Brain Research 657 (1994) 14–22

Research report

Effects of *iboga* alkaloids on morphine and cocaine self-administration in rats: relationship to tremorigenic effects and to effects on dopamine release in nucleus accumbens and striatum

S.D. Glick [a,*], M.E. Kuehne [b], J. Raucci [a], T.E. Wilson [b], D. Larson [b], R.W. Keller Jr. [a], J.N. Carlson [a]

[a] *Department of Pharmacology and Toxicology (A-136), Albany Medical College and the Capital District Center for Drug Abuse Research and Treatment, Albany, NY 12208, USA*

[b] *Department of Chemistry, University of Vermont, Burlington, VT 05405, USA*

Accepted 7 June 1994

Abstract

Ibogaine, a naturally occurring alkaloid, has been claimed to be effective in treating addiction to opioid and stimulant drugs and has been reported to decrease morphine and cocaine self-administration in rats. The present study sought to determine if other *iboga* alkaloids, as well as the chemically related *harmala* alkaloid harmaline, would also reduce the intravenous self-administration of morphine and cocaine in rats. Because both ibogaine and harmaline induce tremors, an effect that may be causally related to neurotoxicity in the cerebellar vermis, the temorigenic activities of the other *iboga* alkaloids were assessed. Lastly, in view of the involvement of the dopaminergic mesolimbic system in the actions of drugs of abuse, the effects of some of the *iboga* alkaloids on extracellular levels of dopamine and its metabolites in the nucleus accumbens and striatum were determined. All of the tested alkaloids (i.e., ibogaine, tabernanthine, R- and S-coronaridine, R- and S-ibogamine, desethylcoronaridine, and harmaline) dose-dependently (2.5–80 mg/kg) decreased morphine and cocaine intake in the hour after treatment; decreases in morphine and cocaine intake intake were also apparent the day after administration of some but not all of these alkaloids (i.e., ibogaine, tabernanthine, desethylcoronaridine, and the R-isomers of coronaridine and ibogamine). In some rats, there were persistent decreases in morphine or cocaine intake for several days after a single injection or after two or three weekly injections of one or another of these alkaloids; R-ibogamine produced such effects more consistently than any of the other alkaloids. At the doses used to assess effects on drug self-administration, ibogaine, tabernanthine, desethylcoronaridine and harmaline all induced tremors for at least 2–3 h; both enantiomers of both coronaridine and ibogamine induced very weak or no tremors. Using in vivo microdialysis, the effects of the R- and S-enantiomers of coronaridine and ibogamine on extracellular dopamine levels in the nucleus accumbens and striatum were compared. The R-enantiomers decreased dopamine levels in both brain regions whereas the S-enantiomers produced no significant changes in dopamine levels in either region. The results of this study indicate that the 'anti-addictive' and tremorigenic effects of the *iboga* alkaloids can be dissociated and that long-term effects of these alkaloids on drug self-administration appear to be related to initial decreases in dopaminergic activity in specific brain areas.

Key words: Ibogaine; Harmaline; Tabernanthine; Coronaridine; Ibogamine; Desethylcoronaridine; Morphine; Cocaine; Drug self-administration

1. Introduction

Ibogaine, one of several alkaloids found in the root bark of the African shrub *Tabernanthe iboga*, has been claimed, in two United States patents (number 4,499,096, Feb. 12, 1985 and number 4,587,243, May 6, 1986), to be effective in treating opiate (heroin) addiction and stimulant (cocaine and amphetamine) abuse, respectively. The treatment supposedly interrupts the 'physiological and psychological aspects' of addiction and eliminates the desire to use drugs. In both opiate and stimulant syndromes, a single oral treatment of

* Corresponding author. Fax: (1) (518) 262-5799.

ibogaine or its salts in dosages of 6 to 19 mg/kg is said to be effective for about 6 months; a series of four treatments is claimed to eliminate addictive behavior for approximately 3 years. Using an animal model of drug addiction, we have sought to determine whether these claims can be substantiated under controlled conditions. In our initial study [12], ibogaine dose-dependently decreased morphine self-administration in the hour after ibogaine treatment (acute effect) and, to a lesser but significant extent, a day later (aftereffect). In some rats there was a persistent decrease in morphine intake for several days or weeks after a single injection of ibogaine whereas other rats began to show such persistent changes after two or three weekly injections, and a few rats appeared to be entirely resistant to prolonged aftereffects. Similar effects of ibogaine on cocaine self-administration in rats were recently reported by Cappendijk and Dzoljic [1].

In humans, as in rats, ibogaine's efficacy as an anti-addictive therapy appears to vary substantially from one individual to another; even the most ardent supporters of ibogaine's usefulness would probably concede that at least 30% of treated addicts do not decrease their drug intake. Ibogaine also exhibits several side effects that may limit its therapeutic utility. In addition to having stimulant and hallucinogenic properties, ibogaine induces tremors. Very similar tremors are induced by harmaline, another natural alkaloid that is chemically related to ibogaine but is derived from a different plant (*Peganum harmala*). Both ibogaine- and harmaline-induced tremors appear to be due to activation of an olivo-cerebellar pathway [3,14,20], and in rats, high doses of both agents have recently been shown to produce damage to the cerebellar vermis, presumably a result of overstimulation of cerebellar Purkinje cells [19,20]. It has been suggested that ibogaine-induced cerebellar damage may mediate ibogaine's anti-addictive effects [28]. In the present study, the effects of several *iboga* alkaloids as well as harmaline on morphine and cocaine self-administration in rats were assessed. The primary objective was to determine if the anti-addictive (i.e., decreased drug self-administration) and temorigenic activities of ibogaine-like compounds could be dissociated and, as a corollary, to determine if an *iboga* alkaloid could be identified that was less temorigenic (i.e., probably safer) yet more effective as an anti-addictive agent than ibogaine.

