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Short communication

Differential effects of ibogaine on behavioural and dopamine sensitization to cocaine

Karen K. Szumlinski *, Isabelle M. Maisonneuve, Stanley D. Glick

Center for Neuropharmacology and Neuroscience, MC-136, Albany Medical College, 47 New Scotland Avenue, Albany, NY 12208, USA

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Abstract

To investigate a possible basis for the proposed anti-addictive property of ibogaine, the effects of ibogaine (40 mg/kg, i.p., 19 h earlier) on the expression of sensitization induced by cocaine were investigated. Ibogaine pretreatment potentiated the increase in the stereotypic effects of a cocaine challenge (20 mg/kg) in both sensitized (5 × 15 mg/kg, i.p.) and acutely treated rats. However, while ibogaine pretreatment did not significantly alter the dopamine response in the nucleus accumbens to acute cocaine, it abolished the expression of cocaine-induced dopamine sensitization. This result demonstrates that ibogaine pretreatment can reverse one of the neuroadaptations produced by chronic cocaine administration, an effect that may contribute to its putative anti-addictive property.

Keywords: Ibogaine; Cocaine; Sensitization; Dopamine; Stereotypy; Drug addiction

1. Introduction

The naturally occurring indole alkaloid, ibogaine, is being investigated currently for its putative ''anti-addictive'' properties (for review, see Glick and Maisonneuve, 1998). Although the neural mechanism(s) underlying ibogaine's effects are still unclear, drug experience appears to render an animal more sensitive to the effects of ibogaine and related agents on drug-induced behaviour (for review, see Glick et al., 2000; Szumlinski et al., 2000c). For example, pretreatment (19 h earlier) with either ibogaine or a synthetic congener, 18-methoxycoronaridine (18-MC), can produce a greater increase in the motor effects of both cocaine (Szumlinski et al., 1999a,b,c, 2000d) and methamphetamine (Szumlinski et al., 2000a) in stimulant-experienced vs. stimulant-naive rats.

Repeated, intermittent stimulant exposure can induce a sensitization of dopamine transmission in the mesolimbic pathway and this action is implicated in both the motor-sensitizing (e.g., Kalivas and Stewart, 1991) and addictive effects (e.g., Kalivas et al., 1993; Robinson and Berridge, 1993, but see Di Chiara, 1999) of many drugs of abuse. A corollary of the sensitization theories of addiction is that anti-addictive drugs should block the expression of sensitization (be it behavioural and/or neurochemical). The present study examined this hypothesis using the putative anti-addictive drug, ibogaine (e.g., Frenken, 2000; Sheppard, 1994), in rats with previous cocaine experience.

2. Materials and methods

2.1. Drugs

Ibogaine HCl and cocaine HCl, obtained from Sigma, were dissolved in water and saline, respectively, and were injected i.p. in doses expressed as the salt.

2.2. Design and procedures

Female Sprague–Dawley rats were implanted stereotaxically with a guide cannula over the shell nucleus accumbens, as described previously (Szumlinski et al., 2000b). The day after surgery, rats were randomly assigned to groups that received once daily injections of either saline or cocaine (15 mg/kg) for 5 days. Following the 5th injection, animals were withdrawn from chronic

* Corresponding author. Tel.: +1-518-262-5801; fax: +1-518-262-5799.

E-mail address: szumlik@mail.amc.edu (K.K. Szumlinski).

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treatment for 2 weeks. On the last day of withdrawal, rats were placed in a dialysis chamber where a calibrated probe (2 mm probe, CMA) was lowered into the guide cannula. The dialysis probe was continuously perfused with artificial cerebral spinal fluid (146 mM NaCl, 2.7 mM KCl, 1.2 mM $CaCl_2$ and 1.0 mM $MgCl_2$) at a rate of 1 μl/min. Animals were then pretreated with either ibogaine (40 mg/kg, i.p.) or vehicle. The next day (1100 h), collection of perfusates began. After 2 h of baseline collections, the rats received their test injection of cocaine (20 mg/kg, i.p.) (1300 h, 19 h following ibogaine pretreatment). The collection of dialysate samples was then continued for 3 h.

2.3. Catecholamine assay

Dialysate samples from brains in which the probe was accurately placed within ±0.5 mm of the shell of the nucleus accumbens were assayed for dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) by high-performance liquid chromatography (HPLC) with electrochemical detection using an HPLC system with an ESA Coulochemm II electrochemical detector, as described previously (Szumlinski et al., 2000b).

2.4. Behavioural scoring

A behavioural intensity rating scale, adapted from Kalivas et al. (1988), was used to quantify the stereotypy expressed by the animals during the injection sessions. Rats were observed for 30 s, during the minute that preceded dialysate removal (i.e., every 20 min), beginning at the last hour of baseline dialysate sampling and continuing until the completion of the microdialysis session. Behaviour was rated as follows: (1) asleep or still; (2) inactive, grooming or mild licking; (3) locomotion (all four feet move in 30 s), rearing or sniffing; (4) any combination of two of locomotion, rearing or sniffing; (5) continuous sniffing for 30 s without locomotion or rearing; (6) continuous sniffing for 30 s with locomotion or rearing; (7) patterned sniffing for 15 s; (8) patterned sniffing for 30 s; (9) continuous gnawing or focused grooming (''skin-picking''-like behaviour); and (10) bizarre diskinetic movements or seizures.

