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Local effects of ibogaine on extracellular levels of dopamine and its metabolites in nucleus accumbens and striatum: interactions with D-amphetamine

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Systemic administration of ibogaine (40 mg/kg, i.p.) has been reported to induce both acute (1–3 h) and persistent (19–20 h) changes in extracellular levels of dopamine and its metabolites in the nucleus accumbens and striatum. In the present study, local administration of ibogaine to the striatum and nucleus accumbens produced effects that mimicked both the acute and persistent effects of systemic administration: perfusion with high concentrations (200 and 400 μM) of ibogaine mimicked the acute effects (decreased extracellular dopamine levels and increased extracellular metabolite levels) whereas perfusion with a low concentration (10 μM) of ibogaine mimicked the persistent effects (decreased extracellular levels of DOPAC). These results indicate that ibogaine acts directly in brain regions containing dopaminergic nerve terminals and that long-lasting effects of systemically administered ibogaine might be mediated by persisting low levels of ibogaine. Locally administered ibogaine (10 μM) was also found to enhance the effects of systemically administered D-amphetamine (1.25 mg/kg, i.p.) on extracellular dopamine levels, and conversely, systemically administered ibogaine (40 mg/kg, i.p.; 19 h pretreatment) enhanced the effects of locally administered D-amphetamine (1–10 μM). These results indicate that, in addition to a metabolic mechanism implicated previously, a pharmacodynamic mechanism contributes to the interaction between ibogaine and D-amphetamine. The relevance of such mechanisms to claims regarding ibogaine's anti-addictive properties is unclear.

INTRODUCTION

Two United States patents (H. Lotsof, 1985, No. 4,499,096; H. Lotsof, 1986, No. 4,587,243) have claimed that ibogaine, an alkaloid found in the root of the African shrub *Tabernanthe iboga*, is effective in treating both opioid (heroin) and stimulant (amphetamine and cocaine) addiction. A single oral treatment of ibogaine or its salts in dosages of 6–19 mg/kg has been claimed to be effective for about six months, interrupting the 'physiological and psychological aspects' of addiction and eliminating the desire to use drugs; a series of four treatments has been claimed to be effective for approximately 3 years. Recent animal studies, in this laboratory as well as in others, have provided some evidence that is consistent with these claims. In rats, ibogaine was found to decrease intravenous morphine self-administration[9], reduce morphine-induced increases in motor activity[13], and block morphine-induced dopamine release in limbic and striatal brain regions (11). In mice, ibogaine was found to antagonize cocaine- and D-amphetamine-induced locomotor stimulation[17,18]. However, data seemingly inconsistent with an anti-addictive property of ibogaine have also been obtained: in rats, ibogaine was found to enhance cocaine- and D-amphetamine-induced dopamine release in brain as well as to potentiate cocaine and D-amphetamine-induced motor activity[10,12,18]. Pretreatment with ibogaine has also been found to raise D-amphetamine levels in brain, possibly due to inhibition of D-amphetamine metabolism[8].

All of the ibogaine–drug interactions described above occurred over time periods that exceeded ibogaine's reported[4] sojourn in the body; despite an estimated half-life of approximately 1 h in rodents[4], the effects of ibogaine on the responses to morphine, cocaine and D-amphetamine were apparent for many hours or days after ibogaine administration. There are

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at least three possible explanations for this apparent discrepancy between drug level and drug effect: (i) ibogaine might produce neuronal damage – data from studies on tissue levels[13] of dopamine and its metabolites have not been consistent with this interpretation, however; (ii) ibogaine might persist, at low levels, for much longer periods of time than has been thought to be the case; and (iii) ibogaine may have an active metabolite with a very long half-life. One experiment that would be relevant to discriminating between these explanations, particularly (ii) and (iii), would be to administer ibogaine locally in brain and determine whether systemic effects can be mimicked. If long-term systemic effects can be mimicked by acute, locally administered ibogaine, this would imply either that explanation (ii) is likely and/or that a metabolite involved in explanation (iii) has an ibogaine-like pharmacology.

Ibogaine's interaction with morphine appears to involve a direct action of ibogaine (or an active metabolite) in the brain, although the precise site of this action in the brain is unknown. However, in rats, a pharmacokinetic mechanism appears to be at least partly responsible for ibogaine's interaction with D-amphetamine[8], and it is not clear if ibogaine also interacts pharmacodynamically with D-amphetamine in the brain. Here, again, an investigation of the effects of locally administered ibogaine would be useful as a means of determining if and where ibogaine itself acts in the brain.