2. Materials and methods

2.1. Drugs

Ibogaine hydrochloride and harmaline hydrochloride were purchased from the Sigma Chemical Company (St. Louis, MO). The R- and S-enantiomers of ibogamine and coronaridine (structures shown in [2]) as well as racemic desethylcoronaridine were synthesized by M.E. Kuehne, T.E. Wilson and D. Larson at the University of Vermont. Tabernanthine was supplied by P. Potier, CNRS, Institute of Chemistry of Natural Substances, Gif-sur-Yvette, France. All drugs were administered intraperitoneally; doses are expressed as the hydrochloride salts. Different drugs and doses (or saline) were administered to different groups of rats; rats were injected fifteen minutes before a morphine or cocaine self-administration session. Drug injections were usually made on Wednesdays and, in some cases, repeated injections were made at weekly intervals.

2.2. Subjects and apparatus

The subjects were naive female Sprague–Dawley (Taconic, Germantown, NY) rats approximately 3 months old and weighing 230–250 g at the beginning of the experiment; female rats were used because they grow at a much slower rate than males and are less likely than males to outgrow their intravenous cannulas. Rats were housed singly in Wahmann hanging cages and maintained on a normal light/dark cycle (lights on/off at 7:00 a.m./7:00 p.m.). All self-administration testing was conducted in twelve BRS/LVE operant test cages, each enclosed in a sound attenuated cubicle. Responses on either of two levers (mounted 15 cm apart on the front wall of each test cage) were recorded on an IBM compatible 386 computer with a Med Associates, Inc. interface. The intravenous self-administration system consisted of polyethylene-silicone cannulas constructed according to the design of Weeks [30], BRS/LVE harnesses and commutators, and Harvard Apparatus infusion pumps (no. 55–2222).

2.3. Self-administration procedures

Shaping of the bar-press response was initially accomplished by training rats to bar-press for water. Cannulas were then implanted in the external jugular vein according to procedures described by Weeks [30]. Self-administration testing began with a single 24-h session followed by daily 1-h sessions, 5 days (Monday-Friday) a week; rats were tested about the same time each day, during the middle of the light cycle. Depending upon the group, a lever-press response produced either a 20 μl (morphine) or 50 μl (cocaine) infusion of drug solution (0.01 mg of morphine sulfate or 0.1 mg of cocaine hydrochloride) in about 0.2 (morphine) or 0.5 (cocaine) second. Since all rats generally weighed 250 ± 20 g, each response delivered approximately 0.04 mg/kg of morphine or 0.4 mg/kg of cocaine; these doses are about two to four times the threshold doses required for maintaining self-administration behavior (e.g. [8,10]). One non-contingent drug infusion was administered at the beginning of each session. Experiments to assess the effects of the *iboga* and *harmala* alkaloids were begun when baseline self-administration rates stabilized ($\leq 10\%$ variation from one day to the next across 5 days), usually after 2 weeks of testing.

2.4. Microdialysis and HPLC procedures

Under pentobarbital anesthesia, rats (female Sprague–Dawley) were implanted stereotaxically with guide cannulas over the nucleus accumbens and striatum so that, when inserted, the tips of the dialysis probes would be located in the nucleus accumbens (rostral, +1.6 mm from bregma; lateral, ± 1.5 mm; ventral, −8.6 mm from the skull surface) and in the striatum (rostral, +0.5 mm; lateral, ± 2.9 mm; ventral, −7.0 mm) [21]. The two cannulas were fixed firmly in the skull with dental cement. One cannula was implanted in the left side of the brain, and the other in the right side of the brain; the side (left or right) assigned to each region (nucleus accumbens or striatum) was alternated from animal to animal.

At least 4 days after surgery, a rat was placed in a dialysis chamber, a cylindrical (30 cm diameter) Plexiglas cage providing free access to food and water. Probes (3 mm; BAS/CMA MF-5393) were then lowered into the guide cannulas. The dialysis probes were continuously perfused with a solution containing 146 mM NaCl, 2.7 mM KCl, 1.2 mM $CaCl_2$, 1.0 mM $MgCl_2$ and 0.05 mM ascorbic acid at a flow rate of 1 μl/min. On the next morning (15–20 h later), the dialysis experiment was carried out on a freely moving animal. Twenty minute fractions were collected in vials containing 2 μl of 5 N perchloric acid solution (containing 5 mg/l EDTA and 5 mg/l sodium metabisulfite). Upon completion of an experiment, rats were killed and histological analysis [26] of each brain was performed to verify the locations of the two probes.

Perfusate samples were analyzed by HPLC with electrochemical detection. The HPLC consisted of a Waters pump (model 510), a WISP autosampler (model 712), a Phase Separation Spherisorb column (S3 ODS2; 10 cm × 4.6 mm) and a Waters detector (model 464). The mobile phase consisted of 6.9 g/l sodium monobasic phosphate, 495 mg/l heptane sulfonic acid, 80 mg/l disodium EDTA, and 100 ml/l methanol; the solution was adjusted with HCl to pH 3.7 and was pumped at a rate of 1.2 ml/min. Chromatograms were processed using Maxima 820 software.

Concentration estimates were expressed as uM or nM concentrations of the compounds in the dialysate fluid. Previous work has demonstrated that dialysate concentrations of dopamine (DA) and DOPAC are highly correlated ($r \geq 0.9$) with extracellular levels of these compounds as determined in 'no net flux' studies [9].

Prior to use in vivo, in order to identify 'bad' probes [9], each probe was calibrated in vitro at room temperature in an artificial CSF solution gassed with argon and containing DA (15 pm/ml), DOPAC (1.5 nm/ml) and HVA (0.75 nm/ml). In vitro recoveries averaged 30–35% and probes having in vitro recoveries of less than 20% were not used in vivo.

2.5. Tremor testing procedures

Whole body tremors were assessed in two ways. Direct visual observations were made of rats confined in a Plexiglas cylindrical (9 inches in diameter) enclosure; videotapes were sometimes made so that initial observations could be confirmed at a later time. Tremors were rated as absent, moderate or intense on a minute to minute basis for 30 min, beginning 15 min after drug administration. An automated and quantitative technique, based on a method originally designed for mice by other investigators [22], was also developed and utilized. Briefly, a Plexiglas enclosure was mounted on an audio speaker, the output of which was connected to a Hewlett-Packard 3392A integrator; the sensitivity of the integrator was adjusted such that random locomotor activity was generally ignored while large peaks representing tremors could be readily identified. Tremors were recorded and counted for 30 min, beginning 15 min after drug administration.

