point represent S.E.M.

4. Discussion

The present study used the CTA design to assess the role of Na^+ channel blockade and the role of peripheral actions in cocaine's aversive effects. As described, cocaine, procaine and cocaine methiodide each dose-dependently suppressed saccharin consumption with the magnitude of cocaine's suppression greater than procaine and cocaine methiodide at each dose tested. On the Aversion Test, subjects receiving the low dose of cocaine did not significantly differ in saccharin consumption from those receiving the high dose of procaine and cocaine methiodide or the medium dose of cocaine methiodide. Furthermore, animals receiving the medium dose of cocaine did not significantly differ in saccharin consumption from those receiving the high doses of procaine and cocaine methiodide.

Given that procaine was effective at inducing aversions, it appears that Na^+ channel blockade may, in part, be responsible for mediating cocaine's aversive effects. However, the weaker aversions induced by procaine relative to cocaine suggest that additional processes may be at work in the mediation of cocaine's aversive effects. One possibility is that Na^+ channel blockade is working in concert with monoamine transporter inhibition to induce aversions with cocaine. If the aversive properties of cocaine are mediated by Na^+ channel and monoamine transporter inhibition, it is reasonable to expect that an analog acting on only one of these processes would produce effects that are qualitatively similar but lesser in magnitude. In this study, procaine, relative to cocaine, follows such a pattern.

Similar to the results with procaine, the aversions induced by peripherally administered cocaine methiodide followed the dose-dependent pattern of cocaine but to a lesser degree, thus, strongly implicating a peripheral action in the mediation of cocaine's aversive effects. That is, some action of cocaine in the PNS appears to be contributing to its aversive effects given that cocaine methiodide's actions are limited to the PNS only (Hemby et al., 1994). However, relative to cocaine, the weaker aversions induced by cocaine methiodide suggests that cocaine's aversive effects are not mediated in the PNS alone.

It should be noted that the reported differences in inducing aversions could be due to other differences between cocaine, procaine and cocaine methiodide, e.g., relative binding affinity and efficacy at various receptors. At the Na^+ channel, IC_{50} values (μM) for cocaine and procaine are 57 and 440, respectively (Wilcox et al., 2001). As such, higher doses of procaine might be needed to produce results comparable to those of cocaine when investigating the effects of Na^+ channel blockade with these compounds. The data presented in this study are consistent with this position. At the low dose of cocaine (18 mg/kg), the reduction in saccharin consumption is not significantly different from the high dose of procaine (50 mg/kg), suggesting that with higher doses procaine may be equally efficacious as cocaine in Na^+ channel inhibition. It is important to note also that in addition to procaine acting at the Na^+ channel, it (at higher concentrations) may have some effects at the DA transporter, another possible site at which cocaine's aversions may be mediated. However, procaine's binding affinity at this site is marginal when compared to cocaine. At the DA transporter, procaine has an IC_{50} value (μM) of 153 and cocaine has a value of 1.0 (Wilcox et al., 2001). Therefore, the ratio of procaine/cocaine for Na^+ channel and DA-transporter affinities (IC_{50}) are 7.72 and 153, respectively. Furthermore, other studies have demonstrated the failure of procaine to mediate dopamine-dependent processes (Ikemoto, 2003; Morency and Beninger, 1986; Delfs et al., 1990) at doses comparable to the highest used in this study (Rigon and Takahashi, 1996; Hemby et al., 1994; although see Spyraki et al., 1982).

Although cocaine methiodide has been reported to have reduced affinity for the DA transporter relative to cocaine (Abraham et al., 1992), recent studies have demonstrated its ability to induce cardiovascular effects similar to cocaine at equimolar doses (Dickerson et al., 1999) and to induce behavioral effects comparable to cocaine when administered ICV at doses lower than those used for the comparison with cocaine (Hemby et al., 1994). In addition, cocaine methiodide induces lethality that, on an equal molar basis, is comparable to that seen with cocaine (Witkin et al., 1993). As such, cocaine methiodide appears to generalize to cocaine on a number of levels when the doses are matched on a molar basis. If this is the case, then the weaker aversions induced with cocaine methiodide relative to cocaine implicate both CNS and PNS activity in the mediation of cocaine's aversive effects.

