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ORIGINAL INVESTIGATION

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Ibogaine and the dopaminergic response to nicotine

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Abstract There is increasing evidence that the rewarding effect of nicotine is mediated by the mesolimbic dopamine system. The first objective of this study was to examine the dopamine response to repeated IV infusions of nicotine. Using in vivo microdialysis in awake and freely moving male Sprague-Dawley rats, we demonstrated that IV nicotine infusions (0.16 mg/kg or 0.32 mg/kg per infusion) produced increases in extracellular dopamine levels that were dose- and infusion order-dependent. Acute tolerance was evidenced by the smaller dopamine response produced by a second infusion of nicotine, administered 1 h after the first one. Tolerance was reversible, since the dopamine response to a second infusion of nicotine was unchanged when the interval between the infusions was increased to 3 h. Ibogaine, an alkaloid found in *Tabernanthe iboga*, is claimed to decrease smoking and to have an anti-nicotinic action. The second objective of this study was to establish whether this claim has any neurochemical basis. Pretreatment with ibogaine (40 mg/kg, IP) 19 h prior to the first nicotine infusion (0.32 mg/kg per infusion) significantly attenuated the increase in extracellular dopamine levels induced by the nicotine infusions, suggesting that ibogaine may decrease the rewarding effect of nicotine.

Key words Nicotine · Acute tolerance · Ibogaine · Dopamine · Microdialysis · In vivo · Rat

Introduction

There is increasing evidence that the rewarding effect of nicotine is mediated by the mesolimbic dopaminergic pathway, which originates in the ventral tegmental area and innervates the nucleus accumbens. Studies indicate that nicotine has the ability to activate the mesolimbic dopaminergic neurons: increases in dopaminergic neuronal firing rate (Grenhoff et al. 1986), dopamine synthesis (Carr et al. 1989) and dopamine release (Imperato et al. 1986) have been reported after acute systemic nicotine administration. Nicotine self-administration is reduced when release of dopamine is either ineffective (i.e., after administration of dopamine receptor antagonists) or absent (i.e., 6OHDA lesions of the mesolimbic dopaminergic system) (Corrigall and Coen 1991; Corrigall et al. 1992). However, study of the rewarding effects of nicotine may be complicated by the fact that nicotine interacts with nicotinic cholinergic receptors which have been found readily to desensitize by chronic exposure to nicotine, both in vitro (Bullock et al. 1994) and in vivo (Benwell et al. 1995). The first objectives of this study were to examine the dopamine response to repeated IV infusions of nicotine and to ascertain whether acute tolerance could be observed in vivo.

Ibogaine, an alkaloid found in *Tabernanthe iboga*, is claimed to be effective in interrupting opiate, cocaine and alcohol dependence disorders (Lotsof 1985, 1986, 1989). Preclinical studies in this and other laboratories have shown that ibogaine can reduce self-administration of morphine and cocaine in rats (Cappendijk and Dzoljic 1993; Glick et al. 1994). In addition, ibogaine alters morphine- and cocaine-induced dopamine release in the mesolimbic pathway (Maisonneuve et al. 1991; Maisonneuve and Glick 1992). Ibogaine is also claimed to decrease smoking (Lotsof 1991) and to have an anti-nicotinic action. A recent study (Benwell et al. 1996) reported that ibogaine decreases nicotine-induced dopamine release. Unfortunately, dilution of ibogaine in ethanol may have confounded the reported findings. It is known that both ibogaine and ethanol interact with NMDA receptors (Popik et al. 1994; Chu et al. 1995) and interactions between ethanol and nicotine

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have already been reported (Blomqvist et al. 1993; Lapin et al. 1995). The second objective of this study was therefore to reexamine whether the anti-nicotinic claim attributed to ibogaine has any neurochemical basis.

