Pharmacology, Biochemistry and Behavior 99 (2011) 688–695

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Alcohol-preferring (P) rats are more sensitive than Wistar rats to the reinforcing effects of cocaine self-administered directly into the nucleus accumbens shell

Simon N. Katner *, Scott M. Oster, Zheng-Ming Ding, Gerald A. Deehan Jr., Jamie E. Toalston, Sheketha R. Hauser, William J. McBride, Zachary A. Rodd

Department of Psychiatry, Institute of Psychiatric Research, Indiana University School of Medicine, Indianapolis, IN 46202, USA

ARTICLE INFO

Article history:
Received 15 March 2011
Received in revised form 16 June 2011
Accepted 18 June 2011
Available online 25 June 2011

Keywords:
Intracranial self-administration
Nucleus accumbens shell
Reinforcement
Alcohol-preferring rats
Ethanol
Cocaine

ABSTRACT

Wistar rats will self-administer cocaine directly into the nucleus accumbens shell (AcbSh), but not into the nucleus accumbens core. In human and animal literature, there is a genetic association between alcoholism and cocaine dependency. The current experiment examined whether selective breeding for high alcohol preference is also associated with greater sensitivity of the AcbSh to the reinforcing properties of cocaine. P and Wistar rats were given cocaine (0, 100, 200, 400, or 800 pmol/100 nl) to self-infuse into the AcbSh. Rats were given cocaine for the first 4 sessions (acquisition), artificial CSF for sessions 5 and 6 (extinction), and cocaine again in session 7 (reinstatement). During acquisition, P rats self-infused 200–800 pmol cocaine (59 infusions/session), whereas Wistar rats only reliably self-infused 800 pmol cocaine (38 infusions/session). Furthermore, P rats received a greater number of cocaine infusions in the 200, 400 and 800 pmol cocaine groups compared to respective Wistar groups during acquisition. Both P and Wistar rats reduced responding on the active lever when aCSF was substituted for cocaine, and reinstated responding in session 7 when cocaine was restored. However, P rats had significantly greater infusions during session 7 compared to session 4 at all concentrations of cocaine tested, whereas Wistar rats only displayed greater infusions during session 7 compared to session 4 at the 400 and 800 pmol cocaine concentrations. The present results suggest that, compared to Wistar rats, the AcbSh of P rats was more sensitive to the reinforcing effects of cocaine. The reinstatement data suggest that the AcbSh of P rats may have become sensitized to the reinforcing effects of cocaine. Overall, the findings from this study support a genetic association between high alcohol preference and greater sensitivity to the reinforcing effects of cocaine.

1. Introduction

Cocaine and alcohol are frequently co-abused. The majority of cocaine users (up to 90%) report co-administering EtOH during cocaine binges (Brookoff et al., 1996; Magura and Rosenblum, 2000). The high prevalence of co-abuse of alcohol with cocaine in humans has been postulated to be predicated upon both a common genetic factor that predispose an organism to abuse multiple substances, including alcohol, and the interaction of the drugs within the organism (Uhl, 2004, 2006; Uhl et al., 2008). Individuals predisposed to abuse alcohol and other drugs of abuse are disproportionally reactive to alcohol and other drugs of abuse when given alone, and co-administration of alcohol and other drugs of abuse result in further divergence (Schuckit, 1994a,b; Kareken et al., 2010; Uhl et al., 2008; Piazza and Le Moal, 1996).

In addition to previously mentioned literature, a number of studies have focused at directly assessing the genetic influence on alcohol dependency (AD) and cocaine dependency (CD) in humans. In a detailed COGA study, the rate of CD was approximately 2.5 fold higher in individuals with a genetic predisposition for alcoholism than the general population (Nurnberger et al., 2004). Similar findings were reported in a study that examined the effects of a family history of alcohol-related problems. For example, if a strict DSM-IV AD diagnosis was used for family history positive, the odds ratio was 1.6 for co-morbid CD and AD in family history positive individuals, or if the criterion for family positive was reduced to alcohol abuse and not AD, the odds ratio increased (Compton et al., 2002). In a twin study, there was strong linkage for familial factors between major depression, AD, and CD (Lin et al., 1996).

