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Interactions between ibogaine, a potential anti-addictive agent, and morphine: an in vivo microdialysis study

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Ibogaine, an indolalkylamine, has been claimed to be effective in abolishing drug craving in heroin and cocaine addicts. The present study used in vivo microdialysis to determine the effects of ibogaine on extracellular levels of dopamine (DA) and its metabolites and the effects of ibogaine pretreatment on morphine stimulation of brain DA systems. Acutely, ibogaine (40 mg/kg i.p.) decreased extracellular DA levels in the striatum, increased them in the prefrontal cortex and had no significant effects in the nucleus accumbens. Nineteen hours after ibogaine injection, DA levels were still decreased in the striatum and the metabolite levels were lower in all three regions. When injected 19 h prior to a morphine challenge (5 mg/kg i.p.), ibogaine (40 mg/kg, i.p.) prevented the rise in DA levels in all three regions normally observed after a morphine injection. A high dose of morphine (30 mg/kg i.p.), administered alone, produced no increase in extracellular DA levels; it is therefore unclear whether ibogaine antagonized or potentiated the effects of the lower dose of morphine. Regardless of the nature of this interaction, it appears that ibogaine affects brain DA systems for a period of time that exceeds its elimination from the body and, during this time, alters the responses of these systems to morphine.

Ibogaine; Morphine; Dopamine; Microdialysis; Striatum; Nucleus accumbens; Prefrontal cortex

1. Introduction

Ibogaine is the main alkaloid found in the root of *Iboga tabernanthe* (Apocynaceae family), a shrub that grows in West Central Africa. In that part of the world, ibogaine is used at low doses to combat fatigue, hunger and thirst and at high doses for its hallucinogenic properties. In the western world, ibogaine has never been extensively used as a psychostimulant or hallucinogen. Only a few studies have been done concerning the biochemical and physiological properties of ibogaine. Yet, in 1985 and 1986, two US patents (Lotsof, 1985; 1986, patent number: 4,499,096 and 4,587,243) described the potential efficacy of ibogaine in treating opiate and stimulant addiction. The purpose of the work presented herein was to explore the neurochemical basis of the possible anti-addictive property of ibogaine.

Studies of intracranial electrical self-stimulation and intracranial drug self-administration have revealed the major role of dopaminergic systems in the reward process (Wise and Bozarth, 1982), specifically the dopaminergic mesocortical and mesolimbic systems. In these two systems, cell bodies are located in the ventral tegmental area and the neurons project either to the prefrontal cortex or to the nucleus accumbens. Using microdialysis, Di Chiara and Imperato (1988) reported that acute administration of amphetamine, cocaine, morphine, nicotine and ethanol, all known to be addictive drugs, increased the extracellular dopamine (DA) levels in the nucleus accumbens and to a lesser extent in the striatum. Also, it has been shown that amphetamine and cocaine can raise extracellular DA levels in prefrontal cortex (Moghaddam and Bunney, 1989; Maisonneuve et al., 1990). The mechanisms by which these drugs increase DA levels differ for each drug. Amphetamine mainly increases DA release (Parker and Cubeddu, 1986). Cocaine blocks DA reuptake (Heikkila et a., 1975). Morphine, nicotine and ethanol increase dopaminergic neuronal firing (Matthews and German, 1984; Clarke et al., 1985; Mereu et al., 1984). The common denominator in the mechanism of drug addiction (drug-seeking behavior) appears to be an increase in dopamine neurotransmission in the mesolimbic and/or mesocortical pathways.

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Our initial hypothesis was that if ibogaine is really an anti-addictive drug, it should be able to alter DA neurotransmission in the nucleus accumbens and/or prefrontal cortex, in such a way that addictive drugs could no longer activate the reward pathway. Using microdialysis, we first studied the time course of extracellular DA after i.p. injection of ibogaine or morphine (the latter being a prototypical drug of abuse); then we investigated the effects of a combination of the two drugs on the same systems. These experiments were performed in the three major DA regions of the brain. We selected the nucleus accumbens and the prefrontal cortex for the reasons cited above. We included the striatum because it contains 80% of the brain's DA terminals. The dose of ibogaine used was 40 mg/kg; this was the minimal dose found to maximally decrease morphine intake in a self-administration paradigm (Glick et al., 1991).