Materials and methods

Chemicals

Nicotine hydrogen bitartrate and mecamylamine HCl were obtained from Sigma (St Louis, Mo., USA) and dissolved in saline. The pH of the nicotine solution was adjusted to pH 7.0 with a small amount of 10 M NaOH. The doses of nicotine are expressed as the free base; a 250 g rat received either 40 µg or 80 µg nicotine when infused with either the "low" or "high" dose, respectively. These doses of nicotine, administered as boli, would be convulsive; however, in our study these doses were administered as slow infusions and did not produce seizures. During the infusion of nicotine, tolerance and to a lesser extent elimination may have reduced the convulsive effect of nicotine; tolerance has been demonstrated to occur within minutes and possibly seconds (Bullock et al. 1994; Lester and Dani 1995), and elimination would began as soon as nicotine enters the blood compartment. Although we did not measure nicotine plasma concentration ourselves, according to Miller et al. (1977) and Plowchalk et al. (1992), the lower nicotine dose should lead to plasma levels peaking around 55–60 ng/ml at the end of the infusion; this is about one and a half times the levels observed in smokers (Gupta et al. 1995). Ibogaine HCl was purchased from RBI (Natick, Mass., USA) and dissolved in sterile water at a concentration of 10 mg/ml.

Surgical procedure

For all animal experiments the "Principles of laboratory animal care" (NIH publication No. 85–23, revised 1985) were followed. Under pentobarbital anesthesia (50 mg/kg, IP) male Sprague-Dawley rats (250–300 g) had their external jugular vein catheterized with a polyethylene-silicone catheter and one guide cannula was implanted stereotaxically over the nucleus accumbens. The coordinates were chosen such that, when inserted, the tips of the dialysis probes were located in the medial portion of the shell area of the nucleus accumbens: AP, + 1.6 mm and L, ± 0.7 mm with respect to bregma, V, −8.6 mm from the surface of the skull (Paxinos and Watson 1986). The animals were allowed to recover from surgery for 4 days.

Ibogaine pretreatment

Rats were pretreated with ibogaine (40 mg/kg, IP) 19 h prior to the first infusion of nicotine (0.32 mg/kg per infusion). This dose and pretreatment interval has been reported to disrupt morphine and cocaine self-administration (Glick et al. 1991, 1994; Cappendijk and Dzoljic 1993) and to alter morphine-, cocaine- and *d*-amphetamine-induced dopaminergic effects (Maisonneuve et al. 1991, 1992; Maisonneuve and Glick 1992).

In vivo microdialysis experiment

The night before the dialysis experiment, the rat was placed in a chamber with free access to food and water. With the rat briefly anesthetized with Brevital (0.05 ml IV), a dialysis probe (Carnegie Medicin probe: 2 mm) was inserted through the guide cannula. Artificial CSF containing 146 mM NaCl, 2.7 mM KCl, 1.2 mM $CaCl_2$ and 1.0 mM $MgCl_2$ was delivered by a Harvard syringe pump at a flow rate of 1 µl/min. Collection of perfusate began the next day. Fifteen-minute fractions were collected in vials containing 1.5 µl 1.1 M perchloric acid solution (containing 50 mg/l EDTA and 50 mg/l sodium metabisulfite). Before the end of the sixth baseline sample the catheter was primed (25 µl in 2 min). At the beginning of the seventh sampling period the rats received 5-min IV infusion of nicotine (0.16 or 0.32 mg/kg per infusion, expressed as free base). One or 3 h later they received a second identical infusion. The collection of dialysate samples was stopped 1 h after the last infusion. To confirm the nicotinic specificity of the response, a group of rats received mecamylamine (5 mg/kg, IP) 30 min prior to the first infusion of nicotine. Upon completion of an experiment, the catheter's functional status was assessed by IV injection of 0.05 ml Brevital. The rats were then killed by an overdose of pentobarbital. Brains were removed and frozen, and 50 µm coronal sections were sliced in a cryostat. The tracks left by the probes were identified and their exact positions determined by reference to the Paxinos and Watson atlas (1986). Strict criteria were applied to determine whether the locations of the probes were acceptable or not: the tracks were not to be visible at the bottom of the brain, and had to be within a third of the distance separating two easily recognizable landmarks: the midline and the anterior commissure. Only the dialysates of animals whose tracks were in the correct locations were analyzed.

