Brain Research, 579 (1992) 87–92

BRES 17668

Interactions of ibogaine and D-amphetamine: in vivo microdialysis and motor behavior in rats

I.M. Maisonneuve, R.W. Keller Jr. and S.D. Glick

Department of Pharmacology and Toxicology, Albany Medical College, Albany, NY 12208 (USA)

(Accepted 10 December 1991)

Key words: Ibogaine; D-Amphetamine; Nucleus accumbens; Striatum; Microdialysis; Locomotor activity

Ibogaine, an indolalkylamine, has been proposed for use in treating stimulant addiction. In the present study we sought to determine if ibogaine had any effects on the neurochemical and motor changes induced by D-amphetamine that would substantiate the anti-addictive claim. Ibogaine (40 mg/kg, i.p.) injected 19 h prior to a D-amphetamine challenge (1.25 mg/kg, i.p.) potentiated the expected rise in extracellular dopamine levels in the striatum and in the nucleus accumbens, as measured by microdialysis in freely moving rats. Using photocell activity cages, the same ibogaine pretreatment enhanced the stimulatory motor effects induced by a wide range of D-amphetamine doses (0.625, 1.25, 2.5 or 5 mg/kg, i.p.). These findings suggest that ibogaine might increase the reinforcing efficacy of D-amphetamine. However, since high doses of D-amphetamine can be aversive, the potentiation of D-amphetamine's effects by ibogaine might also lead to a decrease in the reinforcing efficacy of D-amphetamine.

INTRODUCTION

Ibogaine, an indolalkylamine, has been proposed for use in treating opiate[17] and stimulant addiction[18]. Consistent with the first of these claims, it has been reported that, in rats, ibogaine decreases intravenous morphine self-administration[10] and blocks the increase in limbic and striatal dopamine (DA) release, as well as the increase in motor activity, induced by a low dose (5 mg/kg, i.p.) of morphine[20]. The mechanism by which ibogaine inhibits the effects of morphine is unclear. In an effort to gain further insights into ibogaine's mechanisms of action, we examined ibogaine's interaction with D-amphetamine, a stimulant known to interact with DA neurons by a mechanism different from that of morphine.

The reinforcing property of D-amphetamine has been linked to the activation of mesolimbic DA neurones. DA receptor antagonists decrease the rewarding effects of intravenously self-administered D-amphetamine[29,30]. 6-Hydroxydopamine lesions of the nucleus accumbens produce a significant and persistent decrease in D-amphetamine self-administration of D-amphetamine[19] and inhibit D-amphetamine-stimulated locomotion[16]. Rats will self-administer D-amphetamine directly into the nucleus accumbens[14]. Injections of D-amphetamine into the nucleus accumbens will also induce hyperactivity[6]. Thus the actions of D-amphetamine on the DA terminals of the nucleus accumbens appear to activate pathways mediating both reward and locomotion[28].

The aim of the present study was to determine if ibogaine would have any effects on the neurochemical and motor changes induced by D-amphetamine that might substantiate the anti-addictive claim with regard to stimulants. We first studied, simultaneously, the effects of ibogaine pretreatment (40 mg/kg, i.p.) on the time-course of changes in extracellular DA and in locomotion induced by D-amphetamine (1.25 mg/kg, i.p.). Then, in order to characterize the dose–response interaction between ibogaine and D-amphetamine, the effects of the same pretreatment on motor activity elicited by D-amphetamine were determined across a wide range of D-amphetamine doses (0.625–5.0 mg/kg).

MATERIALS AND METHODS

Drugs

Ibogaine HCl was obtained from Sigma Chemical Co. and was dissolved in water at a concentration of 20 mg/ml. D-Amphetamine sulfate, obtained from Sigma Chemical Co., was dissolved in saline. Both drugs were injected intraperitoneally (i.p.) in doses expressed as the salt. The dose of ibogaine (40 mg/kg) was the same as that previously used in comparable studies with morphine[20]. The dose of D-amphetamine (1.25 mg/kg) used in the microdialysis experiment was selected because it is known to elicit a maximal in-

Correspondence: I.M. Maisonneuve, Department of Pharmacology and Toxicology (A-136), Albany Medical College, Albany, NY 12208, USA. Fax: (1) (518) 445-5799.

crease in motor activity in the first hour after administration[13,15].