Using the technique of in vivo microdialysis, the present study sought to determine if ibogaine, locally administered to the cell body and terminal regions of the nigrostriatal and mesolimbic systems, could mimic previously reported effects[11,12] of systemically administered ibogaine on dopamine release and metabolism in the striatum and nucleus accumbens. In addition, the locus of ibogaine's interaction with D-amphetamine was further explored in experiments in which either ibogaine was administered systemically and D-amphetamine was administered locally, or D-amphetamine was administered systemically and ibogaine was administered locally.

MATERIALS AND METHODS

Drugs

Ibogaine-HCl and D-amphetamine sulfate were obtained from Sigma Chemical Co.; when administered systemically (intraperitoneally), ibogaine was dissolved in water at a concentration of 20 mg/ml and D-amphetamine was dissolved in saline at a concentration of 1.25 mg/ml. Systemic doses (expressed as salts) of ibogaine (40 mg/kg) and D-amphetamine (1.25 mg/kg) were the same as those used in previous studies[8–13]. When administered via microdialysis perfusion, the concentrations of each drug (1–10 μM and 40–400 μM for ibogaine, and 1–10 μM for D-amphetamine) were chosen, using information from previous studies (e.g. 1), so as to mimic expected brain concentrations after systemic administration (see Discussion).

Subjects and surgery

Under pentobarbital anesthesia, female Sprague–Dawley (Taconic, Germantown, NY) rats 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)[15]. The two cannulas were fixed firmly in the skull with dental cement.

Microdialysis procedure

At least 3 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/CMed MF-5393) were then lowered into the guide cannulas. Prior to use, each probe was calibrated in vitro at room temperature in an artificial CSF solution gassed with argon and containing dopamine (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 dopamine and its metabolites. 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[19] of each brain was performed to verify the locations of the two probes.

Catecholamine assay

Perfusate samples were analyzed by HPLC with electrochemical detection. The HPLC system consisted of a Waters pumps (model 510), a WISP autosampler (model 712), an ESA CA80 column and a Waters electrochemical 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, and 50 ml/l methanol; it was adjusted with HCl to pH 3.6 and was pumped at a rate of 1.2 ml/min. Electrochemical detection was at +0.75 V vs. Ag/AgCl. Chromatograms were processed using the software Maxima 820.

Experimental protocol

Two series of experiments were conducted. In the first series, ibogaine was administered locally, via microdialysis perfusion for 40 min, to either the striatum or nucleus accumbens; effects on extracellular levels of dopamine, DOPAC and HVA were measured for 2 h afterwards (80 min after cessation of ibogaine perfusion). Two concentration ranges (low and high) of ibogaine were studied: 1–10 μM and 40–400 μM. In some experiments, ibogaine was administered locally to the substantia nigra or ventral tegmental area while dialysates were collected from the striatum or nucleus accumbens, respectively. Local drug administration was achieved with the use of a 'liquid switch' (CMA/110), which permitted the source of the perfusion fluid to be changed (the control procedure was to use the same 'liquid switch' to change to another source of normal perfusion fluid).

In the second series of experiments, the interaction between ibogaine and D-amphetamine was investigated. In some experiments, ibogaine was administered systemically (40 mg/kg, i.p.) and, 19–21 h later, D-amphetamine (1 and 10 μM) was administered locally (microdialysis perfusion for 40 min) in the striatum or nucleus accumbens; dialysates were collected for 2 h after the beginning of each D-amphetamine perfusion. In other experiments, ibogaine (10 μM) was administered locally (microdialysis perfusion for 40 min) in either the striatum or nucleus accumbens and, upon cessation of the ibogaine perfusion, D-amphetamine was administered systemically (1.25 mg/kg, i.p.); dialysates were collected for 3 h after D-amphetamine administration.

Statistical analysis

Statistical analyses were done on the data expressed as percents of the respective mean basal values in order to equate for between-subject differences. Repeated measure analyses of variance (ANOVA) were used to test for time, pretreatment and regional effects. Post-hoc analyses were carried out using Newman–Keuls multiple comparisons tests. *t*-Tests were performed to evaluate any differences between basal levels.