Catecholamine assay

Dialysate samples were assayed for dopamine by HPLC with electrochemical detection. The HPLC system consisted of a Waters 712 Wisp autosampler, a Waters 510 solvent delivery system, a Spherisorb C18 column and a Waters 464 electrochemical detector with a working electrode set at a potential of 0.79 V with respect to a silver-silver chloride reference electrode. The mobile phase consisting of 6.9 g/l sodium monobasic phosphate, 500–560 mg/l heptane sulfonic acid, 100 mg/l disodium EDTA and 120 ml/l methanol, was adjusted with HCl to pH 3.6 and was pumped at a rate of 1.2 ml/min. Chromatograms were integrated, compared to standards and analyzed using Hewlett-Packard ChemStation software.

Statistical analysis

The data, expressed as percent of baseline, were analyzed using analysis of variance (ANOVA) with repeated measures followed by Newman-Keuls tests for post-hoc comparisons when necessary. Control rats, which received a saline injection either 19 h or 30 min prior to the first infusion of nicotine (0.32 mg/kg per infusion), or no pretreatment showed similar effects, and their data were pooled for all subsequent analyses.

Results

DA, DOPAC, and HVA basal extracellular levels

Two-way ANOVAs with repeated measures (groups, six basal values expressed as picomol/10 µl) showed that basal levels of dopamine, dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) were not different from one group to another. For all groups pooled, these extracellular levels were in

picomol/10 µl ± SEM: for dopamine, 0.0126 ± 0.0009, for DOPAC, 8.115 ± 0.666, for HVA, 3.366 ± 0.353.

Effects of nicotine on extracellular dopamine levels

Effects of two nicotine concentrations (Fig. 1)

A three-way ANOVA with two repeated measures (nicotine doses, four time points for two infusion periods) revealed that nicotine increased extracellular dopamine levels in a dose-dependent manner [dose $F(1, 11) = 10.006$, $P < 0.009$]; the effects of the first and second infusions were different [infusion effect, $F(1, 11) = 19.272$, $P < 0.001$]. Further analysis of the main effect of dose determined that the changes in dopamine levels induced by the two doses were markedly different during the first 15 min of the first infusion period (Newman-Keuls tests: $P < 0.00015$).

Nicotine also increased extracellular levels of DOPAC and HVA, but in a non-dose-dependent manner. However, the increases induced by the second infusion were of smaller amplitude than the ones induced by the first infusion [infusion × time interaction for DOPAC, $F(3, 33) = 8.19$, $P < 0.0003$; for HVA, $F(3, 33) = 3.95675$, $P < 0.016$].

In addition, rats which received two 5-min IV saline infusions, 1 h apart, showed no changes in dopamine, DOPAC and HVA levels (data not shown).

Effects of mecamylamine pretreatment

Mecamylamine, a nicotinic antagonist, injected IP 30 min prior to the first infusion, completely abolished the dopamine (Fig. 2), DOPAC and HVA responses (Fig. 3) induced by nicotine (0.32 mg/kg per infusion) [treatment × time interaction, for dopamine, $F(7, 70) = 3.68$, $P < 0.0019$; for DOPAC, $F(7, 70) = 10.83$, $P < 0.00001$; for HVA $F(7, 70) = 8.73$, $P < 0.00001$]. In fact, in all mecamylamine-treated rats none of the data points following nicotine infusions was different from the corresponding basal values.