Animal preparation

Under pentobarbital anesthesia, female Sprague–Dawley rats were implanted stereotaxically with guide cannulas over the nucleus accumbens and striatum so that, when inserted, the tips of the dialysis probes were 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; and ventral, −7.0 mm)[21]. The two cannulae were fixed firmly to the skull with dental cement. Female rats were used so that the results could be compared to those obtained in earlier studies[10,20].

Microdialysis procedures

At least 3 days after surgery, the rats were injected i.p. with saline (2 ml/kg) or ibogaine (40 mg/kg). The next day, the dialysis experiment was carried out on a freely moving animal. The rat was placed in a cylindrical plastic cage with free access to food and water. Probes were reused 3–5 times and were calibrated, prior to each experiment, in vitro at room temperature in an artificial CSF solution gassed with argon (with DA 15 pm/ml, DOPAC 1.5 nm/ml and HVA 0.75 nm/ml). All values were corrected for recovery which ranged from 25 to 40% for DA and its metabolites. After calibration, the probes (3 mm probes; BAS/CMed MF-5140) were lowered into the guide cannulae. In order to prevent damage to the dialysis membrane, rats were lightly anesthetized with methohexital (40 mg/kg) when probes were inserted. The probe inlets were connected to a Harvard pump through a liquid swivel. The collection vials were placed in a holder on the swivel tether so that the samples could be removed without disturbing the animal. 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. Collection of brain perfusate began 3 h and 40 min after the probes were inserted. Twenty-min 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). Four baseline samples were taken before intraperitoneal injection of D-amphetamine (1.25 mg/kg). The drug effects were then monitored for 3 h. The interval between saline or ibogaine pretreatment and D-amphetamine administration was 19 h and had been chosen to match earlier studies[20]. Upon completion of an experiment, rats were killed and histological analysis[25] of each brain was performed to verify the location of the two probes.

Catecholamine assay

Perfusate samples were analyzed by HPLC with electrochemical detection; the HPLC system consisted of a Waters pump (model 510), a WISP autosampler (model 712), an ESA CA80 column and a Waters detector (model 464). The mobile phase consisted of 6.9 g/l sodium monobasic phosphate, 250 mg/l heptane sulfonic acid, 80 mg/l disodium EDTA, 50 ml/l methanol, was adjusted with HCl to pH 3.6 and was pumped at a rate of 1.2 ml/min. Chromatograms were processed using the software Maxima 820.

Motor-activity monitoring

Rats were maintained on a normal light/dark cycle (lights on/off at 07.00 h/19.00 h) and experiments were conducted during the light phase in a quiet room. Motor activity was assessed in two different ways: with photocell activity cages and rotometers. In photocell activity cages[12], interruptions of any of the infrared photocell beams were recorded by an Apple IIe computer. Rats were pretreated with saline (2 ml/kg) or ibogaine (40 mg/kg) 19 h before the administration of saline (1 ml/kg) or D-amphetamine (0.625–5 mg/kg). Immediately after the D-amphetamine injection rats were placed in activity cages and locomotion was measured for 3 h. The second method involved the group of rats that were dialyzed. In the dialysis chamber, the rats were attached to a computerized rotometer system[11], sensitive to both locomotor and stereotypic behaviors. Quarter turns (90° turns), an index of motor activity, were recorded while dialysate samples were collected.

Statistical analysis

Statistical analyses of microdialysis effects were done on data expressed as percents of the respective mean basal values in order to equate for between-subject differences. A repeated measure analysis of variance (ANOVA) was used to test for time, pretreatment and regional effects. Post-hoc analyses were carried out using the Newman–Keuls multiple comparison tests. *t*-Tests were performed to evaluate any differences between basal levels. Statistical analyses of behavioral data were done on non-transformed data. Correlation coefficients were calculated on the association between each animal's DA values (13 values, expressed as percent of baseline) and its correspondent number of quarter turns for the same sampling period.