RESULTS

Effects of local ibogaine perfusion on dopamine and its metabolites

Fig. 1a and b shows the effects (% of baseline) of 1 and 10 μM ibogaine on extracellular concentrations of dopamine, DOPAC and HVA in the striatum and nucleus accumbens; in some experiments, 1 and 10 μM were administered sequentially and, in other experiments, 10 μM alone was administered. The one significant and clear finding was that ibogaine, at 10 μM, decreased DOPAC in both the nucleus accumbens and striatum (significant effects of time, ANOVA, $P < 0.05$–0.02 and significant changes from baseline beginning, in all cases, from 20 min after the start of 10 μM ibogaine perfusion, Newman–Keuls, $P < 0.05$–0.01; also, when compared to control data, shown in Fig. 2, all of the same effects were significant, $P < 0.05$).

Concentrations of 40 μM and 80 μM ibogaine had no significant effects on dopamine, DOPAC or HVA in either the striatum or nucleus accumbens (data not shown). However, as shown in Fig. 2a and b, 200 μM and 400 μM ibogaine decreased extracellular levels of dopamine and increased extracellular levels of DOPAC and HVA in both the nucleus accumbens and striatum (significant drug × time interactions, $P < 0.05$–0.001, ANOVA, and significant changes from baseline and from control, Newman–Keuls, $P < 0.05$–0.001).

Local administration of ibogaine (1–10 μM and 200–400 μM) to the substantia nigra or ventral tegmental area had no effect on extracellular levels of dopamine, DOPAC and HVA in the ipsilateral striatum or nucleus accumbens, respectively (data not shown).

Interaction of systemically administered ibogaine with locally administered D-amphetamine

In both regions ibogaine pretreatment (40 mg/kg, i.p.) resulted in significant decreases in basal DOPAC levels ($P < 0.05$) but no significant changes in basal dopamine or HVA levels, although all values tended to be lower. Estimated extracellular basal levels (mean ± S.E.M.), in saline- vs. ibogaine-pretreated groups, were as follows: in nucleus accumbens, dopamine 9.72 ± 1.38 vs. 7.62 ± 1.02 nM, DOPAC 4.31 ± 0.33 vs. 2.74 ± 0.38 μM, HVA 2.11 ± 0.29 vs. 1.58 ± 0.25 μM; and in striatum, dopamine 13.88 ± 2.02 vs. 12.24 ± 1.84 nM, DOPAC 4.98 ± 0.51 vs. 3.28 ± 0.41 μM, HVA 3.21 ± 0.43 vs. 2.39 ± 0.38 μM. These levels, corrected for probe recovery, were based on four baseline samples taken 17–18 h after ibogaine or saline injections and probe insertion.

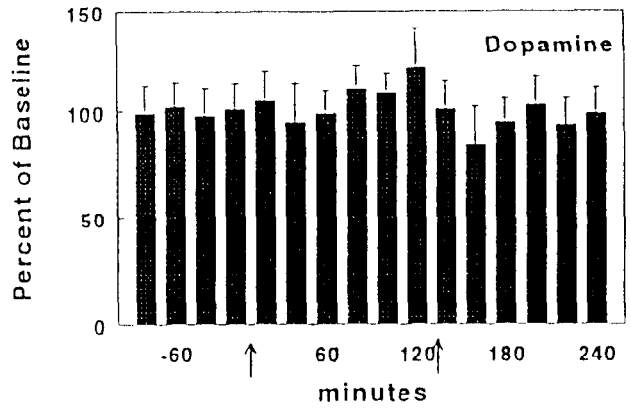
Fig. 3 shows that locally administered D-amphetamine (1 and 10 μM) increased extracellular levels of dopamine (significant effects of time, $P < 0.001$, ANOVA); ibogaine pretreatment (19 h earlier) enhanced this effect, and to a greater extent in the nucleus accumbens than in the striatum (significant pretreatment × region × time interaction, $P < 0.05$, and significant pretreatment × time interactions, $P < 0.01$ and 0.05, in the nucleus accumbens and striatum, respectively). In the nucleus accumbens, effects of ibogaine pretreatment (compared to saline) were significant ($P < 0.05$–0.01) at all time points except 100 and 120 min; in the striatum, effects of ibogaine pretreatment were only significant at the 40, 160 and 180 min time points, $P < 0.05$). Ibogaine pretreatment had no significant effects on D-amphetamine-induced decreases in DOPAC and HVA levels (data not shown).