3. Results

3.1. Drug self-administration

Fig. 1 shows the initial acute effects of all of the alkaloids on morphine and cocaine self-administration. Each drug produced a dose-related depression of morphine and cocaine intake (ANOVA, $P < 0.001$ in every case). The potencies of the various alkaloids were very similar with the exception that desethylcoronaridine was approximately twice as potent as any of the other

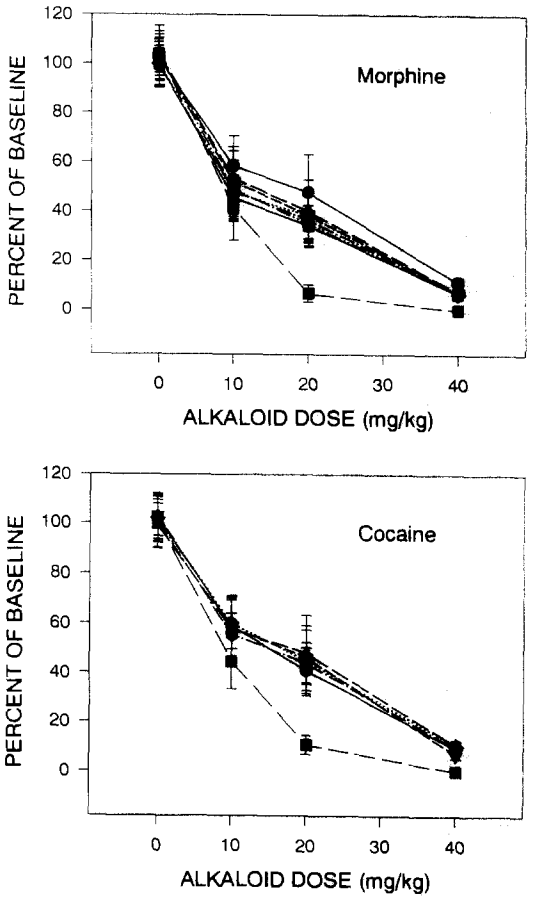

Fig. 1. Acute effects of ibogaine, harmaline, tabernanthine, desethylcoronaridine, R-coronaridine, S-coronaridine, R-ibogamine and S-ibogamine on morphine and cocaine self-administration. Each data point is the mean (±S.E.) from 3–8 rats. Baseline was calculated as the average rate for the three sessions preceding drug or saline (0 mg/kg) treatment. All doses of all drugs had significant effects (ANOVA and *t*-tests, $P < 0.05$–0.001); the only drug that differed significantly from any other was desethylcoronaridine (dashed line with square data points), which was approximately twice as potent as all of the other drugs.

drugs. Figs. 2 and 3 show that ibogaine (40 mg/kg), R-ibogamine (40 mg/kg), R-coronaridine (40 mg/kg), tabernanthine (40 mg/kg) and desethylcoronaridine (20 mg/kg), each administered for the first time, depressed morphine and cocaine intake for at least a day afterwards. In each of these cases, a group × days interaction was significant ($P < 0.05$ in a two-way ANOVA), and paired t-tests with baseline values were significant ($P < 0.05$–0.01) for days 1 and 2 in the indicated treatment groups. The extent of these aftereffects (one or more days later) on drug self-administration varied substantially from rat to rat; responses beyond a day later (Day 2) ranged from no further effect to a prolonged depression of morphine or cocaine intake, lasting up to several weeks in a few rats. In general, the aftereffects on cocaine intake were more variable than those on morphine intake; R-iboga-

mine produced the most consistent aftereffects on both morphine and cocaine self-administration.

Fig. 4 shows individual examples of the aftereffects of several of the *iboga* alkaloids. When such aftereffects were not apparent for particular rats, repeated injections of the same alkaloids were made, usually at weekly intervals. Fig. 5 shows examples of data from rats that were administered an *iboga* alkaloid three times: on the first two occasions there were no obvious effects beyond the day of injection whereas, after the third injection, morphine or cocaine intake was clearly depressed for at least several days afterwards. Some rats showed prolonged aftereffects following a second injection whereas others showed no aftereffects lasting more than a day even following three injections. There was one exception to the latter generality: prolonged aftereffects always appeared to occur by the third injection of R-ibogamine.

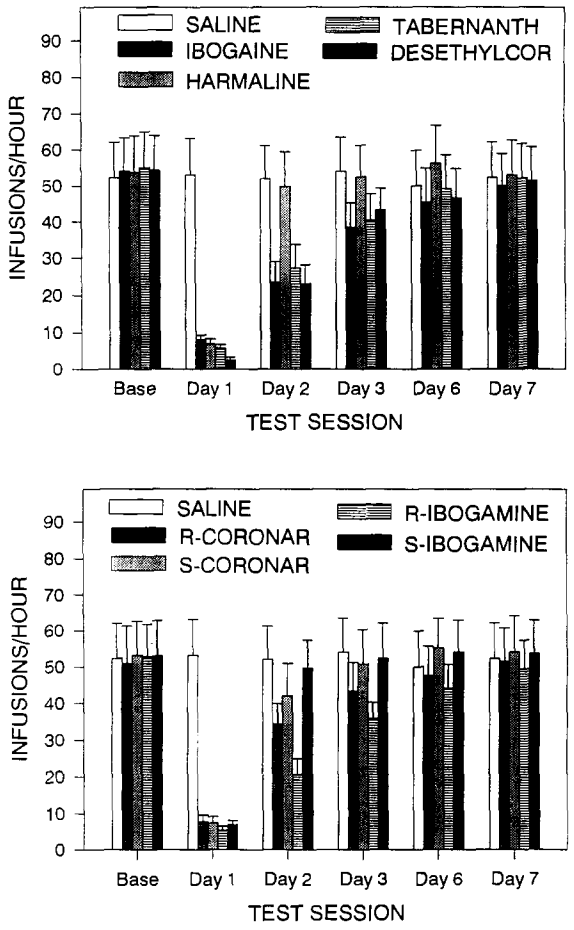

Fig. 2. Aftereffects of alkaloids (20 mg/kg for desethylcoronaridine and 40 mg/kg for all others) on morphine self-administration. Each data point is the mean (±S.E.) from 5–8 rats. 'Base' refers to the baseline rate of responding, calculated as the average for the three sessions preceding drug or saline treatment. There were significant effects on Day 1 for all drugs (see Fig. 1) and on Day 2 for ibogaine, tabernanthine, desethylcoronaridine, R-coronaridine and R-ibogamine (ANOVA and t-tests, $P < 0.05$–0.001).