2. Materials and methods

2.1. Animal preparation

Under pentobarbital anesthesia, female Sprague-Dawley rats were implanted stereotaxically with guide cannulas in two of the following regions: nucleus accumbens, striatum and medial prefrontal cortex. The coordinates for the guide cannula placement in the nucleus accumbens were: rostral + 1.6 mm from bregma, lateral ±1.5 mm, ventral −4.6 mm from the skull surface. For the striatum they were: rostral +0.5 mm, lateral ±2.9 mm and ventral −3.0 mm. To reach the medial prefrontal cortex area, the guide cannula was placed at a lateral angle of 14° from vertical (tip of the guides more medial than the top) with the following coordinates: rostral +2.7 mm, lateral ±1.9 mm and ventral −2.2 mm (Paxinos and Watson, 1986). The two cannulas were fixed firmly to the skull with four screws and dental cement.

2.2. Dialysis procedures

At least four days after surgery, the dialysis experiment was carried out on a freely moving animal. The rat was placed in a cylindrical plastic cage where it had free access to food and water. Probes were reused one to five times and were calibrated in vitro at room temperature prior to each experiment. All values were corrected for recovery. After being calibrated at room temperature in an artificial CSF solution gazed with argon, the probes (3 mm probes; BAS/CMed MF-5140) were lowered into the guide cannulas. In order to prevent damage to the dialysis membrane, rats were lightly anesthetized with methohexital when probes were inserted. The tips of the probes were 4 mm lower than the tips of the guides. The probe inlets were connected to a Harvard pump through a liquid swivel. The collection tubes 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 (mM) 146 NaCl, 2.7 KCl, 1.2 $CaCl_2$, and 1.0 $MgCl_2$ at a flow rate of 1 μl/min. Collection of brain perfusate began about 3 h 40 after the probes were inserted. 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). Four baseline samples were taken before i.p. injection of a drug. The drug effects were then monitored for 3 h. Upon completion of an experiment, rats were killed and histological analysis (Shapiro et al., 1983) of each brain was performed to verify the location of the two probes. When ibogaine-morphine interactions were studied, ibogaine was injected 19 h before the morphine injection, that is, 14 h prior the insertion of the probes.

2.3. Motor behavior monitoring

While in the dialysis chamber, the rats were attached to a computerized rotometer system that allowed counting of quarter (90°) turns (Glick and Cox, 1978).

2.4. Drugs

Ibogaine HCl was obtained from Sigma Chemical Co. and was dissolved in water. Morphine sulfate, obtained from Mallinckrodt Co., was dissolved in saline. Both drugs were injected i.p. The doses used, expressed as the salt, were: ibogaine 40 mg/kg, and morphine 5 or 30 mg/kg.

2.5. Catecholamine assay

Perfusate samples were analyzed by HPLC on an ESA Coulochem System containing three electrodes placed in series, a conditioning cell (−0.1 V) followed by two detecting electrodes. At the first detecting electrode (+0.3 V) the analytes were oxidized and at the second electrode (−0.3 V) they were subsequently reduced. DA metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), were determined on the oxidation channel, while DA levels were determined on the reduction channel to insure maximum selectivity for DA. 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. The chromatographic separation was carried out on an ESA CA-80 column.

2.6. Statistical analysis

Statistical analyses were done on postinjection data expressed as percent of the correspondent basal values in order to equate for between subject differences. A repeated measure analysis of variance (ANOVA) was used to test for drug effect and any significant interaction was decomposed using simple F-tests. T-tests were performed to evaluate any differences between basal levels.

3. Results

3.1. Time course of DA and its metabolites after ibogaine challenge

In the nucleus accumbens (fig. 1), the injection of ibogaine had no significant effects upon the extracellular DA and HVA levels. For DOPAC, the decomposition of a significant drug × time interaction showed that ibogaine increased DOPAC during the first 40 min.