Interaction of locally administered ibogaine with systemically administered D-amphetamine

Fig. 4 shows that, as would be expected (e.g. ref. 12), systemically administered D-amphetamine (1.25 mg/kg, i.p.) increased extracellular levels of dopamine; pretreatment with locally administered ibogaine (10 μM) enhanced this effect, and again, to a greater extent in the nucleus accumbens than in the striatum (significant pretreatment × region × time interaction, $P < 0.05$, and significant pretreatment × time interactions, $P < 0.01$ and 0.05, in the nucleus accumbens and striatum, respectively). In the nucleus accumbens, effects of ibogaine pretreatment (compared to control) were significant ($P < 0.05$–0.02) at all time points from 100 to 200 min; in the striatum, effects of ibogaine pretreatment were only significant at the 120 and 180 min time points, $P < 0.05$). Ibogaine pretreatment had no significant effects on D-amphetamine-induced decreases in DOPAC and HVA levels (data not shown).

DISCUSSION

In a previous study, we found that systemically administered ibogaine (40 mg/kg, i.p.) decreased extracellular levels of dopamine and increased extracellular


Dopamine
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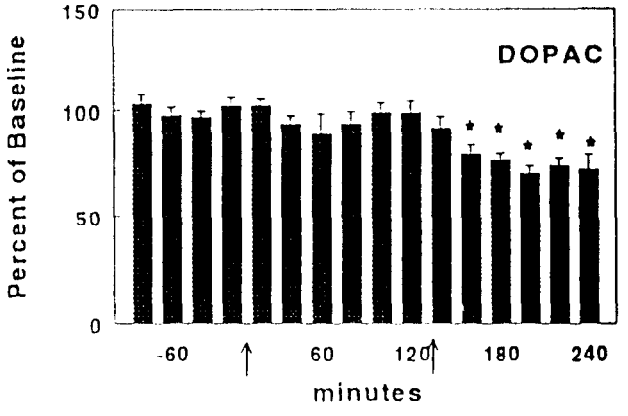
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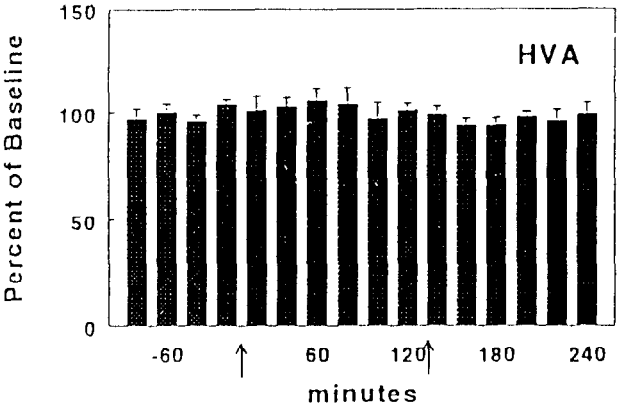
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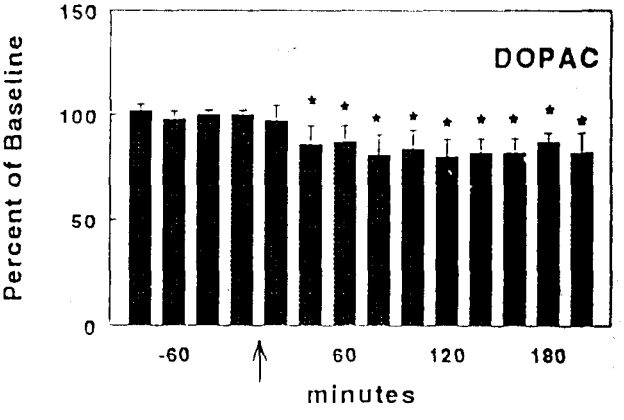
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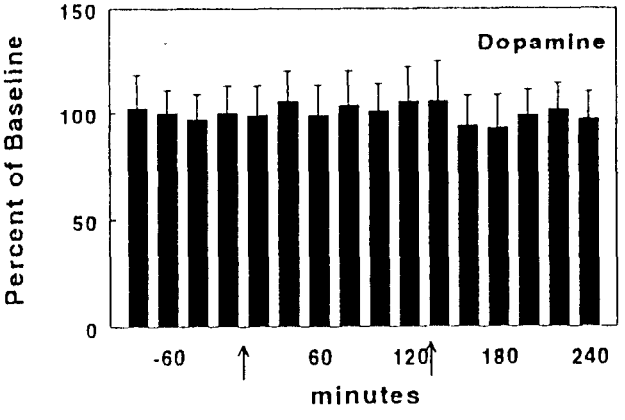
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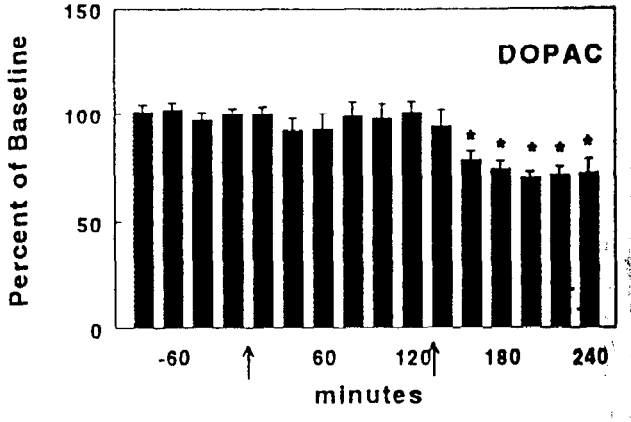
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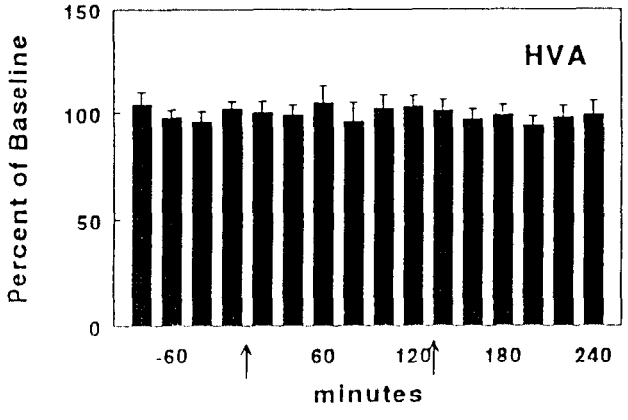
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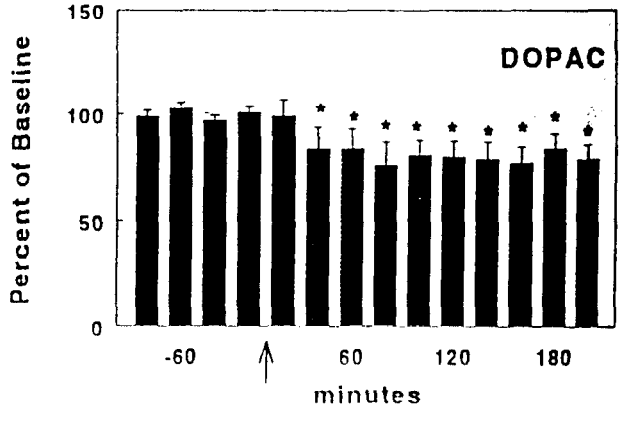
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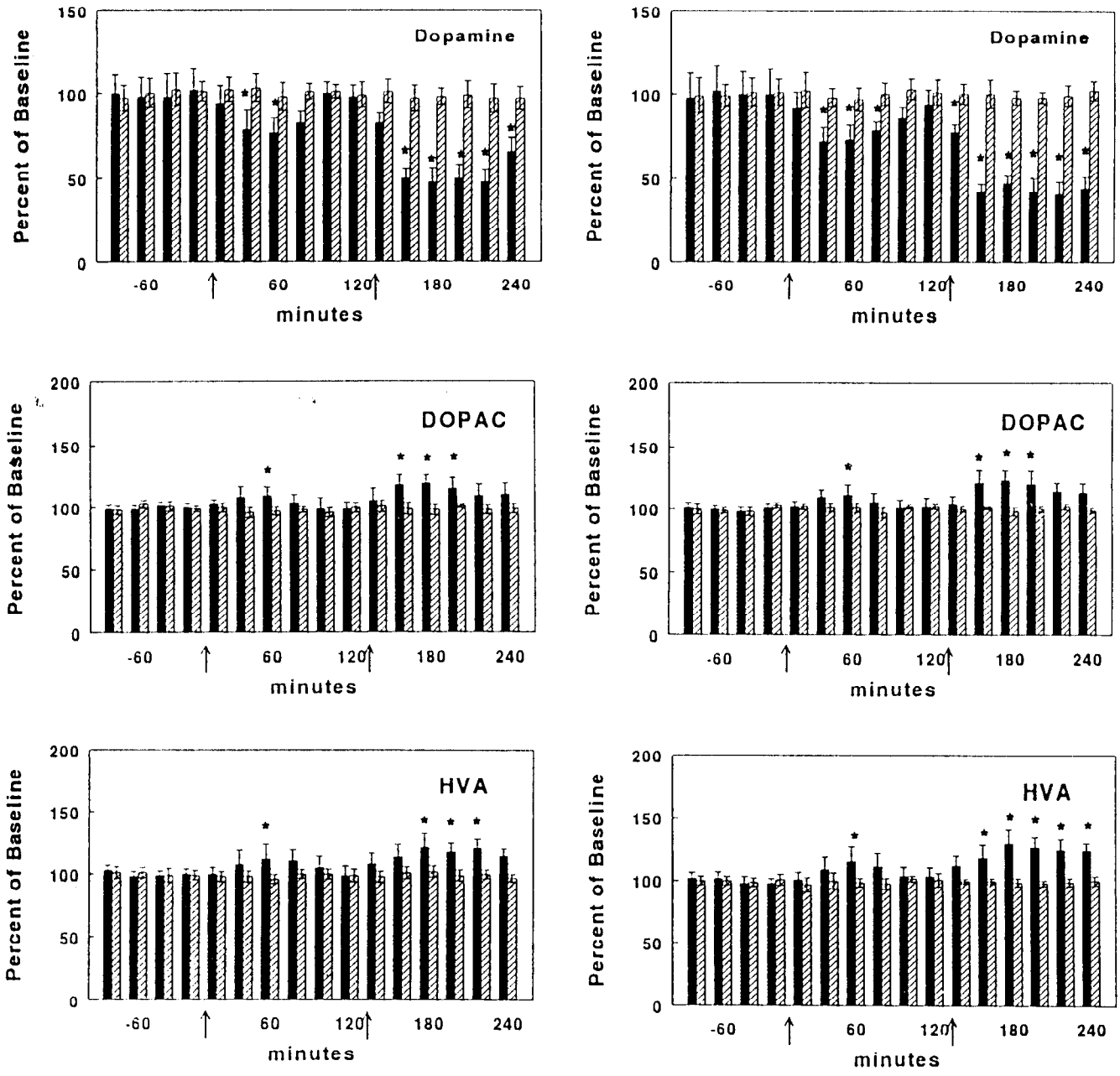