RESULTS

Basal levels of dopamine and its metabolites

Estimated extracellular basal levels, corrected for probe recovery, were as follows: nucleus accumbens DA, 13.6 ± 1.5 nM; 3,4-dihydroxyphenylacetic (DOPAC), 5.82 ± 0.66 μM; homovanillic acid (HVA), 2.52 ± 0.3 μM; and striatum DA, 18.5 ± 2.5 nM; DOPAC, 6.88 ± 0.39 μM; and HVA, 4.54 ± 0.46 μM. These levels were based on the four basal samples taken at a time interval

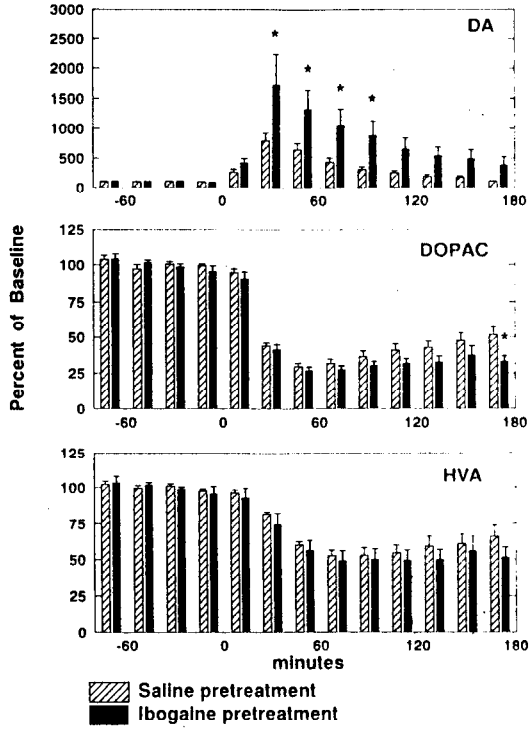

Fig. 1. Time-course of extracellular DA, DOPAC and HVA levels in the nucleus accumbens before and after administration of D-amphetamine (1.25 mg/kg) in rats pretreated with saline (n = 6) or ibogaine (40 mg/kg, n = 6) the day before. Samples were collected at 20-min intervals. Data are expressed as a percent of baseline values (± S.E.M.). $^*P < 0.05$ as compared to saline pretreatment at the same time.

when 86% of dopamine overflow has been shown to be TTX sensitive[9].

Effects of D-amphetamine on dopamine and its metabolites

Injection of D-amphetamine (1.25 mg/kg) in control rats led to an increase in extracellular dopamine (time effect, $P < 0.001$) that peaked in the second sampling period and remained elevated up to 100 min postinjection ($P < 0.05$) in the nucleus accumbens (Fig. 1) and up to 80 min ($P < 0.05$) in the striatum (Fig. 2). The response to D-amphetamine was different in the two regions studied (region × interaction, $P < 0.01$). The peak increase was greater in the striatum (1250%, Fig. 2) than in the nucleus accumbens (790%, Fig. 1). In both regions the D-amphetamine challenge produced a decline in DOPAC and HVA values that was significantly different from their basal values from 20 to 180 min post-amphetamine. Both metabolite decreases were greater in the striatum than in the nucleus accumbens (DOPAC 23% vs 30% of basal levels; HVA 44% vs 53% of basal levels).