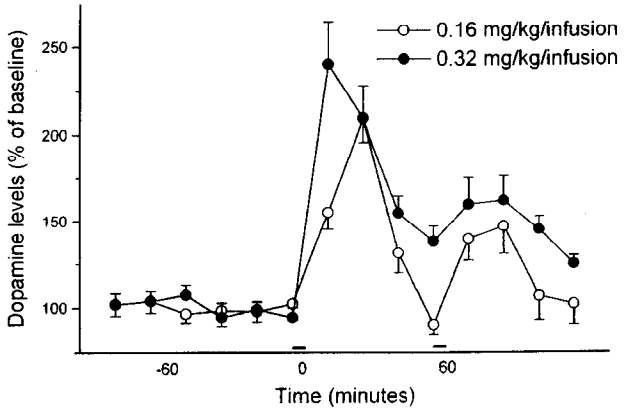

Fig. 1 Extracellular dopamine levels, means ± SEM, expressed as percent of basal values, before and after two 5-min IV infusions of nicotine at time 0 and 60 min. ($n = 6$ for 0.16 mg/kg per infusion and 7 for 0.32 mg/kg per infusion)

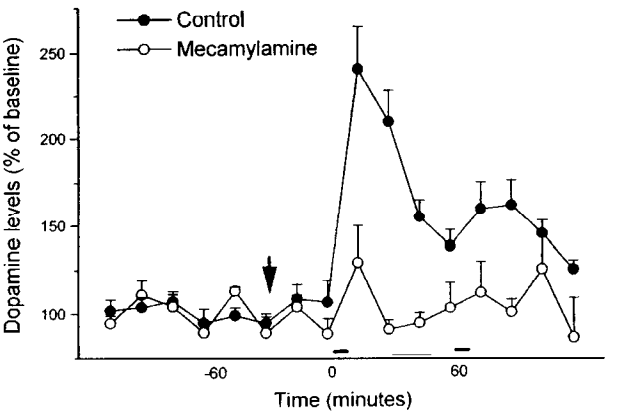

Fig. 2 Effects of mecamylamine (5 mg/kg, IP, $n = 5$), administered 30 min prior to the first nicotine infusion, on extracellular dopamine levels (means ± SEM). All rats received two nicotine infusions (0.32 mg/kg per infusion)

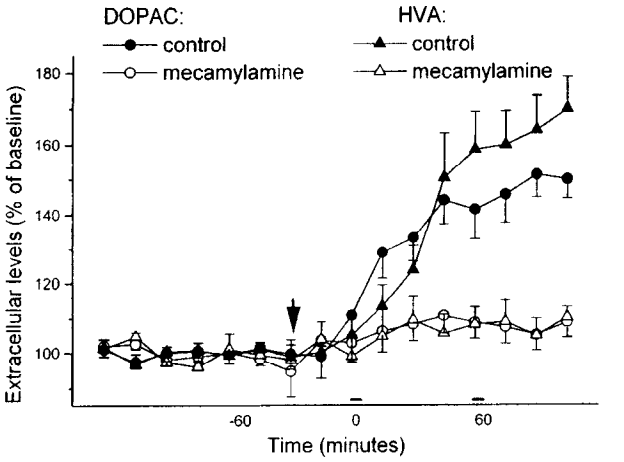

Fig. 3 Effects of mecamylamine (5 mg/kg, IP, $n = 5$), administered 30 min prior to the first nicotine infusion, on extracellular DOPAC and HVA levels (means ± SEM). All rats received two nicotine infusions (0.32 mg/kg per infusion)

Effects of increasing the interval between nicotine infusions (Fig. 4)

In one group of rats the interval between the two nicotine infusions (0.32 mg/kg per infusion) was lengthened to 3 h. The effects on extracellular dopamine levels observed in the hour following the start of each infusion were compared with the effects observed during the corresponding period in 1-h interval infused rats (0.32 mg/kg per infusion). Increasing the interval between infusions changed the effects produced [treatment × infusion interaction, $F(1, 10) = 5.13$, $P < 0.047$]. Newman-Keuls tests demonstrated that the