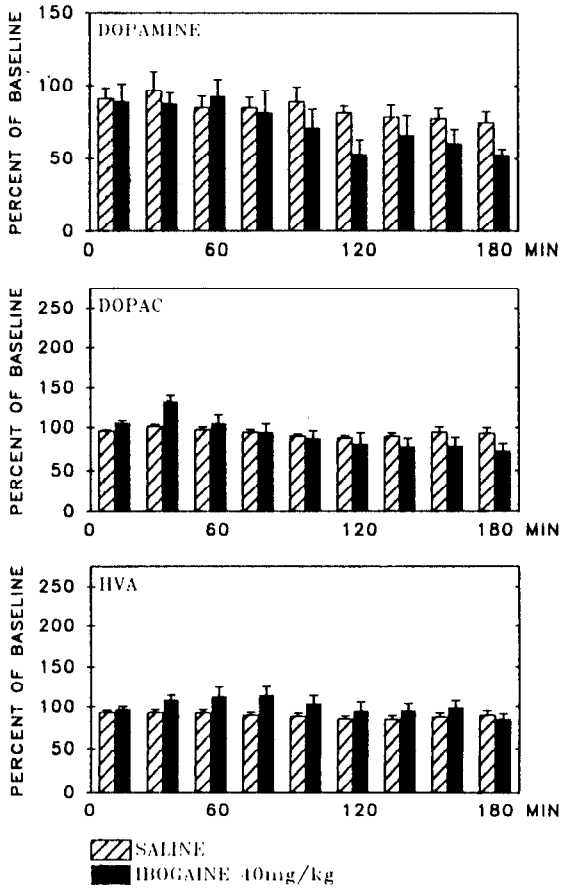

Fig. 1. Time course of extracellular DA, DOPAC and HVA levels in the nucleus accumbens after administration of saline (n = 6) and ibogaine (40 mg/kg, n = 6). Samples were collected at 20 min intervals. Data are expressed as a percent (±S.E.) of baseline values.

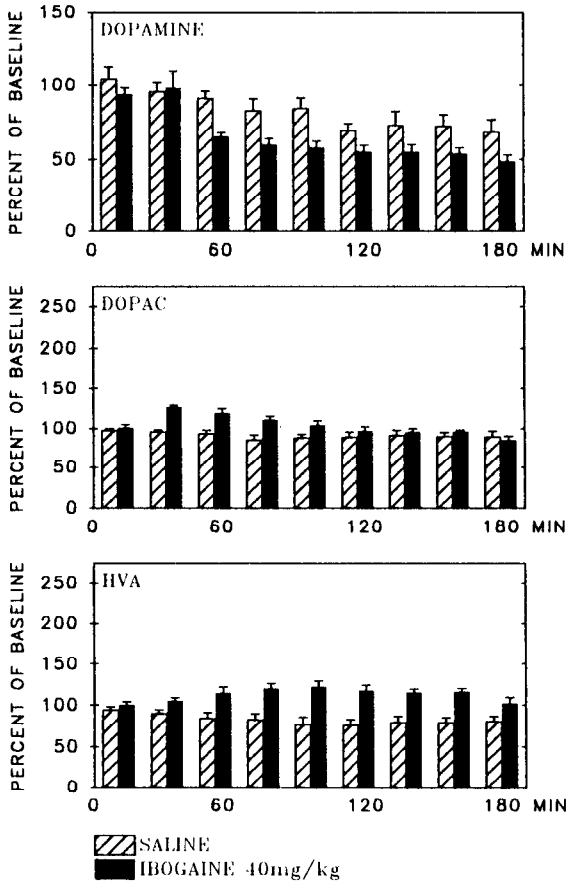

Fig. 2. Time course of extracellular DA, DOPAC and HVA levels in the striatum after administration of saline (n = 6) and ibogaine (40 mg/kg, n = 6). Samples were collected at 20 min intervals. Data are expressed as a percent (±S.E.) of baseline values.

In the striatum (fig. 2), a significant drug effect ($P < 0.01$) due to a sustained decrease in DA levels was observed beginning 40 min after the ibogaine injection. For the two metabolites, a significant drug × time interaction occurred; ibogaine increased DOPAC levels from 40 to 100 min and HVA levels from 60 to 180 min (i.e. until the end of the experiment).