When taken together, the results with procaine and cocaine methiodide raise several important issues. First, it appears that the aversive effects of cocaine are mediated in part by Na^+ channel inhibition. Second, the processes mediating cocaine's aversive effects are not located exclusively in the CNS. Finally, given that the rewarding effects of cocaine appear to be mediated by monoamine transporter inhibition in the CNS, the mechanisms and sites of action for cocaine's aversive effects may not be identical to the processes mediating cocaine reward. While these results show a possible mode of action for cocaine-induced taste aversions, further research is needed to characterize specific mechanisms. Future work should be directed towards isolating and testing the numerous pharmacological effects of cocaine as they relate to behavioral endpoints. Specific monoamine transporter inhibitors (e.g., GBR-12909, fluoxetine) can be employed to determine the relative contributions of cocaine's actions at these sites in the induction of aversions. In addition, quaternary analogs of local anesthetics (e.g., QX-314) can be used to assess the peripheral and central contributions

of Na^+ channel inhibition in aversion conditioning. Assessments such as these will facilitate the characterization of the systems and sites of action mediating the aversive effects of cocaine and will ultimately lead to a better understanding of a major factor affecting the acceptability of this drug of abuse.

Acknowledgement

This research was supported by a grant from the Mellon Foundation to A.L.R. The authors thank Maya Kostova for technical assistance. Requests for reprints should be directed to Kevin B. Freeman, Psychopharmacology Laboratory, Department of Psychology, American University, Washington, DC 20016 or kf6802a@american.edu.

References

Abraham P, Pitner JB, Lewin AH, Boja JW, Kuhar MJ, Caroll FI. N-modified analogues of cocaine: synthesis and inhibition of binding to the cocaine receptor. J Med Chem 1992;35:141–4.

Brodie BB, Kurz H, Schanker LS. The importance of dissociation constant and lipid-solubility in influencing the passage of drugs into the cerebrospinal fluid. J Pharmacol Exp Ther 1960;130:20–5.

Cappell H, LeBlanc AE. Gustatory avoidance conditioning by drugs of abuse: relationships to general issues in research on drug dependence. In: Milgram NW, Krames L, Alloway TM, editors. Food aversion learning. Plenum Publishing;1977. p. 133–67.

Delfs JM, Schreiber L, Kelley AE. Microinjection of cocaine into the nucleus accumbens elicits locomotor activation in the rat. J Neurosci 1990;10:303–10.

Dickerson LW, Rodak DJ, Kuhn FE, Wahlstrom SK, Tessel RE, Visner MS, et al. Cocaine-induced cardiovascular effects: lack of evidence for a central nervous system site of action based on hemodynamic studies with cocaine methiodide. J Cardiovasc Pharmacol 1999;33:36–42.

Etkind SA, Fantegrossi WE, Riley AL. Cocaine and alcohol synergism in taste aversion learning. Pharmacol Biochem Behave 1998;59:649–55.

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

Garcia J, Ervin FR. Gustatory-visceral and telereceptor-cutaneous conditioning: adaptation in internal and external milieus. Comm Behav Bio 1968,1:389–415.

Garcia J, Hankins WG, Rusiniak KW. Behavioral regulation of the milieu interne in man and rat. Science 1974;85:824–31.

Glowa JR, Shaw AE, Riley AL. Cocaine-induced conditioned taste aversions: comparisons between effects in LEW/N and F344/N rat strains. Psychopharmacology 1994:229–32.

Gomez F. Conditioned saccharin aversion induced by self-administered cocaine negatively correlates with the rate of cocaine self-administration in rats. Brain Res 2002;946:214–20.

Goudie AJ, Dickins DW, Thornton EW. Cocaine-induced conditioned taste aversions in rats. Pharmacol Biochem Behav 1977;8:757–61.

Grigson PS, Freet CS. The suppressive effects of sucrose and cocaine, but not lithium chloride, are greater in Lewis than in Fischer rats: evidence for the reward comparison hypothesis. Behav Neurosci 2000;114:353–63.

Heinrichs SC, Klaassen A, Koob GF, Schulteis G, Ahmed S, De Souza EB. Corticotropin-releasing factor receptor blockade enhances conditioned aversive properties of cocaine in rats. Psychopharmacology 1998;136:247–55.

Hemby SE, Jones GH, Hubert GW, Neill DB, Justice JB. Assessment of the relative contribution of peripheral and central components in cocaine place conditioning. Pharmacol Biochem Behav 1994;47:973–9.

Hunt T, Amit Z. Conditioned taste aversion induced by self-administered drugs: paradox revisited. Neurosci Biobehav Rev 1987;11:107–30.