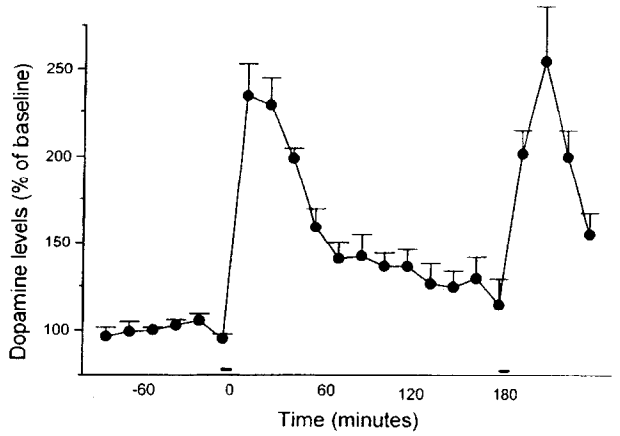

Fig. 4 Extracellular dopamine levels, means ± SEM, expressed as percent of basal values, before and after two 5-min IV infusions of nicotine at time 0 and 180 min (n = 5)

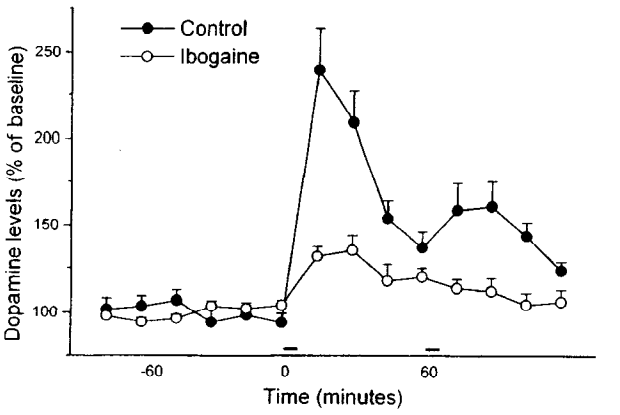

Fig. 5 Effects of ibogaine (40 mg/kg, IP, n = 7) administered 19 h prior to the first nicotine infusion, on extracellular dopamine levels (means ± SEM). All rats received two nicotine infusions (0.32 mg/kg per infusion)

effects produced by the second infusion were significantly different between the two regimens ($P < 0.0015$), while there was no difference in the responses to the first infusion. In addition, the effects produced by the first and second infusions in the 3-h interval group were not different from each other ($P < 0.85$).

Effects of ibogaine on nicotine-induced dopamine changes

A three-way ANOVA with two repeated measures (nicotine doses, four time points for two infusion periods) revealed that ibogaine pretreatment attenuated the increase in extracellular dopamine levels induced by nicotine infusions [treatment × time interaction, $F(3, 36) = 5.39$, $P < 0.004$] without preventing acute tolerance [infusion effect, $F(1, 12) = 25.94$, $P < 0.00027$ and no significant treatment × infusion interaction]; the effects induced by the first infusion were still significantly greater than the ones induced by the second infusion [Newman-Keuls tests, $P < 0.01$] even though the effects of both infusions were markedly attenuated (Fig. 5).

In addition, in ibogaine-pretreated rats, the increases in dopamine metabolites produced by nicotine infusions tended to be of smaller amplitude [treatment effect, for DOPAC, $P < 0.078$, for HVA, $P < 0.11$) than in control rats (Figs. 6 and 7).

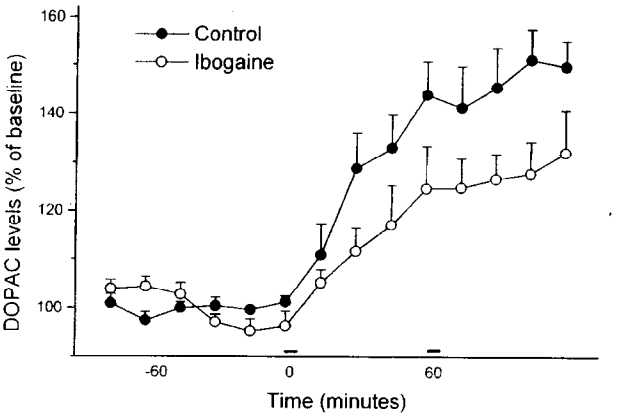

Fig. 6 Effects of ibogaine (40 mg/kg, IP, n = 7) administered 19 h prior to the first nicotine infusion, on extracellular DOPAC levels (means ± SEM). All rats received two nicotine infusions (0.32 mg/kg per infusion)