In humans, cocaine use increases the amount of alcohol consumed in polydrug users (Williamson et al., 1997). Conversely, alcohol consumption is associated with greater cocaine usage (Magura and Rosenblum, 2000). The rate of alcoholism in high-frequency cocaine users was approximately 60% compared to 37% in low-frequency cocaine users (Fox et al., 2005). Subjects with the diagnosis of alcohol dependence are more likely to become cocaine misusers and experience more adverse

* Corresponding author at: Indiana University School of Medicine, Institute of Psychiatric Research, 791 Union Drive, Indianapolis, IN 46202-4887, USA. Tel.: +1 317 278 3406; fax: +1 317 274 1365.
E-mail address: skatner@iupui.edu (S.N. Katner).

0091-3057/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2011.06.021

consequences of cocaine use (Heil et al., 2001; Staines et al., 2001). In addition, alcohol abuse is a common problem among cocaine dependent patients (Miller et al., 1989). Co-administration of alcohol during cocaine binges allows the user to prolong the euphoric effects and diminish the anxiogenic effects of cocaine (Williamson et al., 1997). Additionally, the likelihood to relapse to cocaine and/or alcohol use was greater in individuals who co-abused (Fox et al., 2005).

In animal studies, FAST and SLOW mice, selectively bred for their differential locomotor responses to ethanol, displayed parallel divergence for ethanol and cocaine (Bergstrom et al., 2003). Cocaine increases extracellular dopamine (DA) levels to a greater extent in the nucleus accumbens (Acb) and caudate-putamen in AA (Alko, Alcohol) rats compared to ANA (Alko nonalcohol) rats (Mikkola et al., 2001). In Wistar rats selected for high and low alcohol-preference, locomotor stimulation induced by cocaine was positively correlated with alcohol preference (Stromberg and Mackler, 2005). Additionally, high alcohol consuming Wistar rats were more sensitive to the reinforcing effects of cocaine than low alcohol consuming Wistar rats as measured by conditioned place preference (Stromberg and Mackler, 2005). Alcohol-preferring (P) rats are more resistant to extinguish cocaine self-administration and are more sensitive to a priming dose of cocaine to elicit cocaine-seeking behaviors than alcohol-nonpreferring (NP) rats (Lê et al., 2006).

The intracranial self-administration (ICSA) technique has been used to identify specific brain regions involved in the initiation of response-contingent behaviors for the delivery of a reinforcer (Bozarth and Wise, 1980; Goeders and Smith, 1987; McBride et al., 1999). The ICSA procedure has successfully isolated discrete brain regions where opioids (Bozarth and Wise, 1981; Devine and Wise, 1994), amphetamine (Hoebel et al., 1983; Phillips et al., 1994), acetaldehyde (Rodd-Henricks et al., 2002), and ethanol (Gatto et al., 1994; Rodd-Henricks et al., 2000) produce their reinforcing effects. Previous ICSA research indicated that cocaine was self-administered into the medial prefrontal cortex (mPFC; Goeders and Smith, 1983) and posterior, but not anterior, ventral tegmental area (VTA; Rodd et al., 2005). Cocaine is self-administered by Wistar rats directly in the AcbSh, but not in the AcbC (Rodd-Henricks et al., 2002). In addition, ICSA studies have found that P rats have a greater sensitivity to the reinforcing actions of ethanol compared to Wistar rats in the AcbSh (Engleman et al., 2009).

The goal of the present study was to compare the dose-response effects for the self-infusion of cocaine into the AcbSh of selectively bred alcohol preferring (P) and Wistar rats. The Wistar rat is the founding stock of the P rat. The hypothesis to be tested is that selective breeding for high alcohol preference is also associated with increased sensitivity to the reinforcing effects of cocaine in the AcbSh.