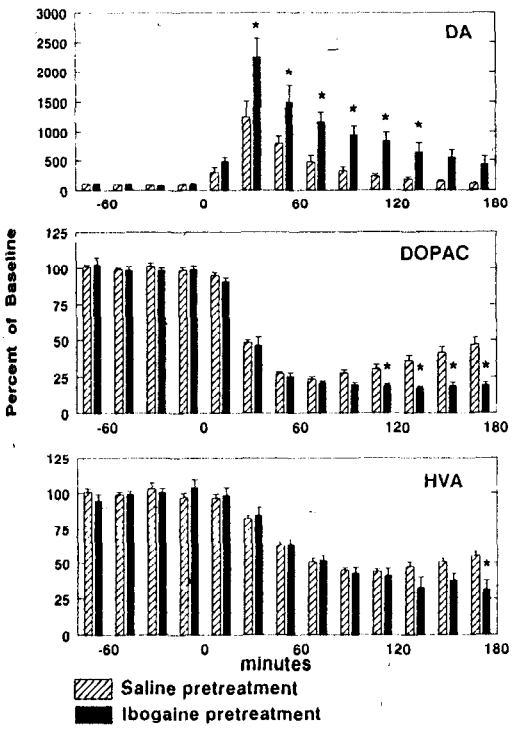

Fig. 2. Time-course of extracellular DA, DOPAC and HVA levels in the striatum before and after administration of D-amphetamine (1.25 mg/kg) in rats pretreated with saline ($n = 6$) or ibogaine (40 mg/kg, $n = 6$) the day before. Samples were collected at 20-min intervals. Data are expressed as a percent of baseline values (± S.E.M.). $^*P < 0.05$ as compared to saline pretreatment at the same time.

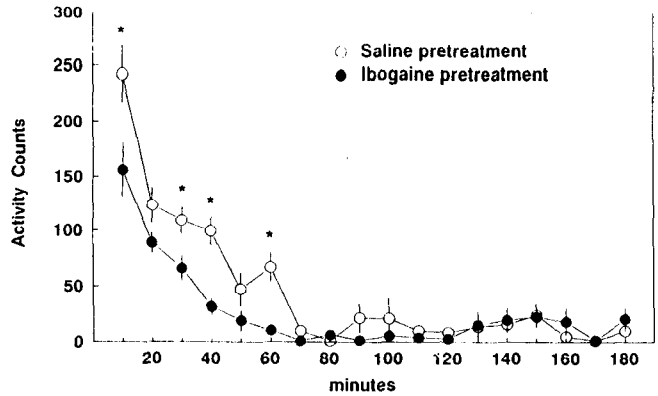

Fig. 3. Effects of saline ($n = 6$) or ibogaine ($n = 6$) on locomotor activity 19–22 h after their administration. Each point represents the average activity counts (± S.E.M.) for a period of 10 min. $^*P < 0.05$ as compared to saline pretreatment at the same time.

Effects of ibogaine on dopamine metabolite changes induced by D-amphetamine

Pretreatment with ibogaine had no significant effects on basal extracellular DA levels 19 h later (accumbens, 15.1 ± 3.0 nM; striatum, 19.0 ± 3.5 nM); however, it decreased DOPAC levels significantly in the nucleus accumbens (4.67 ± 0.44 μM, $P < 0.05$) and tended to lower DOPAC in the striatum (6.02 ± 0.78 μM) as well as HVA levels in both regions (accumbens, 1.88 ± 0.18 μM; striatum, 3.96 ± 0.58 μM). Administration of