In the prefrontal cortex (fig. 3), a significant drug × time interaction for DA, DOPAC, and HVA was observed. Ibogaine increased extracellular DA levels from the second to the eighth sampling periods with significant changes occurring during the second, fourth and sixth sampling periods. Simple F-tests confirmed an immediate and lasting increase in DOPAC levels and a similarly persistent increase in HVA levels that began 40 min after ibogaine administration.

3.2. Time course of DA and its metabolites after morphine challenge in naive rats

A dose of 5 mg/kg of morphine produced a significant increase in extracellular DA, DOPAC and HVA levels in all three regions. In the nucleus accumbens

(fig. 4) a significant main effect of drug ($P < 0.01$) was found for DA, in accordance with the immediate and sustained increase in extracellular DA levels. The decomposition of a drug × time interaction for the two metabolites revealed that both were increased 20 min after the morphine injection. Although DOPAC levels returned to basal levels during the last sampling period, the increase in HVA levels was still present at the end of the experiment (180 min). In the striatum (fig. 5), a drug × time interaction was present for DA and its metabolites. DA, DOPAC and HVA were all increased 40 min after the drug injection; DA and DOPAC were back to normal in the last 40 min of the experiment, whereas the increase in HVA was maintained until the end of the experiment. In the prefrontal cortex (fig. 6), a significant main effect of drug ($P < 0.02$) was found for DA, in accordance with the persistent increase in extracellular DA levels. The decomposition of a drug × time interaction for the two metabolites revealed that both followed the same time course, i.e. an increase beginning 1 h after injection and still present at the end of the experiment.

In contrast to the effects of a low dose of morphine,

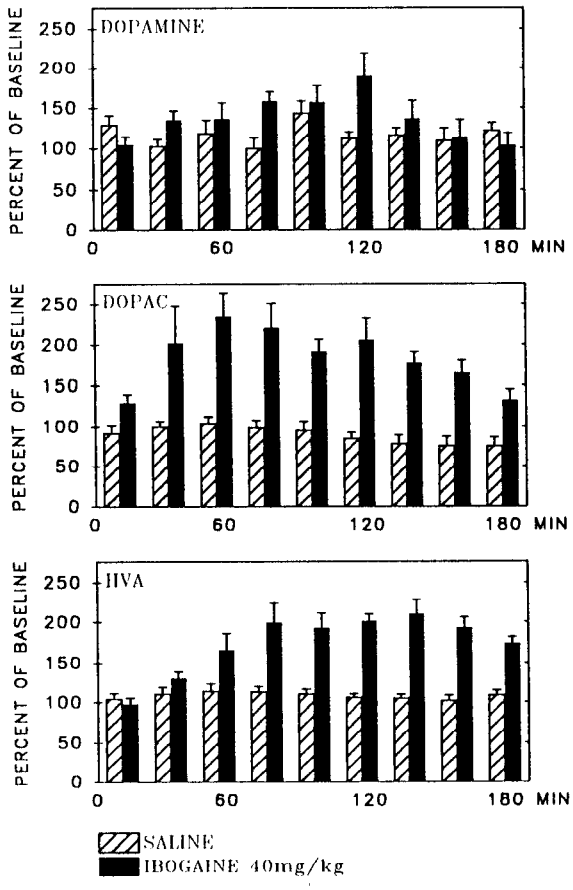

Fig. 3. Time course of extracellular DA, DOPAC and HVA levels in the prefrontal cortex after administration of saline (n = 6) and ibogaine (40 mg/kg, n = 6). Samples were collected at 20 min intervals. Data are expressed as a percent (± S.E.) of baseline values.

