Pharmacology Biochemistry and Behavior, Vol. 63, No. 3, pp. 457–464, 1999

0091-3057/99/$–see front matter

PII S0091-3057(99)00038-6

Ibogaine Enhances the Expression of Locomotor Sensitization in Rats Chronically Treated With Cocaine

KAREN K. SZUMLINSKI, ISABELLE M. MAISONNEUVE AND STANLEY D. GLICK

Department of Pharmacology and Neuroscience, Albany Medical College, Albany, NY 12208

Received 26 June 1998; Revised 11 December 1998; Accepted 22 December 1998

SZUMLINSKI, K. K., I. M. MAISONNEUVE AND S. D. GLICK. *Ibogaine enhances the expression of sensitization in rats chronically treated with cocaine.* PHARMACOL BIOCHEM BEHAV **63**(3) 457–464, 1999.—Pretreatment (19 h) with the putative antiaddictive agent, ibogaine, has been shown previously to potentiate cocaine-induced locomotion in rats. The present study demonstrates that the magnitude of this effect of ibogaine is dependent on the previous cocaine history of the animal, on the time following ibogaine treatment, and on the number of ibogaine treatments. Compared to rats with no previous cocaine experience, ibogaine pretreatment (40 mg/kg, IP, 19 h earlier) markedly enhanced the expression of locomotor sensitization in response to a cocaine challenge injection (7.5 mg/kg) in rats that were chronically treated with cocaine (15 mg/kg, IP, daily for 5 days). Tolerance to cocaine-induced locomotor sensitization appeared to occur in vehicle-pretreated chronic cocaine controls. Following a second series of identical treatments (beginning 3–4 days after the initial treatment series), locomotor responding to the cocaine challenge was further enhanced by a second ibogaine injection in chronically cocaine-treated animals. Twenty-four hours later, when animals were challenged again with cocaine in the absence of any further ibogaine pretreatment, the effect of ibogaine had dissipated. Consistent with previous studies from this laboratory, these data demonstrate that ibogaine can enhance sensitivity to the psychomotor stimulant effect of cocaine. The results of the present study further indicate that the extent of this effect depends on the animal's history of exposure to both ibogaine and cocaine. © 1999 Elsevier Science Inc.

Ibogaine Cocaine Locomotor activity Sensitization Rats

THE naturally occurring indole alkaloid, ibogaine, is being currently investigated for its antiaddictive properties (7,16,45). Both human anecdotal reports and preclinical studies indicate that a single dose of ibogaine can produce prolonged (from 1 day to several weeks) decreases in the self-administration of a wide variety of drugs of abuse [including, cocaine (7,14,16), morphine (16,18,49), nicotine (49), and alcohol (45)]; repeated ibogaine dosing may further prolong these effects (7,15,16,18,31). The neural mechanism(s) underlying ibogaine's antiaddictive effects are unclear. Receptor binding studies demonstrate that ibogaine binds with moderate affinity to kappa opioid receptors (10,17), the NMDA subtype of glutamate receptor (17,43), and the serotonin transporter (36), all of which may contribute to this drug's mechanism of action. Noribogaine [(12); hydroxyibogamine], the only known metabolite of ibogaine (19), also appears to have affinity for these same receptors (40). Additionally, in in vivo microdialysis studies, ibogaine affects the dopaminergic responses in the nucleus accumbens to various drugs of abuse (e.g., cocaine, amphetamine, morphine, and nicotine), and the latter actions may mediate effects of ibogaine on the rewarding properties of abused drugs (30,55,56).

Ibogaine affects drug-induced locomotor behavior, an effect mediated presumably by the mesencephalic dopamine systems (2,56). The effects of ibogaine on locomotion appear to depend on a number of factors. These include: the type and dose of drug administered [e.g., (32,41)], the species studied (3,48), the sex of the animal (39), and the time after ibogaine injection (4,28,32,35). The previous drug history of the animal is also important. For example, ibogaine produces greater decreases in morphine-induced locomotion in rats chronically treated with morphine, compared to acutely treated animals (41). Recently, it was reported that ibogaine has differential

Requests for reprints should be addressed to Stanley D. Glick, Department of Pharmacology and Neuroscience (A-136), Albany Medical College, 47 New Scotland Avenue, Albany, NY 12208.

effects on amphetamine-induced locomotion, depending on prior amphetamine experience (3). Consistent with previous reports (32,35), a single injection of ibogaine increased the amphetamine-induced locomotor hyperactivity in acute amphetamine-treated rats. However, the same ibogaine treatment decreased amphetamine-induced locomotor responding in chronic amphetamine-treated rats (3).