3. Results

3.1. Baseline catecholamine concentrations

Neither chronic cocaine treatment (5 × 15 mg/kg) (Chronic effect, $P = 0.34$) nor ibogaine pretreatment (40 mg/kg) (Pretreatment effect, $P = 0.39$) altered the basal concentrations of dopamine in the accumbens during baseline sampling. Compared to vehicle animals, ibogaine pretreatment lowered the basal concentrations of both DOPAC and HVA in chronic cocaine rats only [for DOPAC: Chronic Treatment × Pretreatment, $F(1,24) = 6.02$, $P = 0.022$; for HVA: interaction, $F(1,24) = 5.71$, $P = 0.03$] (see Table 1).

Table 1
Effects of ibogaine (40 mg/kg, 19 h earlier) or vehicle on the basal levels of dopamine and its metabolites, DOPAC and HVA of rats treated chronically with either cocaine (5×15 mg/kg) or saline. Data are expressed as pmol/10 μl (mean ± S.E.M.)

	Chronic saline		Chronic cocaine	
	Vehicle ($n = 8$)	Ibogaine ($n = 6$)	Vehicle ($n = 7$)	Ibogaine ($n = 7$)
Dopamine	0.007 ± 0.000	0.008 ± 0.002	0.005 ± 0.001	0.007 ± 0.002
DOPAC	5.290 ± 1.333	9.330 ± 1.333	7.801 ± 1.765	3.942 ± 1.432 *
HVA	2.945 ± 0.637	1.849 ± 0.085	3.467 ± 0.0526	1.814 ± 0.582 *

* Denotes $P < 0.05$ vs. respective Chronic saline group (Duncan's Multiple Range post hoc tests).

3.2. Test for dopamine sensitization

A robust sensitization of extracellular levels of dopamine was observed in response to the challenge injection of cocaine in vehicle-pretreated chronic cocaine rats, compared to vehicle-pretreated acute controls [Chronic Treatment × Time, $F(14,182) = 4.93$, $P < 0.0001$] (Fig. 1, top). No sensitization of either DOPAC (interaction, $P = 0.95$) or HVA (interaction, $P = 1.0$) was observed (data not shown).

Ibogaine produced differential effects on cocaine-induced increases in accumbal dopamine in acute vs. chronic cocaine treated rats [Chronic Treatment × Pretreatment × Time, $F(14, 336) = 3.32$, $P < 0.0001$]; compared to vehicle controls, ibogaine did not affect dopamine levels in acute cocaine rats (Pretreatment × Time interaction, $P = 0.80$), but lowered dopamine levels in cocaine sensitized rats [interaction, $F(14,168) = 3.38$, $P < 0.0001$] (Fig. 1, top). Overall, ibogaine pretreatment lowered the extracellular levels of DOPAC [Pretreatment × Time, $F(14,336) = 2.02$, $P = 0.02$] and HVA [interaction, $F(14,336) = 1.94$, $P = 0.02$] in response to cocaine (data not shown).

3.3. Test for behavioural sensitization

As evidenced in Fig. 1 (bottom), a sensitization of stereotypy was observed in response to the challenge injection of cocaine in vehicle-pretreated chronic cocaine rats, compared to vehicle-pretreated chronic saline controls [Chronic Treatment × Time, $F(12,168) = 3.07$, $P < 0.001$]. Ibogaine potentiated the stereotypic activity of both chronic saline and chronic cocaine treated groups [Pretreat-