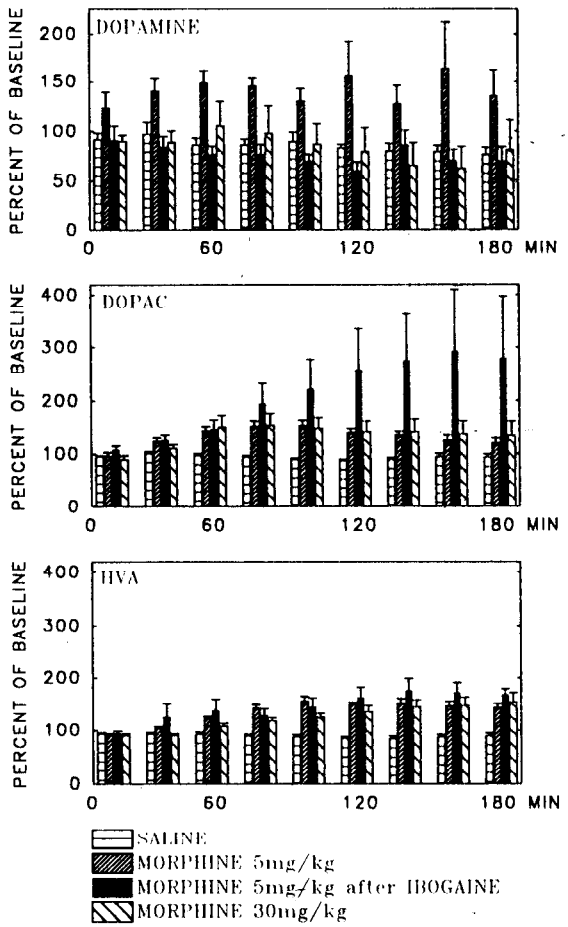

Fig. 4. Time course of extracellular DA, DOPAC and HVA levels in the nucleus accumbens after administration of morphine (5 mg/kg, n = 6, and 30 mg/kg, n = 6) in naive rats and morphine (5 mg/kg, n = 6) in rats pretreated with ibogaine (40 mg/kg) the day before. Samples were collected at 20 min intervals. Data are expressed as a percent (± S.E.) of baseline values.

a dose of 30 mg/kg had no effects on DA levels, but still markedly increased the metabolites in all three regions studied. In the nucleus accumbens (fig. 4), DOPAC increased during the third sampling period and returned to normal in the last two sampling periods. HVA followed the same time course, but shifted later in time. In the striatum (fig. 5), the increase in metabolites occurred later, during the fourth sampling period, and was still present at the end of the experiment. In the prefrontal cortex (fig. 6), the increase in metabolites occurred at different times, 20 min for DOPAC and 80 min for HVA, and persisted for the rest of the experiment.

3.3. Effects of ibogaine pretreatment on basal and morphine-induced changes in levels of DA and its metabolites

Basal levels of DA and its metabolites in rats pretreated with ibogaine 19 h earlier are displayed in