In the present study, to investigate further how ibogaine alters the locomotor activating effects of stimulants after previous stimulant treatment, the effects of ibogaine pretreatment (19 h earlier) on the locomotor response to a low dose challenge injection of cocaine were assessed in rats treated either chronically or acutely with cocaine.

METHOD

Animals

Female (225–250 g) hooded Long–Evans rats (Charles River, NY) were housed in groups of four and allowed food and water ad lib. The animals were maintained on a 12 L:12 D cycle (lights on at 0700 h) in a room carefully controlled for heat and humidity. All testing began at approximately 1130 h.

Apparatus

Locomotion was studied in cylindrical (60-cm) photocell activity cages with three intersecting light beams. Each time a light beam was broken a single activity count was recorded by a 386 computer with Med Associates software.

Drugs

Cocaine hydrochloride (Sigma Chemical Co.) was dissolved in 0.9% saline and injected intraperitoneally at a volume of 1.0 ml/kg. Cocaine was administered at a dose of 15 mg/kg for the chronic treatment phases of the study and a dose of 7.5 mg/kg for the cocaine challenge injections. Ibogaine hydrochloride (40 mg/kg; Sigma Chemical Co.) was dissolved in MilliQ water and injected intraperitoneally at a volume of 4.0 ml/kg.

Design and Procedure

The effects of ibogaine pretreatment on cocaine-induced locomotor activity of acute and chronic cocaine-treated rats were assessed in three sequential phases, the first two of which were separated by a period of 3–4 days. Each of the first two phases consisted of three treatments: chronic cocaine treatment, ibogaine pretreatment, and cocaine challenge; rats received identical treatments during each phase. The third phase, which was conducted 24 h after the second phase, consisted of a cocaine challenge injection only. For chronic treatment, rats received five daily injections of either cocaine (15 mg/kg) or saline, and locomotor behavior was monitored for 1 h, immediately following injection. Two days later, rats were randomly assigned to groups that received an injection of either ibogaine or vehicle. Nineteen hours following ibogaine pretreatment, all rats received a challenge injection of cocaine (7.5 mg/kg), and again locomotor activity was monitored. Thus, four groups in all were tested: chronic saline–vehicle (SAL-VEH), chronic saline–ibogaine (SAL-IBO), chronic cocaine–vehicle (COC-VEH) and chronic cocaine–ibogaine (COC-IBO). Ibogaine was administered 19 h prior to cocaine challenge for three reasons: 1) doses of 40 mg/kg have been reported to increase acute cocaine-induced locomotor activity and decrease cocaine and opiate self-administration when injected at this time; 2) 40 mg/kg ibogaine induces transient tremors that might interfere with locomotor activity, but these tremors typically subside within a few hours postinjection (28); and 3) as discussed in previous studies [e.g., (39)], ibogaine and its metabolite, noribogaine, are barely detectable in the body 19 h after administration, and this is a convenient time to assess its prolonged efficacy. The lower test dose of cocaine was selected for two reasons: 1) locomotor responding to an acute injection of this dose is not affected by ibogaine pretreatment (32); thus, any difference between the chronic treatment groups could be attributed to differences in the prior cocaine history of the animal; and 2) to reduce the expression of cocaine-induced stereotypy (38), which would interfere with the expression of cocaine-induced locomotor behavior. For each injection, rats were transported from their colony room to an experimental room where they were weighed and then injected. Rats were immediately placed in activity cages after each injection with the exception of the ibogaine pretreatment injections when animals were returned to their colony room.

Statistical Analysis

Data were examined for main effects by analysis of variance (ANOVA) for chronic treatment (cocaine vs. saline), injection number (1–10), ibogaine pretreatment (ibogaine vs. vehicle), time (10–60 min), and test (19 h after the first ibogaine injection, 19 h after the second ibogaine injection, and 43 h after the second ibogaine injection). If there were significant effects, the data were decomposed and Student–Newman–Keuls (SNK) post hoc tests were performed (Statistica). As it appeared that ibogaine pretreatment altered the shape of the time course of cocaine-induced locomotion, trend analyses were performed on the data separately for each group on each test.