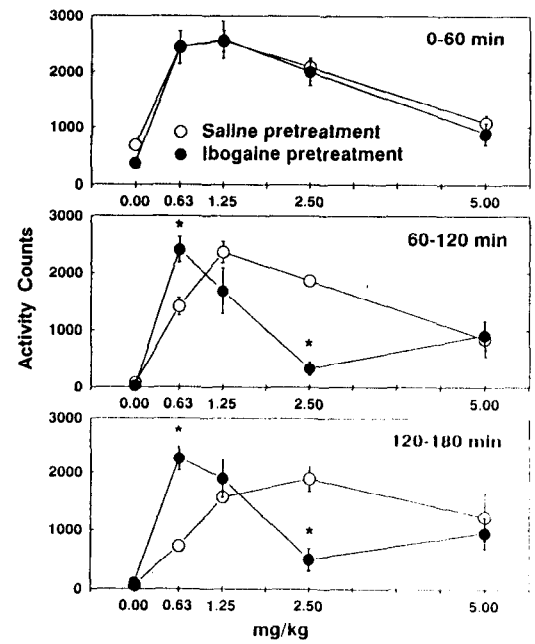

Fig. 4. Effects of a saline or ibogaine pretreatment on the dose response curve of D-amphetamine. D-Amphetamine was administrated at time zero and the pretreatments 19 h earlier. Each point represents the average activity counts (± S.E.M.) of six rats for a period of 1 h. $^*P < 0.05$ as compared to saline pretreatment at the same time.

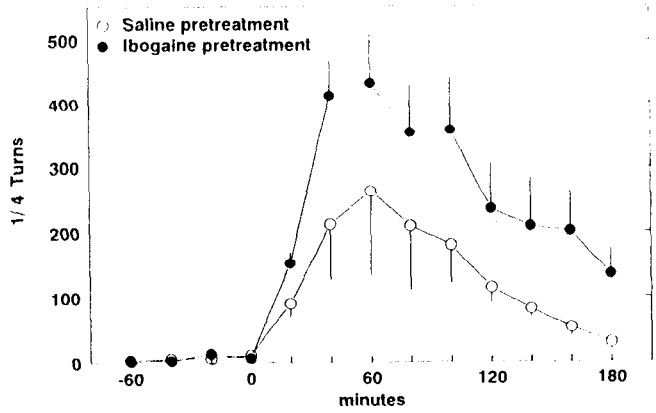

Fig. 5. Effects of of saline (n = 6) and ibogaine (n = 6) pretreatment on motor activity induced by administration of D-amphetamine (1.25 mg/kg) and assessed during the dialysis experiment. Each point represents the average total quarter turns (± S.E.M.) for a period of 20 min.

ibogaine 19 h prior to a D-amphetamine challenge potentiated the rise in extracellular DA from 20 to 100 min after D-amphetamine injection in the nucleus accumbens ($P < 0.05$) (Fig. 1) and from 20 to 140 min post injection in the striatum ($P < 0.05$) (Fig. 2). Ibogaine pretreatment also prolonged the drop in DOPAC levels. This effect was more pronounced in the striatum (100–180 min, $P < 0.05$) (Fig. 2) than in the nucleus accumbens (160–180 min, $P < 0.05$) (Fig. 1). HVA showed the same trend, but reached significance only in the striatum (160–180 min, $P < 0.05$) (Fig. 2).

Effects of ibogaine on behavioral response to D-amphetamine

Ibogaine pretreatment alone had a small inhibitory effect on locomotion 19–20 h after its administration (Fig. 3; Fig. 4 – 0 mg/kg of D-amphetamine, first hour). This effect was significant for the following periods: 0–10 min, 20–40 min and 50–60 min ($P < 0.05$). The statistical analysis of ibogaine's effects on the motor responses induced by a wide range of D-amphetamine doses (Fig. 4) showed no significant effect of ibogaine pretreatment for the first hour but a shift to the left of the D-amphetamine's dose–response curve for the second hour (0.625 mg/kg: $P < 0.0003$; 2.5 mg/kg: $P < 0.0002$) and for the third hour (0.625 mg/kg and 2.5 mg/kg: $P < 0.0002$).

Analysis of the behavioral data collected during the dialysis experiment (Fig. 5) revealed that ibogaine pretreatment tended to potentiate the D-amphetamine-induced motor activity, measured as quarter turns (analysis of variance, $P < 0.08$). With reference to their respective baseline values, D-amphetamine administration enhanced motor activity 40–60 min postinjection in control rats ($P < 0.05$) and 20–100 min in ibogaine-pretreated animals ($P < 0.05$). In the control group, DA levels and corresponding quarter turns were sign correlated in the nucleus accumbens (r = 0.47 0.0001), but not in the striatum (r = 0.2104) ibogaine group, significant correlations were f both regions (accumbens: r = 0.5065, $P < 0.0($ atum: r = 0.6838, $P < 0.0001$).