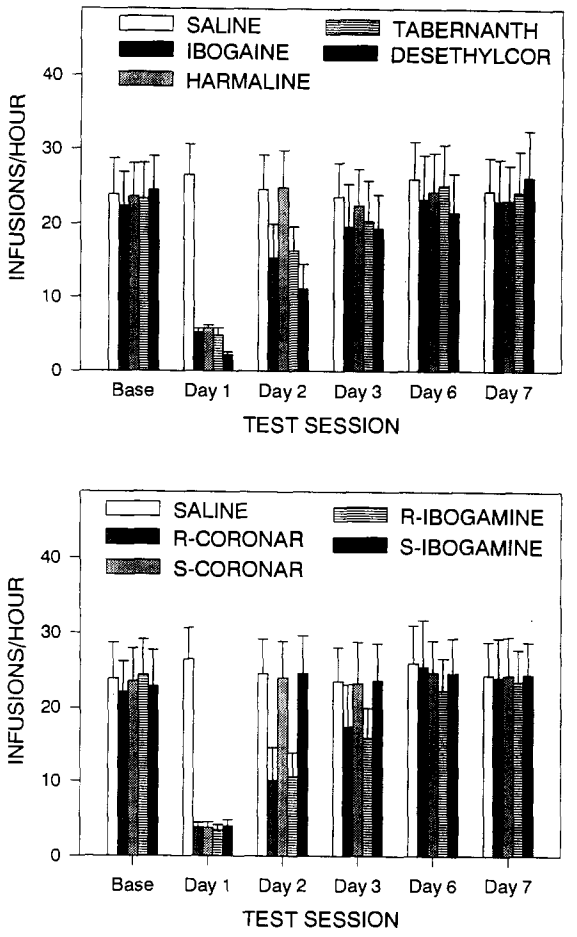

Fig. 3. Aftereffects of alkaloids (20 mg/kg for desethylcoronaridine and 40 mg/kg for all others) on cocaine self-administration. Each data point is the mean (±S.E.) from 4–8 rats. 'Base' refers to the baseline rate of responding, calculated as the average for the three sessions preceding drug or saline treatment. There were significant effects on Day 1 for all drugs (see Fig. 1) and on Day 2 for ibogaine, tabernanthine, desethylcoronaridine, R-coronaridine and R-ibogamine (ANOVA and t-tests, $P < 0.05$–0.001).

The Med Associates interface and software provided cumulative and event records of responding for each self-administration test session. For both morphine and cocaine, normal patterns of responding were characterized by an initial burst of drug intake at the beginning of each session followed by regularly spaced responding thereafter. Two kinds of alkaloid-induced effects were clearly apparent. Acutely, on the day of administration, the dose-related depressions of morphine and cocaine intake induced by all of the alkaloids were characterized by complete suppression of responding early in a session followed by irregularly spaced and sporadic responding thereafter; the highest dose of each of the alkaloids suppressed responding almost entirely in most animals. In contrast, the prolonged aftereffects on morphine and cocaine intake induced by some of the alkaloids were characterized by quite normal patterns of responding; that is, although

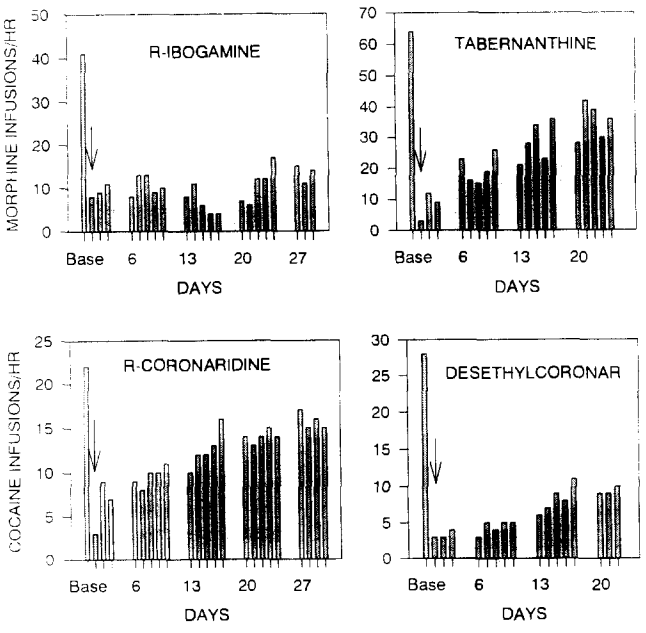

Fig. 4. Individual examples of long-term aftereffects of *iboga* alkaloids on morphine and cocaine self-administration; the doses administered (indicated by arrow) were 20 mg/kg for desethylcoronaridine and 40 mg/kg for the other drugs.

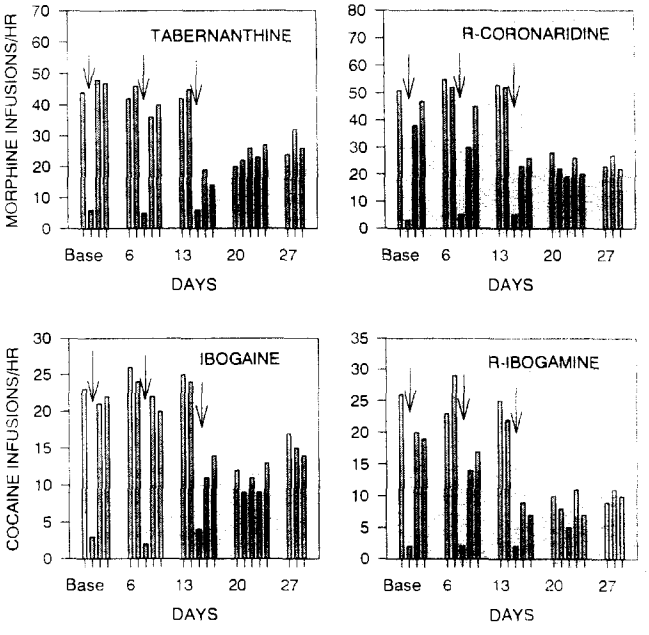

Fig. 5. Individual responses to repeated injections (indicated by arrows) of *iboga* alkaloids (40 mg/kg for all drugs); in each case, prolonged aftereffects only became apparent after the third injection.