RESULTS

Effects of Cocaine Administration on Locomotion During Chronic Treatment

Compared to animals chronically treated with saline, chronic cocaine administration (15 mg/kg) induced high levels of locomotor responding after all injections, in all phases [main effect of chronic treatment, $F(1, 26) = 168.66$, $p < 0.00001$; chronic treatment by injection number interaction, $F(4, 104) = 6.10$, $p < 0.0002$; SNK post hoc tests]. As can be observed in Fig. 1, between the first two phases, no difference was found in cocaine-induced locomotion across chronic treatment (no main effect of test, no interactions with test factor, $p > 0.05$). During both phases, the locomotor activity of chronic cocaine animals was maximal by either injection 2 (phase 1) or injection 3 (phase 2), but then declined to initial levels by injection 5 [main effect of injection number, $F(4, 104) = 5.89$, $p < 0.0003$; SNK post hoc tests]. It should be noted that prior ibogaine pretreatment (43–74 h earlier) did not influence the response of either chronic cocaine- or chronic saline-treated animals on any injection during the second phase of chronic treatment (no interactions with ibogaine pretreatment, data not shown). Thus, the results indicate that chronic cocaine-treated rats displayed a sensitization of the motor stimulant of cocaine by the third injection in each experiment, but that the expression of this sensitization dissipated by the fifth cocaine injection of each chronic treatment period. Additionally, the results indicate that previous treatment with ibogaine (43–74 h earlier) does not alter the motor response of animals to either chronic cocaine or saline treatment.