DISCUSSION

The aims of the present study were to de whether ibogaine would alter neurochemical an ioral changes induced by D-amphetamine and such data could explain ibogaine's potential an tive properties. In addition this study allowed us pare the effects of D-amphetamine on the me and nigrostriatal DA systems.

In both the striatum and the nucleus accumb i.p. administration of 1.25 mg/kg D-amphetam duced a net increase in the extracellular DA l greater release in DA occurred in the striatum effects on DOPAC, and to a lesser extent on HV also more pronounced in the striatum. While t sults do not support the hypothesis that D-ampl preferentially increases mesolimbic DA levels[4], in agreement with the findings of several other tories[22,23]. This divergence in the literature coul result of the sampling of different striatal subre suggested by Pehez et al.[22], and the use of types of probes (transversal versus concentric ever, other methodological differences could also the difference in results. Whereas Carboni et a pared the effects of D-amphetamine using diffe mals for each region, all studies showing a great of D-amphetamine in the striatum than in the accumbens made this comparison in the same a [23].

Pretreatment with ibogaine potentiated the e D-amphetamine on dopamine release in both the accumbens and striatum. D-Amphetamine's net dopamine release is probably the result of sever ent actions. Direct actions of D-amphetamine dopamine release by non-impulse-dependent rel uptake blockade. However, its indirect actions diminish it by activation of autoreceptors by the dopamine. As a result, ibogaine must either inte actions of D-amphetamine that enhance dopa lease or inhibit the actions that tend to diminis

Ibogaine has been demonstrated to have no for D1 and D2 receptors, but to act on voltag dent Na^+ channels[7]; it is unknown whether ibog as an agonist or antagonist at the Na^+ channel tridine, a Na^+ channel agonist, has been show tentiate the DA release induced by D-amphetan

dose that has only a small effect on basal DA levels[1]. By increasing the intracellular sodium, veratridine reverses or at least decreases the inward Na^+ gradient and, as a consequence, facilitates the release of DA, concomitant with Na^+ ions, through the transport carrier[26]. Thus, ibogaine, as a potential Na^+ channel agonist, could acutely potentiate the release induced by D-amphetamine. However, the potentiation of D-amphetamine's effects that we report here occurred 19 h after ibogaine administration, at a time when ibogaine is no longer present in the body (half-life = 1 h in the rodents[8]), but still affecting the dopaminergic system (decrease in basal DA metabolite levels, motor inhibitory effect). It is possible that ibogaine administration results in the formation of an active metabolite with a similar pharmacology and/or that a persistent change in neuronal activity, akin to sensitization, occurs. However, the possibility that ibogaine potentiates D-amphetamine's effects by interfering with its metabolism, resulting in increased brain D-amphetamine levels, cannot be excluded.

A potentiation of D-amphetamine effects by ibogaine pretreatment was also observed in the behavioral studies. Small and intermediate doses of D-amphetamine (up to 2.5 mg/kg) produced dose-dependent stimulatory effects on locomotion. A dose of 5 mg/kg of D-amphetamine enhanced locomotor activity only 2 h after injection when brain D-amphetamine levels should have been reduced by a factor of 2 (D-amphetamine's half-life is about 2 h in rats). Ibogaine shifted the dose–response curve for D-amphetamine to the left during the second and third hour following the stimulant administration. Ibogaine did not seem to affect the increase in locomotion during the first hour after D-amphetamine; however, ibogaine alone produced a decrease in activity during the same period. If this inhibitory effect due to ibogaine alone is subtracted, there is some evidence of a potentiation of D-amphetamine's effects even during the first hour. In fact, when motor activity (quarter turns) was monitored during the dialysis experiment, ibogaine pretreatment immediately enhanced D-amphetamine's effects. In control rats, a significant correlation between the neurochemical and behavioral changes induced by D-amphetamine occurred only in the nucleus accumbens, in agreement with the idea that the locomotor stimulatory effect of D-amphetamine is mediated via DA release in the nucleus accumbens[24,27]. After ibogaine pretreatment, the neurochemical and behavioral effects were significantly correlated in both the nucleus accumbens and the striatum. This suggests that ibogaine, by potentiating D-amphetamine, increases stereotypic behaviors which are thought to be mediated via DA release in the striatum (e.g., ref. 24).