responding was depressed, the effects were distributed uniformly throughout a test session such that the initial burst in responding was shorter and subsequent responses were more widely spaced than during baseline conditions. Fig. 6 shows typical cumulative records of cocaine self-administration by a rat treated with R-ibogamine (single injection of 40 mg/kg); the upper panel is a record of baseline responding on the day prior to R-ibogamine treatment while the bottom panel is the record of responding on the fifth day after R-ibogamine treatment.

3.2. *In vivo microdialysis*

Figs. 7 and 8 show the acute effects of R- and S-ibogamine and R- and S-coronaridine, respectively, on extracellular levels of dopamine (DA) in the nucleus accumbens (NAC) and striatum (STR). The R-

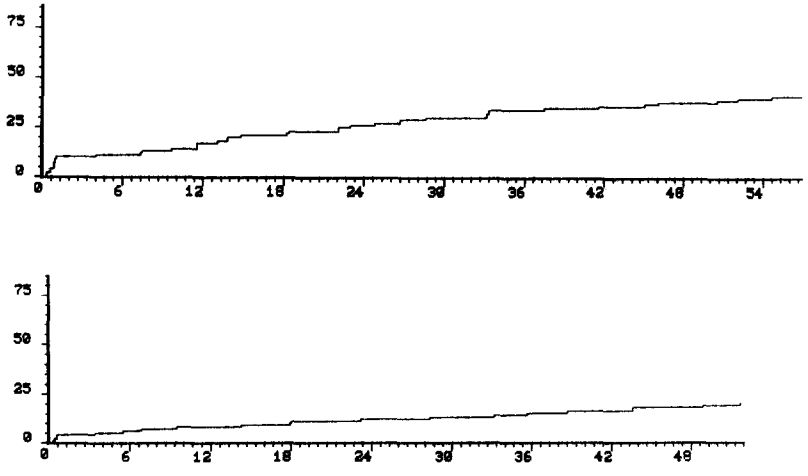

Fig. 6. Cumulative response records (ordinate, responses; abscissa, minutes) of intravenous cocaine self-administration (each response delivered 0.4 mg/kg cocaine) illustrating prolonged aftereffect of R-ibogamine. The upper panel is a record of baseline responding on the day prior to R-ibogamine (40 mg/kg, i.p.) treatment while the bottom panel is the record of responding on the fifth day after R-ibogamine treatment.

enantiomers of ibogamine and coronaridine significantly decreased DA levels (ANOVA, $P < 0.05$–0.01) while the S-enantiomers had no significant effects. There were no significant changes in DOPAC or HVA.

3.3. Tremorigenic effects

Ibogaine (20–40 mg/kg), harmaline (10–40 mg/kg) and desethylcoronaridine (10–40 mg/kg) were obviously tremorigenic for 3–4 h and no attempt was made to compare these drugs quantitatively. However, visual observations and videotape recordings of both R- and S-enantiomers of both ibogamine (40 mg/kg) and coronaridine (40 mg/kg) indicated very little if any tremorigenic activity. The effects of these latter drugs were therefore assessed using the automated testing procedure developed to quantitate tremors. Ibogaine (40 mg/kg) and saline (1 ml/kg) were used as positive and negative controls, respectively. While ibogaine produced a significant increase in movements indicative of tremors, none of the ibogamine and coronaridine enantiomers had effects that differed significantly from the effects of saline.

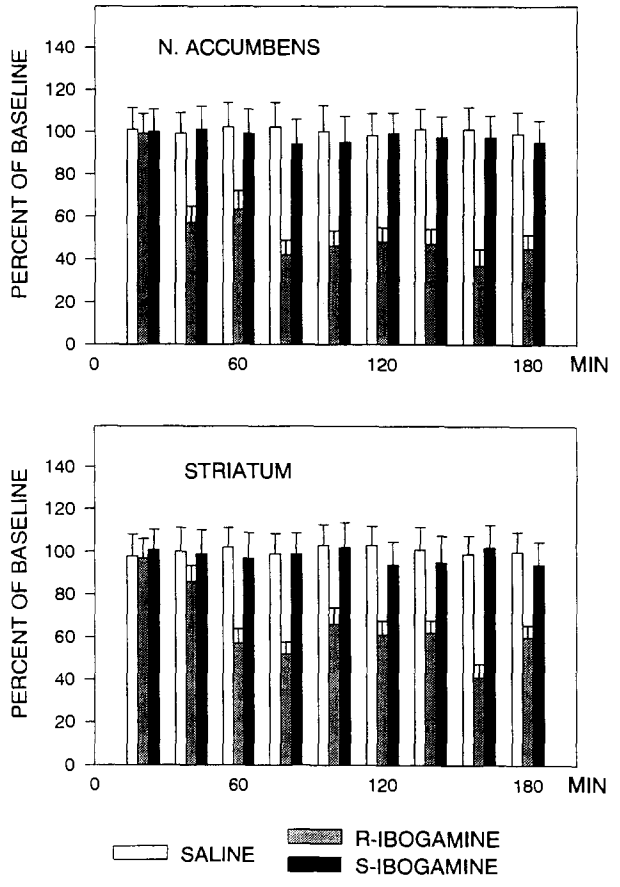

Fig. 7. Time course of extracellular dopamine levels in the nucleus accumbens and striatum after administration of saline ($n = 6$), R-ibogamine (40 mg/kg, $n = 6$), and S-ibogamine (40 mg/kg, $n = 7$). Samples were collected at 20 minute intervals. Data are expressed as a percent (±S.E.) of baseline dialysate values.