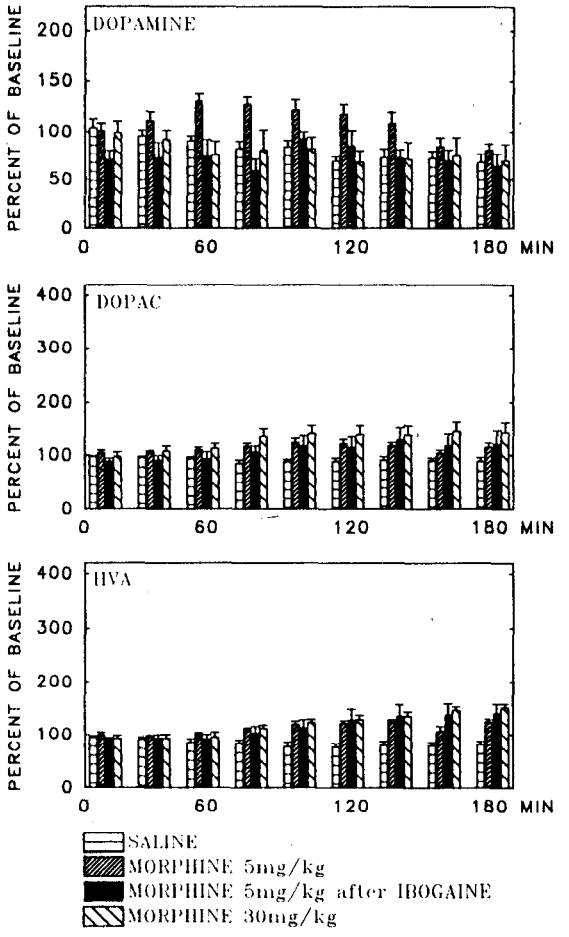

Fig. 5. Time course of extracellular DA, DOPAC and HVA levels in the striatum after administration of morphine (5 mg/kg, n = 6, and 30 mg/kg, n = 6) in naive rats and morphine (5 mg/kg, n = 6) in rats pretreated with ibogaine (40 mg/kg) the day before. Samples were collected at 20 min intervals. Data are expressed as a percent (± S.E.) of baseline values.

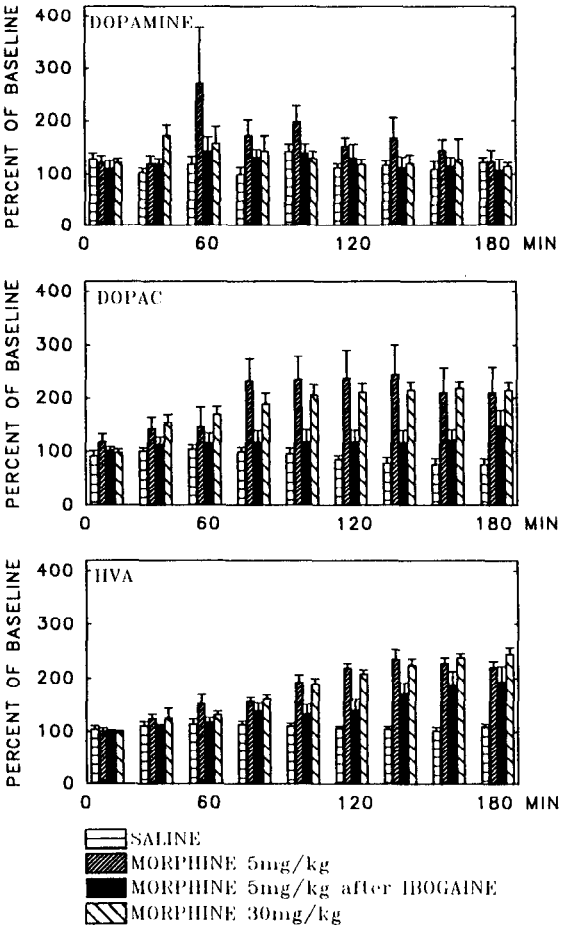

Fig. 6. Time course of extracellular DA, DOPAC and HVA levels in the prefrontal cortex before and after administration of morphine (5 mg/kg, n = 6, and 30 mg/kg, n = 6) in naive rats and morphine (5 mg/kg, n = 7) in rats pretreated with ibogaine (40 mg/kg) the day before. Samples were collected at 20 min intervals. Data are expressed as a percent (± S.E.) of baseline values.

table 1. Compared to the basal values obtained in naive rats, the pretreated rats exhibited significant decreases in extracellular DA levels in striatum ($P < 0.05$) and in metabolite levels in all three regions ($P < 0.05$).

TABLE 1

Estimated extracellular basal values (means ± S.E.) of DA, DOPAC and HVA in prefrontal cortex, nucleus accumbens and striatum in naive and ibogaine-pretreated (40 mg/kg, 19 h beforehand) rats. PFC, prefrontal cortex; NAC, nucleus accumbens; STR, striatum

	DA (nM)	DOPAC (μM)	HVA (μM)
In naive rats			
PFC	2.55 ± 0.2	0.19 ± 0.02	0.38 ± 0.03
NAC	14.27 ± 1.1	4.91 ± 0.60	2.10 ± 0.22
STR	24.00 ± 1.6	6.96 ± 0.44	4.40 ± 0.31
In ibogaine-pretreated rats			
PFC	2.49 ± 0.4	0.04 ± 0.01 [a]	0.12 ± 0.03 [a]
NAC	14.10 ± 2.1	1.94 ± 0.77 [a]	0.81 ± 0.15 [a]
STR	14.38 ± 2.9 [a]	2.73 ± 1.09 [a]	2.04 ± 0.58 [a]

[a] Significantly different from correspondent levels found in naive rats ($P < 0.05$).