2. Methods

2.1. Animals

Female P rats, from the 52nd and 53rd generations, and Wistar rats (Harlan, Indianapolis, IN) weighing 250–320 g at time of surgery were used. Female rats were used in the present study because (a) female rats were used in previous studies involving the ICSA of cocaine (Rodd et al., 2005; Rodd-Henricks et al., 2002; McKinzie et al., 1999), and (b) female rats appear to maintain their body weights and head size better than male rats for more accurate stereotaxic placements (Ikemoto et al., 1997a,b; Rodd-Henricks et al., 2000, 2002 and 2003). Rats were double-housed upon arrival and maintained on a 12-h reverse light–dark cycle (lights off at 0900 h). Although not systematically studied, the estrus cycle did not appear to have a significant effect on ICSA behavior in the present study, or in previous ICSA studies (Gatto et al., 1994; Ikemoto et al., 1997a,b; Rodd-Henricks et al., 2000; Rodd-Henricks et al., 2002; Rodd-Henricks et al., 2003), as indicated by no obvious fluctuations in self-administrations by female rats given the same dose over several consecutive sessions. Animals used in this study were maintained in facilities fully accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC). All research protocols were approved by the institutional animal care and use committee and are in accordance with the guidelines of the Institutional Care and Use Committee of the National Institute on Drug Abuse, NIH, and the Guide for the Care and Use of Laboratory Animals (National Research Council 2011).

2.2. Drug and vehicle

The artificial cerebrospinal fluid (aCSF) consisted of (in mM): 120.0 NaCl, 4.8 KCl, 1.2 KH_2PO_4, 1.2 Mg SO_4, 25.0 $NaHCO_3$, 2.5 $CaCl_2$, and 10.0 d-glucose. Cocaine (Sigma) was dissolved in the aCSF solution. When necessary, 0.1 N NaOH was added to adjust the pH to 7.4 ± 0.1.

2.3. Animal preparation

While under isoflurane anesthesia, a unilateral 22-gauge guide cannula (Plastics One) was stereotaxically implanted in the right hemisphere of each subject, aimed 1.0 mm above the target region. Coordinates (Paxinos and Watson, 1998) for placements into the AcbSh were 1.2 mm anterior to bregma, 2.1 mm lateral to the midline, and 8.0 mm ventral from the surface of the skull at a 10-degree angle to the vertical. Between experimental sessions, a 28-gauge stylet was placed into the guide cannula and extended 0.5 mm beyond the tip of the guide. Following surgery, all rats were individually housed and allowed to recover 7–10 days. Animals were handled for at least 5 min daily following the fourth recovery day. Subjects were not acclimated to the test chamber prior to the commencement of data collection, nor did they receive any prior operant training.

2.4. General test condition

Testing was conducted in standard two-lever operant chambers as previously described (Ikemoto et al., 1997b; Rodd-Henricks et al., 2002; Rodd et al., 2005). The electrolytic microinfusion transducer (EMIT) system has also been described in detail (Bozarth and Wise, 1980). For testing, subjects were brought to the testing room, the stylet was removed, and the injection cannula screwed into place. To avoid trapping air at the tip of the injection cannula, the infusion current was delivered for 5 s during insertion of the injector, which resulted in a single non-contingent administration of infusate at the beginning of the session. Injection cannulae extended 1.0 mm beyond the tip of the guide. The test chamber was equipped with two levers. Depression of the 'active lever' (FR1 schedule of reinforcement) caused the delivery of a 100-nl bolus of infusate over 5 s followed by a 5-s time-out period. During both the 5-s infusion period and 5-s time-out period, responses on the active lever did not produce further infusions. Responses on the 'inactive lever' were recorded, but did not result in infusions. The assignment of active and inactive lever with respect to the left or right position was counterbalanced among subjects. The active and inactive levers remained the same for each rat throughout the experiment. No shaping technique was used to facilitate the acquisition of lever responses. The number of infusions and responses on the active and inactive lever were recorded. The duration of each test session was 4 h and sessions occurred every other day.

2.5. Dose response

P ($n = 7–8$/dose) and Wistar ($n = 8–12$/dose) rats were randomly assigned to one of five groups. A vehicle group received infusions of aCSF for all seven sessions. The other groups received infusions of 100,