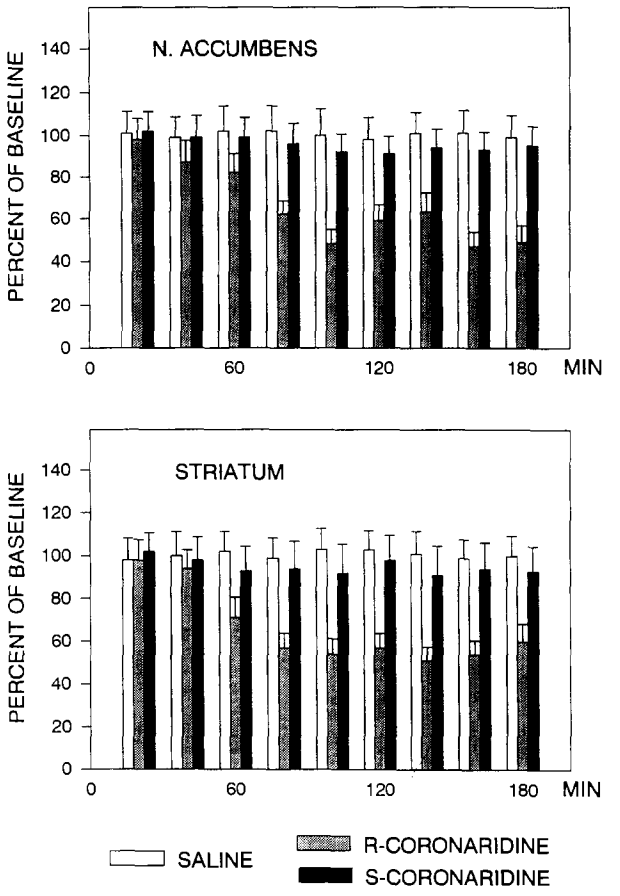

Fig. 8. Time course of extracellular dopamine levels in the nucleus accumbens and striatum after administration of saline ($n = 6$), R-coronaridine (40 mg/kg, $n = 5$), and S-coronaridine (40 mg/kg, $n = 6$). Samples were collected at 20 min intervals. Data are expressed as a percent (±S.E.) of baseline dialysate values.

4. Discussion

All of the *iboga* alkaloids as well as harmaline produced acute reductions in both morphine and cocaine self-administration. These effects may have occurred for a variety of reasons; while specific increases or decreases in the reinforcing efficacies of morphine and cocaine may have occurred, the alkaloids may also have induced non-specific malaise and/or motor deficits incompatible with performance of the operant response. In particular, it would appear that the whole body tremors induced by ibogaine and some of the other alkaloids may have made it difficult or impossible to execute coordinated motor responses. It should be noted, however, that aside from tremors, no other signs of overt toxicity were observed, and that with the ibogamine and coronaridine enantiomers, even tremors were hardly evident.

The aftereffects of the alkaloids on drug self-administration were clearly dissociated from their tremorigenic effects. Alkaloid-induced tremors generally disappeared within 4 h after administration while, for several of the alkaloids, rates of morphine and cocaine self-administration were significantly decreased for one or more days afterwards. Moreover, the efficacies of the alkaloids to induce tremors were unrelated to their efficacies to induce aftereffects on drug self-administration. Thus harmaline, which produces tremors that are very comparable to those produced by ibogaine [20,33], had no significant aftereffects on drug self-administration; and whereas the R-enantiomers of both ibogamine and coronaridine had significant aftereffects on drug self-administration, neither the R- nor the S-enantiomers of these agents produced any significant tremorigenic activity.

Although the acute rate-depressant effects of the alkaloids may have been non-specific, there are several indications that the aftereffects resulted from persistent modulatory actions of the alkaloids on the reinforcing efficacies of morphine and/or cocaine. The same dose of ibogaine that had persistent effects on morphine and cocaine self-administration was shown, in a previous study [12], to have no effect beyond the day of administration in rats bar-pressing for water. In the present study, the aftereffects of the 'active' alkaloids differed depending upon whether the reinforcer was morphine or cocaine. When percent changes on 'Day 2' data (cf. Figures 2 and 3) were compared, both ibogaine and tabernanthine were more effective (t-tests, $P < 0.05$) on morphine self-administration than on cocaine self-administration, R-coronaridine was more effective ($P < 0.05$) on cocaine self-administration than on morphine self-administration whereas R-ibogamine and desethylcoronaridine appeared to be equally effective on morphine and cocaine self-administration.

It should be noted that, in addition to the present and previous [12] results from this laboratory, other investigators have reported comparable aftereffects of ibogaine on intravenous cocaine self-administration in rats [1] as well as on oral cocaine self-administration in mice [25]; however, a lack of any aftereffects on either heroin or cocaine self-administration in rats has also been observed [5]. There were many procedural differences among these studies, including sex and strain of rats, schedule of reinforcement, and day-night cycle. The importance of each of these variables should be systematically assessed.

In a previous study [16], acute administration of ibogaine decreased extracellular levels of DA in the NAC and STR; however, the relevance of such changes to persistent effects of ibogaine on drug self-administration was unclear. In the present study, this issue was addressed by comparing the effects of the R- and S-enantiomers of ibogamine and coronaridine on NAC and STR DA. Since only the R-enantiomers of ibogamine and coronaridine had significant aftereffects on drug self-administration, it was of interest to determine if the neurochemical effects of the R- and S-enantiomers would differ as well. And, indeed, they did differ: R-ibogamine and R-coronaridine significantly decreased DA in the NAC and STR whereas S-ibogamine and S-coronaridine had no significant effects. Although it remains unclear how an acute change in extracellular DA levels can be associated with or responsible for a persistent behavioral effect, the data suggest that further investigation of such a relationship is warranted. It is conceivable, for example, that a decrease in DA release is the first step in a sequence of neurochemical changes that directly mediates a prolonged change in drug self-administration behavior.