Fig. 2. Effects of locally administered 200 μM (first arrow) and 400 μM (second arrow) ibogaine (dark bars) or a control procedure (change of perfusion source; hatched bars) on extracellular levels of dopamine, DOPAC and HVA in the nucleus accumbens (a, left panel) and striatum (b, right panel). Samples were collected at 20-min intervals (ibogaine, $n = 7$; control, $n = 6$). Data are expressed as a percent of baseline values (means ± S.E.M.); asterisks indicate significant differences ($P < 0.05$–0.001, Newman–Keuls) from baseline and from control data.

levels of DOPAC and HVA in the striatum and, to a lesser extent, in the nucleus accumbens[11]. These effects occurred acutely, during the first 3 h after ibogaine administration. Persistent effects of ibogaine were also observed; when measured 19 h after ibogaine administration, extracellular metabolite levels, particularly DOPAC, were decreased[11,12]. Levels of DOPAC in homogenates of striatum and nucleus accumbens were also decreased when measured 19 h after ibogaine administration[13]. In the present study, local administra-

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Fig. 1. Effects of locally administered 1 μM (first of two arrows) and 10 μM (second arrow and lower right arrow) ibogaine on extracellular levels of dopamine, DOPAC and HVA in the nucleus accumbens (a, top 2 panels) and striatum (b, bottom 2 panels). Samples were collected at 20-min intervals ($n = 8$ for 1 and 10 μM; $n = 6$ for 10 μM alone). Data are expressed as a percent of baseline values (means ± S.E.M.); asterisks indicate significant differences ($P < 0.05$–0.01, Newman–Keuls) from baseline and from control data (see Fig. 2).

tion of ibogaine to the striatum and nucleus accumbens produced effects that mimicked both the acute and persistent effects of systemic ibogaine administration; that is, perfusion with high concentrations (200 and 400 μM) of ibogaine mimicked the acute effects (decreased extracellular dopamine levels and increased extracellular metabolite levels) whereas perfusion with a low concentration (10 μM) of ibogaine mimicked the persistent effects (decreased extracellular levels of DOPAC). Inasmuch as local administration of ibogaine to cell body regions (substantia nigra and ventral tegmental area) had no effect on dopamine or metabolite levels in the striatum and nucleus accumbens, it would appear that systemic ibogaine acts only on nerve terminal regions to alter dopamine metabolism.