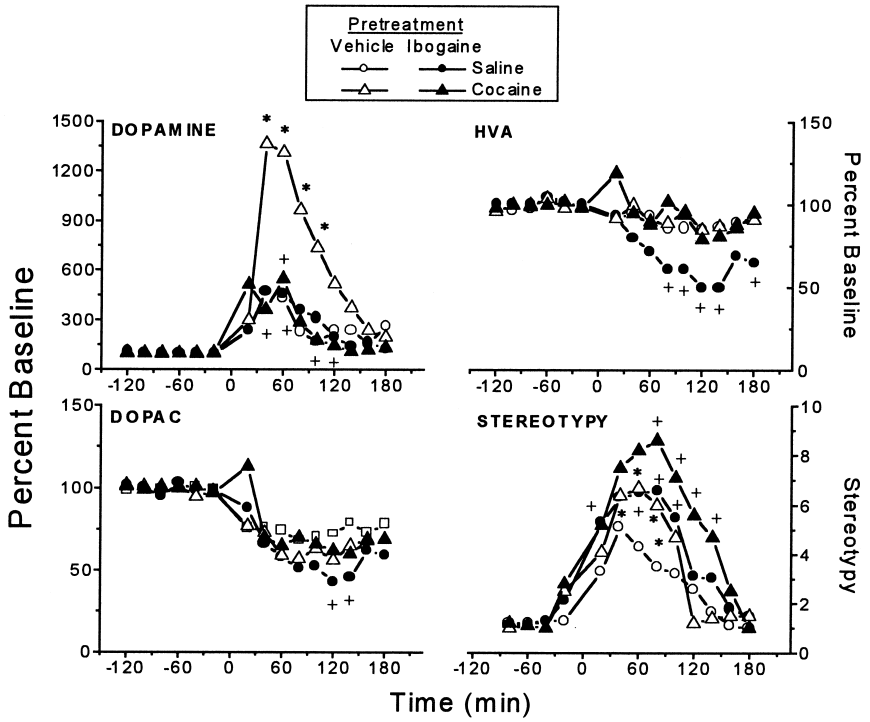

Fig. 1. Effects of ibogaine (40 mg/kg, 19 h earlier; solid) or vehicle (open) on the timecourses of extracellular levels in the accumbens of dopamine (top) and the stereotypic behaviour (bottom) of rats treated chronically with either cocaine (5×15 mg/kg; right) or saline (left) in response to a challenge injection of cocaine (20 mg/kg). Each data point represents the mean percent of baseline of six to eight rats at the indicated times during testing. S.E.M.s ranged from 2% to 30% of the mean for dopamine and from 0% to 2% of the mean for stereotypy. $^{*}P < 0.05$ vs. chronic saline; $+P < 0.05$ vs. vehicle (Duncan Multiple Range post-hoc tests).

ment × Time, $F(12, 312) = 3.14$, $P < 0.00$; no Chronic Treatment × Pretreatment × Time interaction, $P = 0.25$].

4. Discussion

As the phenomenon of sensitization has been theoretically implicated in drug addiction, it was hypothesized that the putative ''anti-addictive'' drug, ibogaine, should block sensitization to cocaine. Consistent with this hypothesis and the results of previous studies (Szumlinski et al., 2000b,d), ibogaine pretreatment (40 mg/kg, 19 h earlier) abolished the expression of dopamine sensitization in the nucleus accumbens in rats with previous cocaine experience (5×15 mg/kg). The present results provide further evidence for a relationship between the attenuating effects of *iboga* agents on drug self-administration in rodents and their ability to block the expression of dopamine sensitization produced by the repeated administration of drugs of abuse.

Recent reports demonstrated that the expression of behavioural sensitization to morphine (Cadoni and Di Chiara, 1999), nicotine (Cadoni and Di Chiara, 2000), amphetamine and cocaine (Cadoni et al., 2000) are coincident with a sensitization of dopamine levels in the nucleus accumbens core. In the cases of cocaine and nicotine, a reduction in dopamine levels in the accumbens shell has been observed in relation to the expression of behavioural sensitization (Cadoni and Di Chiara, 2000; Cadoni et al., 2000). Consistent with this, at least in ibogaine pretreated rats, the magnitude of the behavioural response to cocaine did not correspond with that of the dopamine response in the nucleus accumbens shell. This discrepancy was most notable in the chronic cocaine group where ibogaine pretreatment exerted opposite effects on the expression of motor sensitization (potentiation) and dopamine sensitization in the accumbens shell (blockade). Thus, ibogaine might exert its potentiating effects on motor behavioural sensitization by blocking the increase in dopamine responsiveness in the shell that serves normally to counteract the sensitization of core dopamine responsiveness.

However, a number of past (Glick et al., 2000; Szumlinski et al., 2000b,d) and present results contrast directly with those of Cadoni et al. (1999, 2000). First, in our hands, the chronic administration of drugs of abuse produces a sensitization of both dopamine responsiveness in the nucleus accumbens shell (Glick et al., 2000; Szumlinski et al., 2000b; present study) and motor behaviour (for review, see Szumlinski et al., 2000c). Moreover, in more than one study, the time-courses of both the acute and sensitized motor responses to cocaine are coincident with the changes in extracellular levels of dopamine as measured in the accumbens shell (Glick et al., 2000; Szumlinski et al., 2000d; present study). Lastly, no reduction in the

shell dopamine response to cocaine was observed in any chronic drug treated groups tested to date (Szumlinski et al., 2000d; present study).

From the available data, we hypothesize that the effects of ibogaine and related agents on drug-induced motor sensitization and on drug self-administration are mediated by different underlying mechanisms. The anatomical connectivity (e.g., Jongen-Relo et al., 1993) and function (Ikemoto and Panksepp, 1999; Sokolowski and Salamone, 1998) of the core and shell regions of the nucleus accumbens are distinct. Ibogaine, or related agents, may exert their effects on the expression of motor behaviour by altering dopamine sensitization in the nucleus accumbens core. Consistent with this, a potentiation of acute cocaine-induced motor behaviour by ibogaine was found to be associated with an increase in dopamine levels in the nucleus accumbens core (Maisonneuve and Glick, 1992), but not shell (present study). In contrast, it is hypothesized that the ''therapeutic'' effects of ibogaine, and related agents, involve a reversal of dopamine sensitization in the nucleus accumbens shell, a neuroadaptation implicated in mediating drug-seeking and drug-taking behaviour in addiction.

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