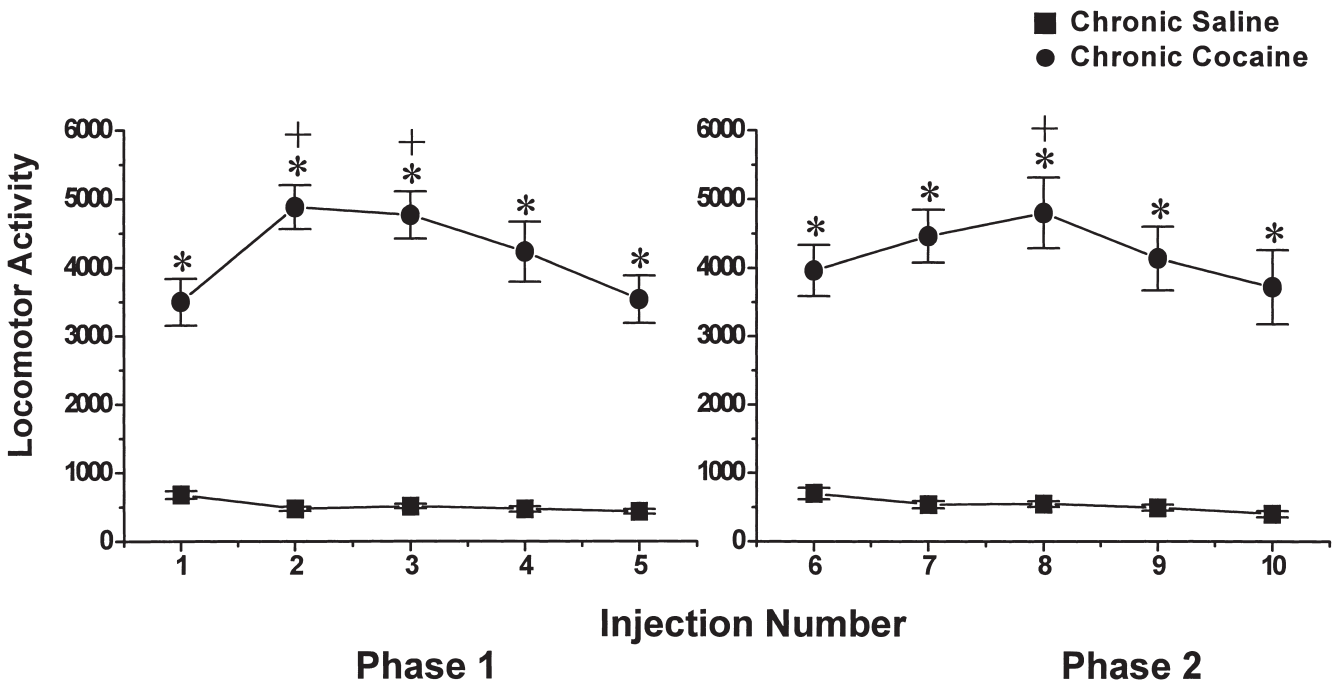


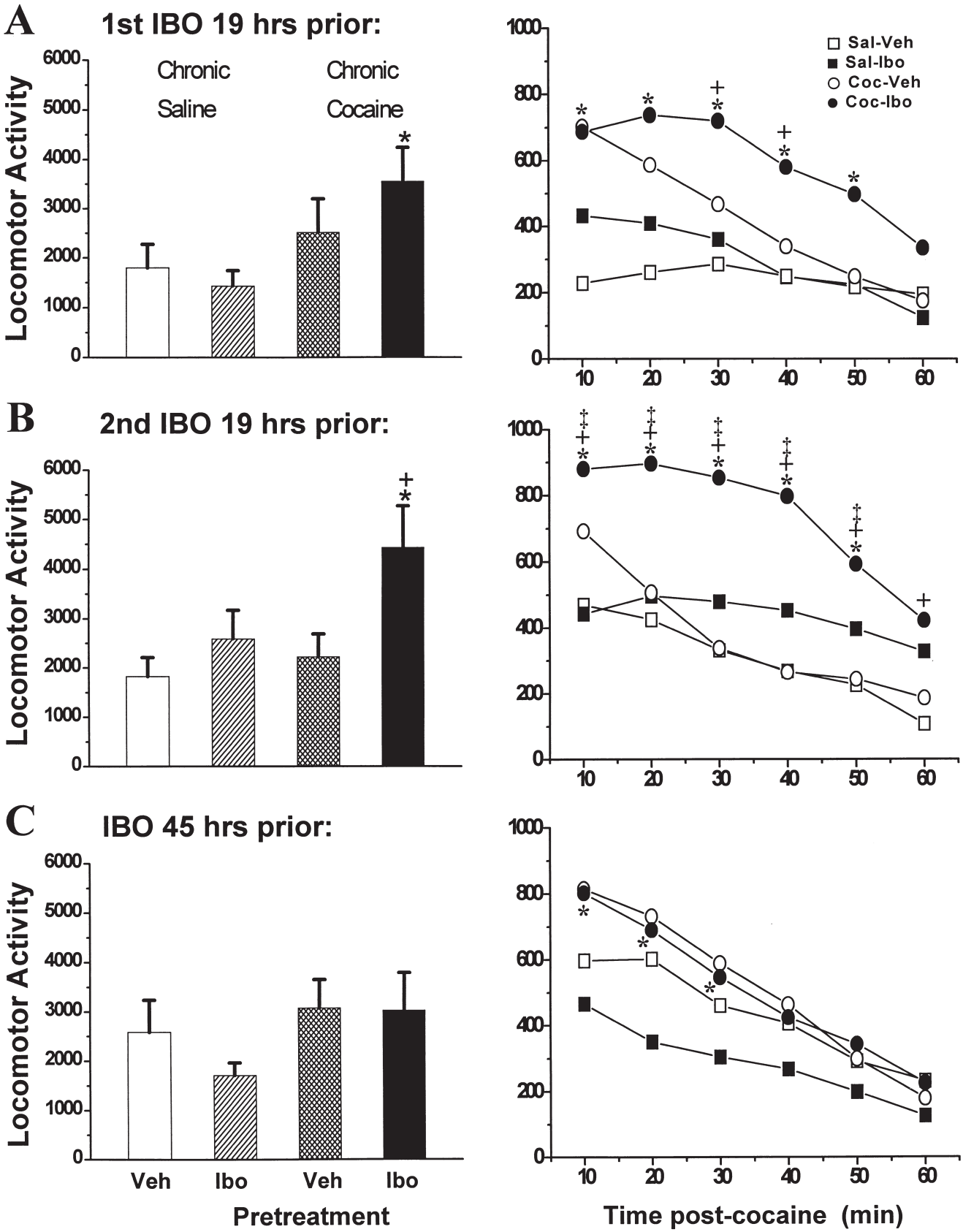
FIG. 1. Locomotor effects of daily chronic treatment with either saline (squares) or 15 mg/kg cocaine IP (circles) during each of the chronic treatment phases (left and right). Each point represents the mean activity counts (±SEM) of 16 rats over a 1-h session. *$p < 0.05$ compared to chronic saline animals, +$p < 0.05$, compared to the first injection of each experiment (SNK post hoc tests).