It is estimated that the systemic dose of ibogaine (40 mg/kg, i.p.) used in this and previous studies should have produced peak brain concentrations of ibogaine of approximately 100 μM (ref. 4), and local perfusion with 200–400 μM ibogaine should have produced similar concentrations (i.e. assuming a recovery of 20–40%).

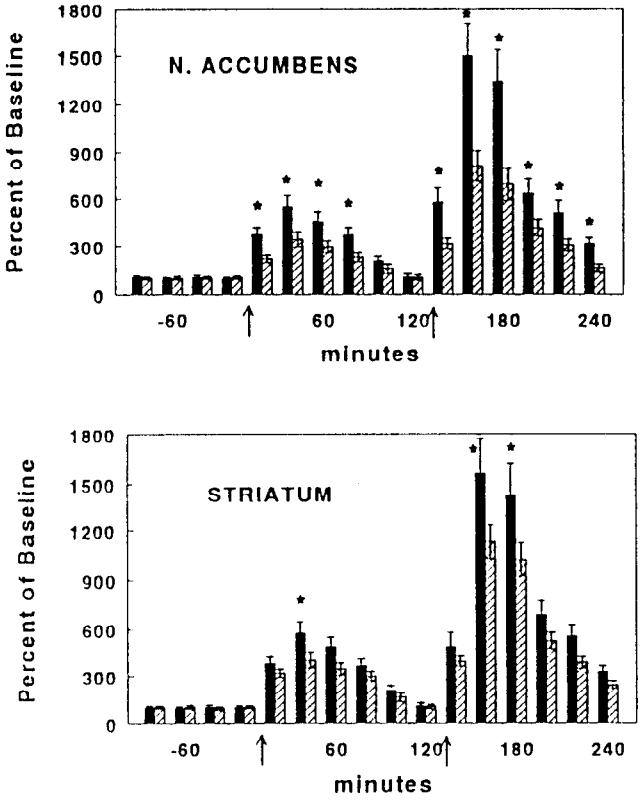

Fig. 3. Time-course of extracellular dopamine in the nucleus accumbens and in the striatum before and after local administration of D-amphetamine (1 μM, first arrow; 10 μM, second arrow) in rats pretreated with ibogaine (40 mg/kg i.p., $n = 6$; dark bars) or saline ($n = 6$; hatched bars) the day before. Samples were collected at 20-min intervals. Data are expressed as a percent of baseline values (means ± S.E.M.); asterisks indicate significant differences ($P < 0.05$–0.01, Newman–Keuls) between ibogaine and saline pretreatment.

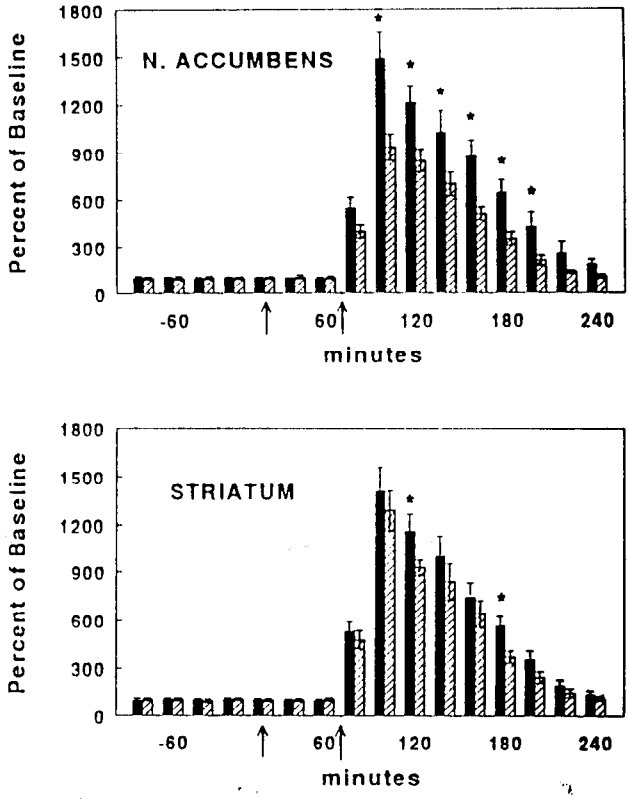

Fig. 4. Time course of extracellular dopamine in the nucleus accumbens and in the striatum before and after administration of D-amphetamine (1.25 mg/kg i.p., second arrow) in rats pretreated (first arrow) with locally administered ibogaine (10 μM, $n = 7$; dark bars) or a control procedure (change of perfusion source, $n = 6$; hatched bars). Samples were collected at 20-min intervals. Data are expressed as a percent of baseline values (means ± S.E.M.); asterisks indicate significant differences ($P < 0.05$–0.02, Newman–Keuls) between ibogaine administration and the control procedure.