Ikemoto S. Involvement of the olfactory tubercle in cocaine reward: intracranial self-administration studies. J Neurosci 2003;23:9305–11.

Matthews JC, Collins A. Interactions of cocaine and cocaine congeners with sodium channels. Biochem Pharmacol 1983;32:455–60.

McNeal ET, Lewandowski GA, Daly JW, Creveling CR. [^{3}H]Batrachotoxinin-A 20α-benzoate binding to voltage-sensitive sodium channels: a rapid and quantitative assay for local anesthetic activity in a variety of drugs. J Med Chem 1985;28:381–8.

Morency MA, Beninger RJ. Dopaminergic substrates of cocaine-induced place conditioning. Brain Res 1986;399:33–41.

National Research Council. Guide for the care and use of laboratory animals. Washington, DC: National Academy Press; 1996.

National Research Council. Guidelines for the care and use of mammals in neuroscience and behavioral research. Washington, DC: National Academy Press; 2003.

Nomikos GG, Spyraki C. Cocaine-induced place conditioning: importance of route of administration and other procedural variables. Psychopharmacology 1988;94:167–73.

Parker LA. Taste avoidance and taste aversions: evidence for two different processes. Learn Behav 2003;31:165–72.

Pickens R, Thompson T. Cocaine-reinforced behavior in rats: effects of reinforcement magnitude and fixed-ratio size. J Pharmacol Exp Ther 1968;161:122–9.

Pitts DK, Marwah J. Autonomic actions of cocaine. Can J Physiol Pharm 1989;67:1168–76.

Revusky S, Garcia J. Learned associations over long delays. In: Bower G, Spence J. editors. Psychology of learning and motivation: advances in research and theory, vol. 4. New York: Academic Press;1970. p. 1–84.

Rigon AR, Takahashi RN. Stimulant activities of dimethocaine in mice: reinforcing and anxiogenic effects. Psychopharmacology 1996;127:323–7.

Riley AL, Freeman KB. Conditioned flavor aversions: assessment of drug-induced suppression of food intake. In: Crawley JN, Gerfen C, McKay R, Rogawski M, Sibley DR, Skolnick P, editors. Curr Pro Neurosci, vol. 8.6E. New York: Wiley; 2004. p. 1–12.

Riley AL, Simpson GR. Cocaine preexposure fails to sensitize the acquisition of cocaine-induced taste aversions. Pharmacol Biochem Behav 1999;63:193–9.

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, NJ: Lawrence Erlbaum Associates; 2001. p. 505–59.

Riley AL, Tuck DL. Conditioned taste aversions: a behavioral index of toxicity. Ann NY Acad Sci 1985;442:272–92.

Ritz MC, Lamb RJ, Goldberg SR, Kuhar MJ. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 1987;237:1219–23.

Rocha BA. Stimulant and reinforcing effects of cocaine in monoamine transporter knockout mice. Eur J Pharmacol 2003;479:107–15.

Shriver DA, Long JP. A pharmacologic comparison of some quaternary derivatives of cocaine. Arch Int Pharmacodyn 1971;189:198–208.

Spyraki C, Fibiger HC, Phillips AG. Cocaine-induced place preference conditioning: lack of effects of neuroleptics and 6-hydroxydopamine lesions. Brain Res 1982;253:195–203.

Taylor K, Ho BT. Comparison of inhibition of monoamine uptake by cocaine, methylphenidate and amphetamine. Res Commun Chem Pathol Pharmacol 1978;21:67–75.

van Haaren F, Hughes CE. Cocaine-induced conditioned taste aversions in male and female Wistar rats. Pharmacol Biochem Behav 1990;37:693–96.

Wilcox KM, Paul IA, Ordway GA, Woolverton WL. Role of the dopamine transporter and the sodium channel in the cocaine-like discriminative stimulus effects of local anesthetics in rats. Psychopharmacology 2001;157:260–8.

Wise RA, Bauco P, Carlezon WA. Self-stimulation and drug reward mechanisms. Ann NY Acad Sci 1992;654:192–8.

Witkin JM, Newman AH, Nowak G, Katz JL. Role of dopamine D_1 receptors in the lethal effects of cocaine and a quaternary methiodide analog. J Pharmacol Exp Ther 1993;267:266–74.

Woolverton WL, Johnson KM. Neurobiology of cocaine abuse. Trends Pharmacol Sci 1992;13:193–200.