Long-term decreases in morphine or cocaine intake lasting for several days and in some cases for several weeks after an *iboga* alkaloid treatment occurred in some rats. It was not possible to predict which rats would respond in this way, although, as noted in a previous report [12], there were again non-significant trends for rats having low baseline rates of drug intake to be less likely to exhibit such effects. When *iboga* alkaloid treatments were repeated at weekly or bi-weekly intervals, some rats that were initially resistant began to show long-term aftereffects; this suggests that there is a continuum of individual differences in sensitivity to these agents and that, with some dosage regimen of some of these agents, most or all rats would show long-term depressions of morphine or cocaine intake. It should be noted that persistent aftereffects after repeated treatment only occurred with those alkaloids producing significant 'day-after' effects and that, of all the alkaloids tested, R-ibogamine produced the most consistent prolonged aftereffects.

The mechanisms underlying the aftereffects of the *iboga* alkaloids are unknown although several possibilities have been suggested regarding ibogaine. One possibility is that the *iboga* alkaloids may persist in the body for long periods of time. In an early study using spectrofluorometry [4], the half-life of ibogaine in rodents was reported to be about one hour, and ibogaine levels in the body were undetectable a day after its administration. However, more recently, using gas chromatography mass spectrometry (GCMS), ibogaine has been detected a day after its administration in rat plasma and brain [7]; and other data indicate that the latter concentrations may be pharmacologically active [13]. Very little is known about the metabolism of ibogaine or other *iboga* alkaloids, and as suggested previously [12,16], it is possible that there are one or more active metabolites having long half-lives.

Ibogaine and related drugs (e.g., tabernanthine) have been suggested to have several neuropharmacological actions, including interactions with serotonergic [27],

muscarinic [4], and benzodiazepine receptors [29]); however, in radioligand binding studies [2], ibogaine and other *iboga* alkaloids were found to have no appreciable affinities for these receptors, although an affinity for kappa opioid receptors was demonstrated for ibogaine, tabernanthine and the racemic forms of coronardine and ibogamine. Ibogaine has been reported to potentiate the analgesic action of morphine [24], and perhaps this effect is attributable to a kappa-mu (ibogaine-morphine) opioid interaction [e.g., 6]. None of the receptor mechanisms have been shown or have even been proposed to be operative for more than a few hours after *iboga* alkaloid administration. In contrast, as reported previously ibogaine induces prolonged (at least 19 h) decreases in the extracellular [16] and tissue [17] levels of dopamine metabolites (DOPAC and HVA) in the NAC and STR; although the cellular basis for these effects are also not understood, the data are certainly consistent with the present self-administration data in terms of the well documented role of dopaminergic systems in morphine and cocaine reinforcement (e.g. 31,32]).

As noted earlier (see Introduction), Molliver [28] has proposed a novel theory that ibogaine-induced cerebellar damage may be responsible for its putative anti-addictive effects. Inasmuch as harmaline has been shown to produce comparable cerebellar damage [20], the lack of persistent effects of harmaline on drug self-administration, as observed in the present study, would appear to disprove Molliver's theory. Ibogaine-induced cerebellar damage has been most closely linked to its tremorigenic activity (cf. [20]). In the present study, the clear dissociation between the tremorigenic efficacies of other *iboga* alkaloids and their persistent effects on drug self-administration is a further indication that the cerebellum is unlikely to underlie or modulate a mechanism of addiction. Furthermore, in a recent histological study [18],we have found that ibogaine-induced cerebellar damage occurs after a high dose (100 mg/kg, i.p.), as reported by O'Hearn and Molliver [18], but not after a lower dose (40 mg/kg, i.p.) used in this and other self-administration studies [1,12].

Assuming that treatment with the 'active' *iboga* alkaloids alters the reinforcing efficacies of morphine and cocaine, the treatment-induced decreases in morphine and cocaine intake could result from either antagonism or enhancement of morphine's and cocaine's actions (e.g. [11]). That is, if an *iboga* alkaloid antagonized a self-administered drug's actions, it would be expected that rats might transiently self-administer more drug in an attempt to compensate for the reduced effect but then self-administer less drug as extinction occurred (i.e., analogous to decreasing the drug infusion dose to below threshold); if an *iboga* alkaloid enhanced a self-administered drug's actions, it would be expected that rats would also self-administer less drug but, in this case, as a way of compensating for the increased effect (i.e., analogous to increasing the drug infusion dose). Although the observed response patterns underlying the alkaloid-induced aftereffects (e.g., Fig. 6) favor the latter interpretation, and there was no evidence of a biphasic extinction pattern of responding that would support the 'antagonist' interpretation, other treatments (e.g., lesions) that disrupt drug self-administration by reducing reinforcing efficacy frequently do so by just decreasing response rates and without producing an extinction pattern of responding [23]. It is therefore not possible to discriminate between these two interpretations on the basis of the present data alone. Furthermore, in other studies involving measurement of locomotor activity, ibogaine pretreatment inhibited morphine-induced stimulation [17] and enhanced cocaine-induced stimulation [15]. Thus the effects of the *iboga* alkaloids on morphine and cocaine self-administration could even represent different kinds of drug interactions that are mediated by different mechanisms.

Acknowledgements

This research was supported by NIDA Grant DA-03817. We thank N. Dong for technical assistance.

References

[1] Cappendijk, S.L.T. and Dzoljic, M.R., Inhibitory effects of ibogaine on cocaine self-administration in rats, *Eur. J. Pharmacol.*, 241 (1993) 261–265.

[2] Deecher, D.C., Teitler, M., Soderlund, D.M., Bornmann, W., Kuehne, M.E. and Glick, S.D., Mechanisms of action of ibogaine and harmaline congeners based on radioligand binding studies, *Brain Res.*, 571 (1992) 242–247.

[3] de Montigny, C. and Lamarre, Y., Rhythmic activity induced by harmaline in the olivo-cerebello-bulbar system of the cat, *Brain Res.*, 53 (1973) 81–95.

[4] Dhahir, H.I., *A comparative study of the toxicity of ibogaine and serotonin*, Doctoral thesis, Ann Arbor, MI, USA, University Microfilm International (1971) 71–25–341.

[5] Dworkin, S.I., *Effects of ibogaine on self-administration of cocaine, heroin and food in rats*, presentation at FDA Drug Abuse Advisory Committee Meeting 26, August, 1993.

[6] Funada, M., Suzuki, T., Narita, M., Misawa, M. and Nagase, H., Blockade of morhine reward through the activation of kappa-opioid receptors in mice, *Neuropharmacology*, 32 (1993) 1315–1323.