The psychomotor stimulant theory of addiction developed by Wise and Bozarth[28] advocates that an increase in nucleus accumbens DA transmission, which leads to enhanced motor activity, is the neurochemical substrate of 'pleasure' or reward and the basis for the addictive property of drugs. Therefore ibogaine, by potentiating the dopaminergic response to D-amphetamine, may increase the reinforcing efficacy of D-amphetamine and enhance its addictive liability. However, studies have also demonstrated that high doses of D-amphetamine are aversive[5,3], and that one high dose of D-amphetamine will cause the rejection of subsequent low doses[5]. Cappel and Leblanc[2] showed in 1973 that even low doses of D-amphetamine can be either rewarding or aversive depending upon the type of behavioral contingency with which the drug is associated. Thus ibogaine, by amplifying the D-amphetamine response, may reduce the rewarding effect of D-amphetamine by making it aversive.

In conclusion, the present data clearly demonstrate that ibogaine enhances the dopaminergic response to D-amphetamine. However, it is uncertain whether this interaction would lead to an increase or decrease in D-amphetamine self-administration. Further studies should address this question directly.

Acknowledgement. This research was supported by NIDA Grant DA-03817.

REFERENCES

1 Butcher, S.P., Faitbrother, I.S., Kelly, J.S. and Arbuthnott, G.W., Amphetamine-induced dopamine release in the rat striatum: an in vivo microdialysis study, *J. Neurochem.*, 50 (1988) 346–355.

2 Cappel, H. and Leblanc, A.E., Punishment of saccharin drinking by amphetamine in rats and its reversal by chlordiazepoxide, *J. Comp. Physiol. Psychol.*, 85 (1973) 97–104.

3 Cappel, H. and Leblanc, A.E., Conditioned aversion to saccharin by single administration of mescaline and D-amphetamine, *Psychopharmacologia*, 22 (1971) 352–356.

4 Carboni, E., Imperato, A., Perezzani L. and Di Chiara, G., Amphetamine, cocaine, phencyclidine and nomifensine increase extracellular dopamine concentrations preferentially in the nucleus accumbens of freely moving rats, *Neuroscience*, 28 (1989) 653–661.

5 Carey, R.J., Acquired aversion to amphetamine solutions, *Pharmacol. Biochem. Behav.*, 1 (1973) 227–229.

6 Costall, B. and Naylor, R.J., Specific asymmetric behaviour induced by the direct chemical stimulation of neostriatal dopaminergic mechanisms, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 285 (1974) 83–91.

7 Deecher, D.C., Teitler, M., Soderlund, D.M., Bornmann, W.G., Kuehne, M.E. and Glick, S.D., Mechanisms of action of ibogaine and harmaline congeners based on radioligand binding studies, *Brain Res.*, in press.

8 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.