Interactions Between Chronic Cocaine Administration and Ibogaine Pretreatment on Total Locomotor Responding to Low-Dose Cocaine

Overall, prior cocaine treatment (two sessions of 5 × 15 mg/kg) enhanced locomotor responding to a low dose of cocaine (7.5 mg/kg) on all three tests [main effect of chronic treatment, $F(1, 24) = 7.27$, $p < 0.013$; no chronic treatment by test interaction, $p = 0.41$]. As can be observed in Fig. 2A and B (left), this overall effect appeared to be due to the high level of locomotion displayed by COC-IBO animals on tests 1 and 2 (both 19 h following ibogaine pretreatment) [main effect of ibogaine pretreatment, $F(1, 24) = 6.45$, $p < 0.018$; chronic treatment by ibogaine pretreatment interaction, $F(1, 24) = 4.86$, $p < 0.04$; no chronic treatment by ibogaine pretreatment by test interaction, $p = 0.42$]. Consistent with previous findings (32), when compared to vehicle-pretreated animals, ibogaine pretreatment (19 h earlier) did not alter the locomotor response to an acute injection of a low dose of cocaine in animals acutely treated with cocaine (SNK post hoc tests). A similar finding was observed for animals chronically treated with cocaine on the first test; when compared to vehicle-pretreated animals, ibogaine pretreatment (19 h earlier) did not significantly alter locomotion induced by the challenge cocaine injection (SNK post hoc tests). Interestingly, however, when compared to their respective chronic saline controls, only ibogaine-pretreated (i.e., not vehicle-pretreated) chronic cocaine animals displayed augmented locomotion in response to the challenge injection on both of the first two 7.5-mg/kg cocaine tests (SNK post hoc tests). This indicates that behavioral sensitization was expressed in COC-IBO animals, but not in COC-VEH controls. This suggests that ibogaine pretreatment (19 h earlier) significantly increases the sensitivity to cocaine's psychomotor stimulant effects in rats with prior cocaine experience.

The enhancing effect of ibogaine pretreatment on cocaine-induced locomotion was clearly augmented in chronic cocaine animals, but not in chronic saline animals, on the second cocaine test [main effect of test, $F(2, 48) = 3.31$, $p < 0.045$; ibogaine pretreatment by test interaction, $F(2, 48) = 9.39$, $p < 0.0004$]. As can be observed in Fig. 2B (left), this was evidenced by a significantly higher level of locomotor responding to cocaine in the COC-IBO group, compared to all other groups tested (including the chronic cocaine controls) (SNK post hoc tests). In addition, comparing the locomotor responses of the groups on test 2 to those on test 1, only COC-IBO animals showed an increase in responding with the additional treatment (SNK post hoc tests; compare Fig. 2A vs. B, left). Thus, it appears that repeated ibogaine treatment may be more effective than single ibogaine treatment in enhancing the locomotor-sensitizing effects of chronic cocaine administration.

Forty-three hours following ibogaine pretreatment (test 3), no difference was observed between any of the four groups tested (Fig. 2C, left). Although COC-IBO animals tended to display behavioral sensitization compared to SAL-IBO controls, this effect was not statistically significant ($p = 0.07$, SNK post hoc tests). Compared to their responses on tests 1 and 2, the only difference between the tests was observed in the COC-IBO animals; this group displayed significantly lower levels of locomotion on test 3, compared to their response on test 2, and no difference was observed between tests 1 and 3 (compare Fig. 2A–C, left). Thus, it appears that ibogaine's ability to increase an animal's sensitivity to the locomotor activating effects of cocaine in chronicly cocaine-treated animals decays between 19–43 h postibogaine administration. This finding is consistent with the above observation (see Fig. 1, left) that prior ibogaine administration in phase 1


A
1st IBO 19 hrs prior:
Chronic Saline
Chronic Cocaine
Locomotor Activity
B
2nd IBO 19 hrs prior:
Locomotor Activity
C
IBO 45 hrs prior:
Locomotor Activity
Veh
Ibo
Veh
Ibo
Pretreatment
Sal-Veh
Sal-Ibo
Coc-Veh
Coc-Ibo
Time post-cocaine (min)

did not significantly alter the locomotor responding of either chronic cocaine- or chronic saline-treated animals on the any injection of the second chronic treatment phase of the study.