[7] Gallagher, C.A., Hough, L.B., Keefner, S.M., Seyed-Mozaffari, A., Archer, S. and Glick, S.D., Identification and quantification of the indole alkaloid ibogaine in biological samples by gas chromatography-mass spectrometry, *Biochem. Pharmacol.*, submitted.

[8] Glick, S.D. and Cox, R.D., Changes in morphine self-administration after brainstem lesions in rats, *Psychopharmacology*, 52 (1977) 151–156

[9] Glick, S.D., Dong, N., Keller, Jr., R.W. and Carlson, J.N., Estimating extracellular concentrations of dopamine and 3,4-dihydroxyphenylacetic acid in nucleus accumbens and striatum using microdialysis: relationships between in vitro and in vivo recoveries, *J. Neurochem.*, in press..

[10] Glick, S.D., Hinds, P.A. and Carlson, J.N., Food deprivation and stimulant self-administration in rats: differences between cocaine and d-amphetamine, *Psychopharmacology*, 91 (1987) 372–374.

[11] Glick, S.D. and Ross, D.A., Neuroanatomical substrates of opiate reinforcement: lateralized effects. In J.E. Smith and J.D. Lane (Eds.), *Neurobiology of Opiate Reward Mechanisms*, Elsevier, Amsterdam, 1983, pp. 309–330.

[12] Glick, S.D., Rossman, K., Steindorf, S., Maisonneuve, I.M. and Carlson, J.N., Effects and aftereffects of ibogaine on morphine self-administration in rats, *Eur. J. Pharmacol.*, 195 (1991) 341–345.

[13] Glick, S.D., Rossman, K., Wang, S., Dong, N. and Keller, R.W., Local effects of ibogaine on extracellular levels of dopamine and its metabolites in nucleus accumbens and striatum: interactions with d-amphetamine, *Brain Res.*, 628 (1993) 201–208.

[14] Llinas, R. and Volkind, R.A., The olivo-cerebellar system: functional properties as revealed by harmaline-induced tremor, *Exp. Brain Res.*, 18 (1973) 69–87.

[15] Maisonneuve, I.M. and Glick, S.D., Interactions between ibogaine and cocaine in rats: in vivo microdialysis and motor behavior, *Eur. J. Pharmacol.*, 21 (1992) 263–266.

[16] Maisonneuve, I.M., Keller, R.W. and Glick, S.D., Interactions between ibogaine, a potential antiaddictive agent, and morphine: an in vivo microdialysis study, *Eur. J. Pharmacol.*, 199 (1991) 35–42.

[17] Maisonneuve, I.M., Rossman, K.L., Keller, R.W. and Glick, S.D., Acute and prolonged effects of ibogaine on brain dopamine metabolism and morphine-induced locomotor activity in rats, *Brain Res.*, 575 (1992) 69–73.

[18] Molinari, H.H., Maisonneuve, I.M. and Glick, S.D., Dose dependence of ibogaine neurotoxicity, *Soc. Neurosci. Abstr.*, 20 (1994) in press.

[19] O'Hearn, E., Long, D.B. and Molliver, M.E., Ibogaine induces glial activation in parasagittal zones of the cerebellum, *NeuroReport*, 4 (1993) 299–302.

[20] O'Hearn, E. and Molliver, M.E., Degeneration of purkinje cells in parasagittal zones of the cerebellar vermis after treatment with ibogaine or harmaline, *Neuroscience*, 55 (1993) 303–310.

[21] Paxinos, G. and Watson, C., *The Rat Brain in Stereotaxic Coordinates*, Academic Press, Orlando, FL, 1986.

[22] Remington, F. and Anisman, H., A simple method for quantifying tremor in rodents, *Pharmacol. Biochem. Behav.*, 4 (1976) 721–723.

[23] Roberts, D.C.S. and Koob, G.F., Disruption of cocaine self-administration following 6-hydroxydopamine lesions of the ventral tegmental area in rats, *Pharmacol. Biochem. Behav.*, 17 (1982) 901–904.

[24] Schneider, J.A. and McArthur, M. Potentiation action of ibogaine (Bogadin TM) on morphine analgesia, *Experientia*, 8 (1956) 323–324.

[25] Sershen, H., Hashim, A. and Lajtha, A., Ibogaine reduces preference for cocaine consumption in C57BL/tBy mice, *Pharmacol. Biochem. Behav.*, 47 (1994) 13–19.

[26] Shapiro, R.M., Badalamenti, J.I. and Glick, S.D., A simple and rapid technique for preparing histological sections of brain, *Pharmacol. Biochem. Behav.*, 19 (1983) 1049–1050.

[27] Sloviter, R.S., Drust, E.G., Damiano, B.P. and Connor, J.D., A common mechanism for lysergic acid, indolalkylamine and phenethylamine hallucinogens: serotonergic mediation of behavioral effects in rats, *J. Pharmacol. Exp. Ther.*, 214 (1980) 231–238.

[28] Touchette, N., Ibogaine neurotoxicity raises new questions in addiction research, *J. NIH Res.*, 5 (1993) 50–55.

[29] Trouvin, J.H., P. Jacqmin, P., Rouch, C., Lesne, M. and Jacquot, C., Benzodiazepine receptors are involved in tabernanthine-induced tremor: in vitro and in vivo evidence, *Eur. J. Pharmacol.*, 140 (1987) 303–309.

[30] Weeks, J.R., Long-term intravenous infusion. In R.D. Myers (Ed.), *Methods in Psychobiology, Vol. 2*, Academic Press, New York, 1972, pp. 155–168.

[31] Wise, R.A., The role of reward pathways in the development of drug dependence, *Pharmacol. Ther.*, 35 (1987) 227–263.

[32] Wise, R.A. and Bozarth, M.A., A psychomotor stimulant theory of addiction, *Psychol. Rev.*, 94 (1987) 469–492.

[33] Zetler, G., Singbartl, G. and Schlosser, L., Cerebral pharmacokinetics of tremor-producing harmala and iboga alkaloids, *Pharmacology*, 7 (1972) 237–248.