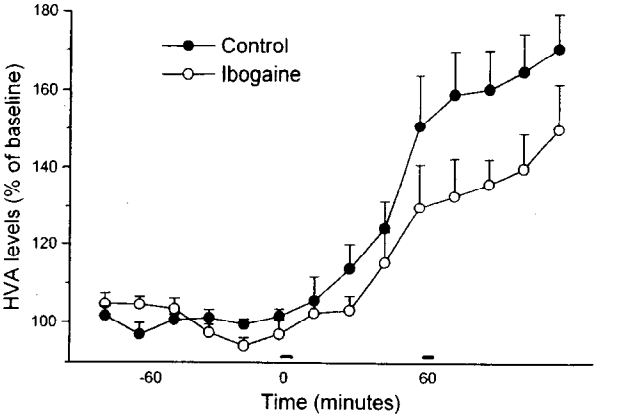

Fig. 7 Effects of ibogaine (40 mg/kg, IP, n = 7) administered 19 h prior to the first nicotine infusion, on extracellular HVA levels (means ± SEM). All rats received two nicotine infusions (0.32 mg/kg per infusion)

Discussion

As already reported by other laboratories (Damsma et al. 1989; Brazell et al. 1990; Benwell and Balfour 1992), nicotine, administered systemically, induces an increase in extracellular dopamine levels in the nucleus accumbens. This effect appears to be receptor

mediated, since the increase is prevented by prior treatment with mecamylamine, a moderately selective central and peripheral nicotinic receptor antagonist. In the nucleus accumbens and ventral tegmental area, 30–40% of nicotinic receptors are located on dopaminergic neurons (Clarke and Pert 1985). Nicotine can interact with nicotinic receptors located on both cell bodies and terminals to enhance dopamine release (Mifsud et al. 1989; Nisell et al. 1994); however, the dominant effect of nicotine has been reported by a number of laboratories to occur via an action in the ventral tegmental area (Yoshida et al. 1993; Corrigall et al. 1994; Nisell et al. 1994). It is noteworthy that increases in the dopamine metabolites, DOPAC and HVA, have been observed after local infusion of nicotine into the ventral tegmental area but not into the nucleus accumbens (Nisell et al. 1994). A difference in the distribution of various possible subunits of the nicotinic channel in the mesolimbic dopaminergic neurons might account for regional variations in the response to nicotine. Each combination of subunits appears to display unique pharmacological and electrophysiological properties (Deneris et al. 1991). In addition, activation of nicotinic receptors located on non-dopaminergic neurons, either in the nucleus accumbens or in the ventral tegmental area, may indirectly affect dopaminergic activity. For example, nicotine has been demonstrated to interact with presynaptic receptors to enhance the release of excitatory amino acids (McGehee et al. 1995). Also, nicotine induced c-*fos* expression in the dorsal and ventral striatum is dependent on NMDA stimulation (Kiba and Jayaraman 1994). Excitatory amino acids, such as glutamate, exert a facilitatory influence on nucleus accumbens dopamine release by actions in both the terminal region (Ohno and Watanabe 1995) and the cell body area (Wang et al. 1994). Therefore it can be postulated that nicotine modulates dopamine release partially via its action on glutamatergic neurons. The high dose of mecamylamine used in this study may have prevented such a putative interaction (Clarke et al. 1994).