In view of ibogaine's reportedly[4] short half-life (1 h), it was previously suggested[9,11] that long-lasting effects of ibogaine might be due to an active metabolite; however, the present data suggest that long-lasting effects of ibogaine might also be attributable to persisting low levels of ibogaine. Perfusion with 10 μM ibogaine should have resulted in local brain concentrations no higher than 2–4 μM, and such levels are probably well below those that could have been detected in former studies[3,20].

We previously reported that systemic ibogaine pretreatment (40 mg/kg, i.p.; 19 h earlier) enhanced the effects of systemically administered D-amphetamine (1.25 mg/kg, i.p.) on locomotor activity and on dopamine release in the nucleus accumbens and striatum[12]. Subsequently we observed that the same ibogaine pretreatment increased brain amphetamine levels at 30 min and 2 h after D-amphetamine injection, suggesting that the functional interactions between ibogaine and D-amphetamine were due to a metabolic interaction, e.g. an ibogaine-induced decrease in hep-

atic metabolism of D-amphetamine[8]. Indeed, at 2 h after D-amphetamine injection, ibogaine pretreatment increased brain amphetamine levels approximately fourfold (see Fig. 2 in ref. 8) and functionally, 2–3 h after D-amphetamine administration, sensitivity to both the neurochemical and behavioral effects of D-amphetamine was also increased approximately fourfold (see Figs. 1, 2 and 4 in ref. 12). However, the present data indicate that even when a peripheral metabolic interaction is precluded, functional interactions between ibogaine and D-amphetamine can still occur. Thus systemic ibogaine enhanced the effects of locally administered D-amphetamine, and locally administered ibogaine enhanced the effects of systemic D-amphetamine. The magnitudes of these interactions were certainly less than those occurring when both drugs were administered systemically[12], suggesting that both metabolic and pharmacodynamic mechanisms contribute to the latter.

The potentiation by ibogaine of D-amphetamine-induced release of dopamine was approximately the same in the nucleus accumbens and striatum when, in a previous study, both drugs were administered systemically[12], whereas in the present study, when one or the other drug was administered locally, the potentiation was greater in the nucleus accumbens than in the striatum. This suggests that the pharmacodynamic interaction between ibogaine and D-amphetamine occurs preferentially in the nucleus accumbens, and that this selectivity can be obscured by a metabolic interaction. Interestingly, ibogaine pretreatment (40 mg/kg, i.p.; 19 h earlier), which has little effect on brain cocaine levels[7], was also found to potentiate cocaine-induced (20 mg/kg, i.p.) increases in extracellular dopamine levels, and to a greater extent in the nucleus accumbens than in the striatum[10].

It is unclear how these neurochemical interactions between ibogaine and stimulants could account for putative anti-addictive effects of ibogaine regarding D-amphetamine or cocaine abuse. By potentiating the dopaminergic responses to stimulants, ibogaine might be expected to increase the reinforcing efficacies of these drugs and enhance their addictive liabilities. However, as noted previously[12], high doses of stimulants can be aversive, subsequently causing the rejection of low doses (e.g. ref. 3); and the potentiation of stimulant effects by ibogaine might also be expected to induce or enhance such aversions, thenceforth decreasing addictive behavior. Indeed, Cappendijk and Dzoljic[2] recently reported that ibogaine (40 mg/kg, i.p.) decreased cocaine self-administration in rats, the results appearing very similar to previous findings with morphine[9]. Curiously, other treatments that have been proposed to decrease addiction to stimulants also potentiate their neurochemical actions. For example, chronic administration of desipramine, a tricyclic antidepressant that is claimed to decrease cocaine use and craving[5,6], has been reported to potentiate increases in extracellular dopamine levels in the nucleus accumbens induced by systemic D-amphetamine[14] and cocaine[10] as well as by locally administered D-amphetamine[1]; and, similar to the ibogaine effects, these desipramine effects appear to be specific to the nucleus accumbens in that no potentiation was observed in the striatum[14]. Further studies should determine if and/or how such a neurochemical change in the nucleus accumbens could be responsible for a decrease in addiction to stimulant drugs.

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