Interactions Between Chronic Cocaine Administration and Ibogaine Pretreatment on the Time Course of Locomotor Responding to Low-Dose Cocaine

On all three tests, when compared to chronic saline-treated animals, chronic cocaine-treated rats displayed higher levels of cocaine-induced locomotion across time [chronic treatment by time interaction, $F(5, 120) = 4.68$, $p < 0.0006$]. As can be observed in Fig. 2A and B (right), this effect appeared to be due to the high level of responding displayed by COC-IBO (19 h earlier) animals [chronic treatment by ibogaine pretreatment by time interaction, $F(5, 120) = 2.25$, $p < 0.05$; no chronic treatment by ibogaine pretreatment by test by time interaction, $p = 0.36$]. On both cocaine challenges 19 h following ibogaine/vehicle pretreatment, COC-IBO rats displayed higher levels of locomotion, compared to their chronic saline-treated counterparts at 10–50 min postcocaine challenge, whereas COC-VEH rats only differed from their respective chronic saline-treated controls at 10 min postchallenge on test 1 (SNK post hoc tests). Consistent with the present findings for total locomotor behavior, the level of locomotion expressed at each time point following cocaine challenge was further enhanced by a second injection of ibogaine [ibogaine pretreatment by time, $F(5, 120) = 2.62$, $p < 0.028$; ibogaine pretreatment by test by time, $F(10, 240) = 2.43$, $p < 0.009$] (compare Fig. 2A and B, right). This effect was only present in COC-IBO rats that displayed higher levels of locomotion on test 2 at 10–50 min postchallenge, compared to those displayed on test 1 (SNK post hoc tests). Also consistent with total locomotor behavior, the amount of locomotion expressed at each time postchallenge did not differ for any group between tests 1 and test 3 (with the exception of SAL-VEH animals, who displayed higher levels of locomotion at 10 min postinjection on test 3 vs. test 1; SNK post hoc tests). Additionally, and also consistent with total locomotor responding data, COC-IBO animals displayed lower levels of locomotion at all times postchallenge on test 3 vs. test 2 (SNK post hoc tests).

Inspection of Fig. 2A and B (right) suggests that ibogaine-pretreatment altered the shape of the time course of locomotion induced by a 7.5-mg/kg challenge injection of cocaine. As the time courses of locomotion did not differ in any group between test 1 and test 2 ($p = 0.036$), the time-course data from both tests were collapsed separately for each group and trend analyses were performed to statistically compare the shapes of the time courses of locomotion between ibogaine- and vehicle-pretreated groups. In SAL-VEH animals, cocaine-induced locomotion decreased linearly as a function of time ($p < 0.0001$), whereas no such linearity was observed in the SAL-IBO group ($p = 0.11$). Instead, a trend towards a quadratic relationship existed between the level of cocaine-induced hyperactivity and time in the SAL-IBO group ($p = 0.07$). Similar, yet more pronounced, was the relationship between locomotor activity and time in chronic cocaine-treated animals. As observed in their chronic saline-treated counterparts, cocaine-induced locomotion expressed by COC-VEH rats decreased linearly as a function of time ($p = 0.003$). In contrast, a significant quadratic relationship was observed between the level of cocaine-induced locomotion and time in the COC-IBO group ($p = 0.001$), with animals displaying maximal levels of locomotor responding to cocaine on both tests from 10–50 min postinjection (SNK post hoc tests). Thus, it appears that ibogaine pretreatment arrests the linear decline in cocaine-induced locomotion across time, and that this effect can be enhanced by previous cocaine history.

Inspection of Fig. 2C (right) suggests that, 43 h postibogaine administration, the quadratic relationship between cocaine-induced locomotion and time was no longer present in ibogaine-pretreated groups. Instead, it appeared that the relationship between locomotion and time was no different from that of vehicle-treated animals [no cocaine by ibogaine interaction, no cocaine by ibogaine by time interaction, $p = 0.5$ and 1.0, respectively]. Performing trend analyses on the four groups revealed that the locomotor behavior of all four groups decreased linearly as a function of time ($p < 0.0001$ for all groups) and no quadratic relationship existed in either the SAL-IBO or COC-IBO groups ($p = 0.5$ for both groups). Thus, it appears that 43 h later, ibogaine pretreatment no longer arrests the decline in cocaine-induced locomotion observed across time.

