Abstract  Rationale: Results of single-dose studies suggest that the effects of pretreatment with the putative anti-addictive compound, ibogaine, on drug-induced locomotor behavior depends on the previous drug history of the animal.  Objectives: To compare the effects of ibogaine pretreatment on the dose-locomotor response function for cocaine in rats treated chronically with either saline or cocaine.  Methods: Rats were chronically treated with either cocaine (15 mg/kg, IP, once daily for 5 days, followed by 2 week withdrawal) or saline. Ibogaine (40 mg/kg, IP) or vehicle was administered and 19 h later, a cocaine dose-locomotor response test was conducted (0, 5, 10, 20 and 40 mg/kg, IP).  Results: Chronic cocaine administration augmented the locomotor response to cocaine in chronic cocaine-treated rats, compared to acutely treated controls. Ibogaine pretreatment enhanced the locomotor effects of cocaine in both chronic and acute cocaine groups. Furthermore, due to the shape of the dose-response curve, in chronic cocaine but not in acute cocaine rats, ibogaine pretreatment enhanced the locomotor response to 5 and 10 mg/kg cocaine while decreasing the locomotor response to 40 mg/kg cocaine.  Conclusions: These data demonstrate definitively that ibogaine can enhance sensitivity to the locomotor stimulant effects of cocaine, an effect which depends, in part, on the previous cocaine history of the animal.

Key words  Ibogaine · Cocaine · Dose-response · Locomotor activity · Sensitization · Rat

Introduction

The naturally occurring indole alkaloid, ibogaine, is being investigated currently for its anti-addictive properties (Cappendijk and Dzoljic 1993; Glick et al. 1994; Rezvani et al. 1995). Both human anecdotal reports and preclinical studies indicate that a single dose of ibogaine can produce prolonged decreases in the self-administration of a wide variety of drugs of abuse, including cocaine, morphine, nicotine and alcohol (Glick et al. 1991, 1994; Cappendijk and Dzoljic 1993; Sheppard 1994; Rezvani et al. 1995). Receptor binding studies demonstrate that ibogaine binds with moderate affinity to kappa opioid receptors (Pearl et al. 1995a), the NMDA subtype of glutamate receptor (Popik et al. 1995) and the serotonin transporter (Mash et al. 1995). Noribogaine (12-hydroxyibogamine), the only known metabolite of ibogaine (Hearn et al. 1995), also appears to have affinity for these same receptors (cf. Glick and Maisonneuve 1998). Given the complex receptor binding profile for ibogaine and its metabolite, the precise neural mechanism(s) underlying ibogaine’s putative anti-addictive effects are unclear. However, in vivo microdialysis studies have demonstrated that ibogaine affects the dopaminergic responses in the nucleus accumbens to many drugs of abuse (Maisonuneuve and Glick 1992; Maisonneuve et al. 1992a,b; Glick et al. 1993, 1994), actions which may mediate ibogaine’s effects on the rewarding properties of abused drugs (e.g., Fibiger and Phillips 1986; Wise and Bozarth 1987; Koob 1992).

Consistent with the many implications for accumbal dopamine transmission in expression of drug-induced locomotion (e.g., Pijnenburg et al. 1975; Broderick 1991; Kuczenski et al. 1991; Camp et al. 1994; Heidbreder and Feldon 1998), ibogaine also alters drug-induced locomotor behavior in both mice (Sershen et al. 1992) and rats (Maisonuneuve and Glick 1992; Maisonuneuve et al. 1992a,b, 1997; Pearl et al. 1995b; Blackburn and Szumlinski 1997; Szumlinski et al. 1998). The effects of ibogaine on locomotion appear to depend on a number of factors, including the type and dose of drug administered (e.g., Maisonuneuve and Glick 1992; Pearl et al. 1995b, 1997), the species studied (e.g., Sershen et al. 1994; Blackburn and Szumlinski 1997; Szumlinski et al. 1999), the sex of the animal (Pearl et al. 1997), the time after...
ibogaine injection (Maisonneuve and Glick 1992; Broderick et al. 1994; Maisonneuve et al. 1997) and the previous drug history of the animal (Pearl et al. 1995b; Blackburn and Szumlinski 1997; Szumlinski et al. 1999). With respect to the latter factor, evidence suggests that prior drug experience may enhance an animal’s sensitivity to the effects of ibogaine on drug-induced behavior. For example, ibogaine produces a greater decrease in morphine-induced locomotion in rats chronically treated with morphine, compared to acutely treated controls (Pearl et al. 1995b). In addition, recent studies using cocaine have demonstrated that ibogaine enhances locomotor responding to a low dose of cocaine (7.5 mg/kg) in rats treated chronically, but not acutely, with this stimulant (Szumlinski et al. 1999). To extend these recent findings, the present study assessed the effect of ibogaine pretreatment (19 h earlier) on the dose-response function for cocaine-induced locomotion in chronic and acute cocaine-treated rats.