After ibogaine pretreatment, a dose of 5 mg/kg of morphine was no longer able to increase the extracellular DA level in any of the three regions (figs. 4, 5 and 6); DA values stayed very close to their basal levels. In contrast, ibogaine pretreatment did not influence the morphine-induced metabolite changes in nucleus accumbens and striatum. In prefrontal cortex, however, ibogaine pretreatment prevented any increase in DOPAC levels normally induced by morphine, and the increase observed in HVA levels was significantly delayed and smaller. There was no significant difference between DA levels following a 5 mg/kg morphine injection in ibogaine pretreated rats and DA levels after 30 mg/kg morphine in naive rats.

3.4. Motor behavior after morphine administration in naive and ibogaine-pretreated rats (table 2)

Naive rats and ibogaine-pretreated rats did not differ in their basal motor activity. A dose of 5 mg/kg of

TABLE 2

Motor activity (total quarter turns) of naive and ibogaine-pretreated rats after administration of saline and morphine (5 and 30 mg/kg).

	Mean total quarter turns ± S.E. after drug injection		
	0-60 min	60-120 min	120-180 min
In naive rats			
Saline	74.1 ± 30.9	18.3 ± 10.8	62.1 ± 50.4
Morphine 5 mg/kg	18.4 ± 3.8	123.7 ± 45.8	155.1 ± 82.5
Morphine 30 mg/kg	10.2 ± 2.5	0.0	0.3 ± 0.24
In ibogaine-pretreated rats			
Morphine 5 mg/kg	9.4 ± 1.0 [a]	0.4 ± 0.27 [a]	12.2 ± 8.3 [a]

[a] Significantly different from corresponding values in naive rats ($P < 0.05$).

morphine, in naive rats, induced a short motor inhibitory period (about 40 min), followed by an intense excitatory period. The same challenge, in ibogaine-pretreated rats, led to a long inhibition of motor activity (about 2 h) and the absence of any excitatory phase. In naive rats, an injection of 30 mg/kg morphine induced a lengthy immobile phase (at least 3 h). In control animals the motor activity was low and did not follow any pattern. The ANOVA analysis confirmed the obvious differences between the latter three treatments and morphine 5 mg/kg in naive rats.

4. Discussion

In the striatum ibogaine decreased DA levels in the extracellular fluid for at least 19 h; its effects on DA metabolites were biphasic, an initial increase followed by a decrease observed 17-19 h later. In the nucleus accumbens, ibogaine had no significant effect on DA levels, it increased DOPAC transiently and decreased DOPAC and HVA a day later. In the prefrontal cortex, ibogaine initially raised extracellular levels of DA and its metabolites, but the latter were markedly decreased a day later. Hence, ibogaine seems to have a very complex action on dopaminergic transmission. The regional differences observed may be the result of different actions of ibogaine expressed to varying degrees in the three regions. For example, ibogaine may be a benzodiazepine inverse agonist (Trouvin et al., 1987) and preferentially activate the mesocortical DA system (Thierry et al., 1976; Abercrombie et al., 1989).

Ibogaine has residual effects on DA and its metabolites 19 h after its administration, in spite of a half-life estimated at 1 h in rodents (Dhahir, 1971). This indicates that either ibogaine is metabolized to an active metabolite with a long half life or induces a long-lasting change (e.g. neurotoxic effects). So far there is no evidence that would exclude the formation of an active metabolite with a long half-life. In our studies the decline in basal values observed 19 h after ibogaine administration could be explained by partial damage to DA neurons accompanied by an increase in firing rate of the remaining neurons. The decrease in the ratio DOPAC/HVA seen in the prefrontal cortex and in the striatum 19 h after an ibogaine pretreatment is consistent with such an effect. However, in 1971, Dhahir performed histological studies on brain tissue of rats pretreated for 30 days with 10 or 30 mg/kg ibogaine and did not report any sign of neuronal damage. We do not know of any published studies in which tissue levels of DA were measured after ibogaine treatment.