DISCUSSION

The present results showed that ibogaine pretreatment (40 mg/kg, 19 h earlier) enhanced motor responding to a low dose (7.5 mg/kg) challenge injection of cocaine in animals chronically administered the drug (5 or 10 injections of 15 mg/kg). Consistent with previous reports from this laboratory (32), ibogaine pretreatment did not affect motor activity induced by an acute low dose of this stimulant. That an ibogaine-induced enhancement of the motor effects induced by the low dose cocaine challenge was observed in rats with chronic cocaine exposure demonstrates that ibogaine can potentiate the motor stimulant effects of a low dose of cocaine within 1 h postcocaine administration, but that this effect depends on the prior cocaine history of the animal. This finding is particularly interesting given that 19 h postinjection, levels of ibogaine and/or its active, metabolite, noribogaine, are extremely low [e.g., (39)]. This finding is consistent with a previous report for morphine in which ibogaine pretreatment (also 19 h earlier) was found to produce a larger decrease in morphine-induced locomotion in animals chronically administered morphine, compared to animals acutely injected with the drug (41). The present results also show that ibogaine's enhancing effect on cocaine-induced motor stimulation was greater in chronic cocaine animals following a second injection of ibogaine, compared to its effect after the first ibogaine injection. This finding is consistent with both experimental (7,16,18) and anecdotal reports [e.g., (31)] that ibogaine's antiaddictive efficacy can be augmented in both rodents and humans with repeated ibogaine dosing.

FIG. 2. Effects of ibogaine (40 mg/kg IP) pretreatment on total activity (left) and on the time-course (right) expression of cocaine-induced (7.5 mg/kg IP) locomotion in animals previously treated chronically with either saline or cocaine. (mean ± SEM). (A) Animals were administered five daily cocaine injections (15 mg/kg IP), pretreated with ibogaine or saline and then challenged with cocaine, 19 h later (test 1). (B) Chronic treatment was repeated and, again, ibogaine or saline was administered 19 h before cocaine challenge (test 2). (C) Forty-three hours following the second ibogaine treatment, animals were administered a third cocaine challenge (test 3). $n = 6$–8 rats per group. $^*p < 0.05$, compared to respective chronic saline group; $^+p < 0.05$, compared to respective vehicle-pretreated group; $^‡p < 0.05$, compared to test 1 (SNK post hoc tests).

Although consistent with reports of ibogaine's effects on acute stimulant-induced locomotion, the present findings appear to contradict those of Blackburn and Szumlinski (3); in this study, chronic amphetamine-treated rats that were pretreated with ibogaine displayed decreased locomotion in response to an amphetamine challenge, compared to vehicle-pretreated controls. Although it may be argued that the discrepancy in findings may be drug related (6), ibogaine potentiates the acute locomotor response to both amphetamine (3,33) and cocaine (32,35) in rats. In addition, ibogaine pretreatment augments both amphetamine- and cocaine-induced increases in striatal and accumbal levels of dopamine (32,33), an effect that presumably mediates ibogaine's behavioral enhancing effects (32). One possibility is that sex differences in ibogaine pharmacokinetics may account for the differential results; male rats were used in the amphetamine study and female rats were selected for the present cocaine study. Indeed, sex differences do exist with respect to ibogaine pharmacokinetics [females have higher brain levels than males 19 h postibogaine; (39)]. However, if this were to account for the differential findings, a greater dampening, not a potentiation, of stimulant-induced locomotor activity would have been expected to occur in the females in the present study.

To account for the differential effect of ibogaine pretreatment between the acute- and chronic-treated groups, Blackburn and Szumlinski (3) suggested that chronic treatment with amphetamine or other stimulants may produce a change in the brain, which is attenuated or blocked with ibogaine pretreatment (3). Based on the present findings, it is suggested instead that prior stimulant experience increases a rat's sensitivity to ibogaine's effects on stimulant-induced behavior. This latter possibility appears more likely given that the locomotor dose–response curve for amphetamine is inverted U-shaped over a narrow dose range (24,27,46), and chronic treatment with amphetamine will shift the dose–response curve to the left (50). Higher doses of psychomotor stimulants are known to induce the expression of stereotypic behaviors that tend to be physically incompatible with locomotion [e.g., (13,38)] and chronic administration of moderate doses of amphetamine will sensitize the expression of these stereotypic behaviors [e.g., (9,47)]. Considering the dose dependency of amphetamine-induced behavior, the attenuation by ibogaine of amphetamine-induced locomotion observed in chronic amphetamine-treated animals (3) most likely resulted from an ibogaine-induced shift from locomotor behavior to stereotypy in chronic amphetamine-treated animals. Such an explanation implies that, like chronic cocaine administration, chronic amphetamine administration, augments ibogaine's ability to enhance the behavioral effects of this stimulant and that, depending on the test dose selected, this enhancement can be manifest either as increased locomotion (present study) or as the induction of stereotypy.