**Materials and methods**

**Subjects**

Female (200–225 g) Sprague-Dawley rats (Taconic, Germantown, N.Y., USA) were housed in groups of four and allowed food and water ad lib. The animals were maintained on a 12-h light cycle (lights on at 0700 hours) in a room carefully controlled for heat and humidity. All testing began at approximately 1000 hours.

**Apparatus**

Locomotion was studied in cylindrical (60 cm) photocell activity cages with three intersecting light beams. The photocells were located equidistantly from each other around the circumference of the cage, 3 cm above the floor. Each time a light beam was broken a single activity count was recorded by a 386 PC computer with Med Associates software. To reduce the probability of misinterpreting repetitive or movements in front of a photocell as locomotion, single activity counts were only recorded by the computer if a single activity count was recorded by the computer if two light beams were broken in succession.

**Drugs**

Cocaine hydrochloride (Sigma Chemical Co., St Louis, Mo., USA) was dissolved in 0.9% saline and injected IP at a volume of 1.0 ml/kg. Cocaine was administered at a dose of 15 mg/kg for the chronic treatment phase of the study and doses of 0, 5, 10, 20 and 40 mg/kg for the dose-response tests for sensitization. Ibogaine hydrochloride (40 mg/kg; Sigma Chemical Co.) was dissolved in MilliQ water and injected IP at a volume of 2.0 ml/kg.

**Design and procedure**

Based on their initial locomotor response to a saline challenge (1 ml/kg; 2-h session, conducted 1–2 days prior to chronic treatment), rats were randomly assigned to chronic treatment groups such that the groups had equivalent baseline activity levels prior to any drug administration. For chronic treatment, rats received five daily injections of either cocaine (15 mg/kg) or saline and locomotor behavior was monitored for 2 h. Prior to each chronic treatment injection, animals were habituated to the activity cages for 30 min following an injection of saline. Following the fifth chronic treatment injection, animals were withdrawn from treatment for 2 weeks. On the last day of withdrawal, rats were randomly assigned to receive a pretreatment injection of either ibogaine (40 mg/kg) or vehicle. Nineteen hours later, the first dose-response test for sensitization was conducted. On this test, rats received one of five cocaine doses (0, 5, 10, 20 or 40 mg/kg) and locomotor behavior was monitored for 2 h. Again, a 30-min habituation period preceded the cocaine injection. Assignment to the test dose was random, except that groups had equivalent mean locomotor performances on injection 5 of chronic treatment. Twenty-four hours following the first dose-response test, rats originally receiving ibogaine pretreatment were pretreated with vehicle and vice versa. Nineteen hours following the second pretreatment, a second, identical dose-response test was conducted (i.e., rats were habituated and then received the same dose of cocaine as on the first test). The order of ibogaine/vehicle pretreatment was counterbalanced across both chronic treatment groups and cocaine test doses.

For each injection day, rats were transported from their colony room to an experimental room where they were weighed and then injected with saline. Rats were immediately placed in activity cages after each injection. After 30 min, animals were removed from the activity cages, injected with the appropriate dose of saline or cocaine and then returned to the activity cage where they remained for 2 h. The only exception to this injection protocol was the ibogaine pretreatment injections, when animals were weighed and injected in the colony room.

**Statistical analysis**

For chronic treatment, data were examined for main effects by analysis of variance (ANOVA) for Chronic treatment (cocaine versus saline) and Injection number (1–10). For the dose-response tests, data were examined for main effects by ANOVA for Chronic treatment, Dose (0, 5, 10, 20, 40 mg/kg cocaine) and Pretreatment (ibogaine versus vehicle). If there were significant effects, the data were decomposed and least significant difference (LSD) post hoc tests were performed (Statistica).

**Results**

**Chronic treatment**

Chronic cocaine administration (15 mg/kg, daily for 5 days) induced high levels of locomotor responding on all injections, compared to animals repeatedly injected with saline [main effect of Chronic treatment, $F(1,4)=245.14$, $P<0.0001$]. However, the locomotion expressed after cocaine did not change as a function of the number of injections [no main effect of, or interaction with, Injection number, $P>0.05$] (Fig. 1, main figure), indicating a lack of locomotor sensitization by injection 5 of chronic cocaine treatment.

The locomotor response to saline of both chronic treatment groups during the 30-min habituation sessions habituated across injections [main effect of Injection number, $F(4,312)=18.54$, $P<0.0001$; no Chronic treatment by Injection number interaction, $P>0.05$]. As can be observed in Fig. 1 (insert), chronic cocaine animals displayed augmented responses to saline on injections 2–5 [main effect of Chronic treatment, $F(1,78)=15.01$, $P<0.0002$; LSD post-hoc tests]. This phenomenon was observed in the absence of any difference in the locomotor responses between the two chronic treatment groups.