9 Drew, K.L., O'Connor, W.T., Kehr, J. and Ungerstedt, U., Characterization of gamma-aminobutyric acid and dopamine overflow following acute implantation of a microdialysis probe, *Life Sci.*, 45 (1989) 1307–1317.
10 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.
11 Glick, S.D. and Cox, R.D., Nocturnal rotation in normal rats: correlation with amphetamine-induced rotation and effects of nigrostriatal lesions, *Brain Res.*, 150 (1978) 149–161.
12 Glick, S.D., Changes in amphetamine sensitivity following frontal cortical damage in rats and mice, *Eur. J. Pharmacol.*, 20 (1972) 351–356.
13 Glick, S.D., Change in sensitivity to D-amphetamine in frontal rats as a function of time: shifting of the dose–response curve, *Psychon. Sci.*, 19 (1970) 57–58.
14 Hoebel, B.G., Monaco, A., Hernandes, L., Aulisi, E., Stanley, B.G. and Lenard, L., Self-injection of amphetamine directly into the brain, *Psychopharmacology*, 81 (1983) 158–163.
15 Jerussi, T.P. and Glick, S.D., Drug-induced rotation in rats without lesions: behavioral and neurochemical indices of a normal asymmetry in nigro-striatal function, *Psychopharmacology*, 47 (1976) 249–260.
16 Kelly, P.H., Saviour, P.W. and Iversen, S.D., Amphetamine and apomorphine responses in rats following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum, *Brain Res.*, 94 (1975) 507–522.
17 Lotsof, H., *Rapid Method for Interrupting the Narcotic Addiction Syndrome*, (1985) Patent number: 4,499,096.
18 Lotsof, H., *Rapid Method for Interrupting the Cocaine and Amphetamine Abuse Syndrome*, (1986) Patent number: 4,587,243.
19 Lyness, W.H., Friedle, N.M. and Moore, K.E., Destruction of dopamine nerve terminals in nucleus accumbens: effect on D-amphetamine self-administration, *Pharmacol. Biochem. Behav.*, 11 (1979) 553–556.
20 Maisonneuve, I.M., Keller Jr., R.W. and Glick, S.D., Interactions between ibogaine, a potential anti-addictive agent, and morphine: an in vivo microdialysis study, *Eur. J. Pharmacol.*, 199 (1991) 35–42.
21 Paxinos, G., and Watson, C., *The Rat Brain in Stereotaxic Coordinates*, Academic Press, Orlando, FL, 1986.
22 Pehez, E.A., Schechter, M.D. and Yamamoto, B.K., Effects of cathinone and amphetamine on the neurochemistry of dopamine in vivo, *Neuropharmacology*, 29 (1990) 1171–1176.
23 Robinson, T.E. and Camp, D.M., Does amphetamine preferentially increase extracellular dopamine in the mesolimbic system?, *Soc. Neurosci. Abstr.*, 115 (1989) 559.
24 Saton, D.M. and Solomon, P.R., Microinjections of D-amphetamine into the nucleus accumbens and caudate-putamen differentially affect stereotypy and locomotion in the rat, *Physiol. Psychol.*, 12 (1984) 159–162.
25 Shapiro, R.M., Badalamenti, J.I. and Glick, S.D., A simple and rapid technique for preparing histological sections of the brain, *Pharmacol. Biochem. Behav.*, 19 (1983) 1049–1050.
26 Sirinathsinghji, D.J.S., Heavens, R.P. and Sikdar, S.K., In vivo studies of the dopamine reuptake mechanism in the striatum of the rat: effects of benztropine, sodium and ouabain, *Brain Res.*, 438 (1988) 399–403.
27 Swerdlow, N.R., Vaccarino, F.J., Almaric, M. and Koob, G.F., The neural substrates for the motor-activating properties of psychostimulants: a review of recent findings, *Pharmacol. Biochem. Behav.*, 25 (1986) 233–248.
28 Wise, R.A. and Bozarth, M.A., A psychomotor stimulant theory of addiction, *Psychol. Rev.*, 94 (1987) 469–492.
29 Yokel, R.A. and Wise, R.A., Increased lever pressing for amphetamine after pimozide in rats: implications for a dopamine theory of reward, *Science*, 187 (1975) 547–549.
30 Yokel, R.A. and Wise, R.A., Attenuation of intravenous amphetamine reinforcement by central dopamine blockade in rats, *Psychopharmacology*, 48 (1976) 311–318.

Note added in proof

Recently obtained data indicate that ibogaine (40 mg/kg, i.p.), injected 19 h before D-amphetamine (1.25 mg/kg, i.p.), increases brain D-amphetamine levels (measured 2 h later by GCMS).