Acutely, morphine is known to increase the firing rate of DA neurons originating in the ventral tegmental area (Matthews and German, 1984). It has been proposed that this effect results from either a direct action of opiates on dopaminergic neurons (Pollard et al., 1978) or the removal of the tonic GABA inhibition on DA neurons (Kalivas et al., 1990). Our findings, using a moderate dose of morphine (5 mg/kg), are in accordance with a morphine-induced DA activation: morphine increased extracellular DA, DOPAC and HVA levels in all three regions. The absence of an increase in DA release following the administration of a high dose of morphine (30 mg/kg) could be explained by a dual modulation of the action potential depending upon the concentration of morphine, as was recently reported in dorsal root ganglion neurons (Shen and Crain, 1989). In the model proposed by Kalivas and coworkers (1990) the effects of a high dose of morphine could be explained by subsequent actions of morphine at other sites that would lead to a blockade of DA release and thus partially antagonize the ventral tegmental activation. In the present study, after a 5 mg/kg dose of morphine, an increase in motor activity occurred at the same time as the rise in striatal DA levels, consistent with the idea that an increase in motor activity is enabled when a threshold level of striatal DA is reached.

In rats injected with ibogaine 19 h beforehand, morphine (5 mg/kg) could no longer induce an increase in DA release. A simple explanation of such an outcome would be an interaction between morphine and ibogaine or its metabolite prior to their actions in the brain. For example, morphine can undergo a N-dealkylation by cytochrome P-450 that can be inhibited by some calcium channel blockers (Renton, 1985). Ibogaine, as a calcium channel blocker (Hajo-Tello et al., 1985; Valette and Leclair, 1977), could have increased the available morphine by delaying its degradation. In order to answer this question, we determined by GCMS the brain concentration of morphine in rats having received either a saline or an ibogaine pretreatment followed, 19 h later, by a 10 mg/kg morphine injection. The similarity in morphine concentrations in all groups

(data not shown) allowed us to reject an interaction between these two drugs that would alter the bioavailability of morphine in the rat brain. Thus, the interaction between ibogaine and morphine probably takes place at the neuronal level. The changes in DA systems induced by ibogaine does not appear to prevent morphine (5 mg/kg) from activating DA neurons, since the metabolites are still increased in the striatum and nucleus accumbens (figs. 4 and 5). One possible site of action of ibogaine might involve the storage pool of DA. This is suggested because the increase in extracellular levels induced by morphine is impulse-dependent and thus mainly vesicular-dependent (Mattews and German, 1984; Buxbaum et al., 1973). Ibogaine might modify some properties of the storage vesicles in such a way that DA neurons would still be able to maintain DA release under basal conditions, but not when stimulated. The lack of increase in metabolites observed in the prefrontal cortex could be explained by the unique characteristics of the mesocortical system (i.e. low ratio of tissue/ extracellular DA levels, high basal firing rate). Another possibility is suggested by the similarities between the responses of the dopaminergic system to a 30 mg/kg morphine challenge in naive rats and the effects of 5 mg/kg morphine in ibogaine-pretreated rats; these two treatments also produced similar changes in motor activity. It is possible that ibogaine might have potentiated morphine such that a low dose of morphine in ibogaine-pretreated rats mimicked the effects of a high dose of morphine in naive rats. This type of interaction has been described between ibogaine and morphine in the context of analgesia. Ibogaine, which by itself does not induce analgesia, potentiated the analgesic effect of morphine (Schneider and McArthur, 1956). The mechanism underlying such an interaction is unclear.

In conclusion, although ibogaine's acute effects on DA systems were different in each region studied, its delayed effects were similar in all regions. In addition, in all regions, ibogaine inhibited the increase in DA transmission normally observed after a moderate dose of morphine. This action could be due to either a blockade or a potentiation of morphine's effects. By preventing the increase in dopaminergic transmission induced by morphine in the nucleus accumbens, ibogaine may decrease the reinforcing efficacy of morphine. Thus, although a definitive mechanism underlying the claims regarding ibogaine's therapeutic effects cannot be specified yet, the results of the present study indicate that such mechanisms merit investigation.

Acknowledgements

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