Several findings are relevant to an understanding of the increase in ibogaine's efficacy on cocaine-induced motor hyperactivity produced by chronic cocaine administration. Chronic cocaine treatment typically causes an enduring increase in extracellular levels of dopamine in the nucleus accumbens and the striatum (20,22,25,42,54), an effect that presumably mediates the behavioral sensitizing effects of this, and other stimulant, drugs [for review, (26)]. Given that ibogaine potentiates the dopaminergic response to acute cocaine in these two regions (32), one possibility is that the expression of behavioral sensitization in chronicly cocaine-treated animals following ibogaine pretreatment reflects the additive effects of increased extracellular levels of dopamine produced by chronic stimulant administration and that produced by ibogaine pretreatment. This suggestion is supported by the observation that the sensitization of motor stimulation appeared to dissipate across the chronic treatment sessions only to reappear in chronic cocaine animals that were pretreated with ibogaine. Although it is not entirely clear why sensitization dissipated across cocaine injections or why sensitization was not expressed in vehicle-pretreated chronic cocaine controls on any of the test days, it does not appear to be related to the induction of stereotypy at later injections. This conclusion is based on findings that 1) the time course of expression of cocaine-induced locomotion was virtually identical on each cocaine injection with animals displaying peak locomotor activity 20–40 min postinjection (data not shown); 2) sensitization was expressed on cocaine injections 2 and 3 (phase 1) and again on injection 7 (injection 2 of phase 2); and 3) sensitization was present in ibogaine-pretreated chronic cocaine animals on both test days. The failure to observe sensitization in the vehicle-pretreated chronic cocaine group on the test days is mostly likely related to the short duration of the withdrawal period used in this study because the expression of stimulant-induced sensitization appears to be more robust when longer periods of withdrawal (i.e., more than 3 days) are employed [e.g., (20,21,29)].

Chronic cocaine administration is known to up- or down-regulate several receptors for which ibogaine and its active metabolite, noribogaine, show moderate binding affinity. For example, chronic cocaine administration has been demonstrated to produce either up- (53) or down-regulations (51,52) of kappa opioid receptors and/or kappa opioid receptor mRNA. Additionally, some evidence suggests that both NMDA receptors (23) and serotonin transporters (1,5) can be upregulated by chronic cocaine administration, effects that do not necessarily correlate with the expression of sensitization [e.g., (5)]. It is possible that such changes were produced by the chronic cocaine treatment regimen in the present study, thereby enhancing ibogaine's efficacy in chronicly cocaine-treated animals.

Another plausible explanation for the dissociation of ibogaine's efficacy between acute and chronicly cocaine-treated animals may be related to differences in the pharmacokinetics of cocaine between these two groups. Although it is not known whether ibogaine decreases cocaine metabolism, as it does amphetamine metabolism (15), chronic cocaine animals displayed a quadratic rather than a linear time course of locomotion when pretreated with ibogaine 19, but not 43 h, prior to cocaine administration; this suggests that ibogaine may be altering the pharmacokinetics of cocaine. If ibogaine did indeed slow cocaine metabolism, this effect would be expected to be enhanced in animals chronically administered cocaine, given that chronic cocaine administration appears to decrease cocaine metabolism in both rats (11,37) and mice (44).

In summary, the present results indicate that ibogaine increases an individual's sensitivity to the psychomotor stimulant effects of cocaine. This effect depends on both the previous drug history of the individual and on the number of ibogaine treatments. Given that the psychomotor stimulant effects of high doses of cocaine can be aversive (8), it is proposed that ibogaine's antiaddictive properties may be related to an ability to increase the aversiveness of cocaine in chronic cocaine users.

ACKNOWLEDGEMENTS

This study was supported by NIDA Grant DA 03817.

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