By administering nicotine IV we were able to demonstrate that, in vivo, nicotine induces an acute and reversible tolerance to its effects on dopamine release. The lack of acute tolerance reported by Damsma et al. (1989) may have been attributable to the long interinjection interval together with the SC route of administration. The most likely explanation for the observed acute tolerance is that nicotinic receptors desensitize quickly after exposure to agonists (Ochoa et al. 1989; Grady et al. 1994). In vitro, nicotine receptor desensitization occurs within minutes at concentrations compatible with the estimated concentration range in the brains of smokers (0.1–1 μM) (Marley 1988; Bullock et al. 1994); desensitization is dose-dependent below 10 μM (Boksa and Livett 1984). In this study it is likely that desensitization began before the end of the first nicotine infusion and was greater after the higher dose. This would explain why dopamine release peaked sooner (in the first 15 min) after the higher dose of nicotine and later (15–30 min) after the lower dose. The reversibility of the desensitization phenomenon coincides with the removal of the drug. The elimination rate of IV nicotine in rats is about 1 h (Plowchalk et al. 1992), and the concentration of nicotine, 3 h after an IV infusion, should be about 10% of the initial concentration. Acute tolerance of the locomotor hyperactivity induced by repeated administration of nicotine has been reported to be reversible (Hakan and Ksir 1991).

Ibogaine has been claimed to be effective in the treatment of nicotine dependence (Lotsof 1991) as well as opiate, stimulant and alcohol dependence (Lotsof 1985, 1986, 1989). Preclinical studies have shown that ibogaine reduces self-administration of morphine and cocaine (Glick et al. 1991, 1994; Cappendijk and Dzoljic 1993) and alters the accumbal dopamine increases that have been linked to their rewarding effects (Maisonneuve et al. 1991; Maisonneuve and Glick 1992). Extending these earlier studies, our present results indicate that ibogaine blocks the dopamine increases induced by nicotine administration as well. Our results corroborate the report of Benwell et al. (1996), except for the effects on the dopamine metabolite, DOPAC. In our study the increases in DOPAC induced by nicotine were attenuated by ibogaine pretreatment, while they were enhanced in Benwell et al.'s report. Possibly, methodological differences, such as the schedule of nicotine administration, differences in probe implantation protocols or ibogaine solution preparation (dilution in water versus in ethanol), could explain the divergence of results. It is interesting to note that ibogaine attenuates the dopamine increases induced by drugs acting preferentially at the cell body area, such as morphine (Maisonneuve et al. 1991) and nicotine (Benwell et al. 1996; this report), and enhances the dopamine responses of drugs acting at the terminal regions, such as cocaine (Maisonneuve and Glick 1992) and *d*-amphetamine (Maisonneuve et al. 1992).

The mechanism(s) by which ibogaine blocked the dopaminergic response to nicotine is unknown, but several sites of action can be hypothesized. The reported interaction of ibogaine with kappa opioid receptors (Deecher et al. 1992; Sweetnam et al. 1995) could influence nicotine's effects. Activation of kappa opioid receptors by U50,488 or by endogenous dynorphin peptides has been demonstrated to inhibit nicotine-induced Ca^{2+} uptake (Bunn and Dunkley 1991) as well as catecholamine secretion (Kumakura et al. 1980) in cultured bovine adrenal medullary cells.

Ibogaine interacts with the NMDA ion channel site, as shown by its ability to displace MK-801 binding, a non-competitive antagonist of NMDA receptors (Popik et al. 1994; Sweetnam et al. 1995; Chen et al. 1996). Ibogaine can therefore block the ionic permeability of the NMDA receptors and antagonize the

effects of NMDA agonists, such as glutamate, as well as any effects of nicotine mediated indirectly via NMDA receptors. The non-competitive NMDA antagonist, MK-801, increases A10 dopamine neuron burst firing rate (French et al. 1993) and the release of dopamine in the nucleus accumbens (Taber and Fibiger 1995). Although these effects would indicate a likely potentiation of nicotinic effects, MK-801 has been demonstrated to inhibit c-Fos expression induced by acute nicotine (Kiba and Jayaraman 1994).

The action of ibogaine as a non-competitive blocker of NMDA channels suggests that it might have an analogous action at nicotinic receptors. Nicotinic and NMDA ion channels share several structural, molecular, functional and pharmacological properties. MK-801, a NMDA antagonist, blocks nicotinic receptors (Ramoa et al. 1990; Briggs and McKenna 1996) and mecamylamine, a nicotinic antagonist, blocks NMDA receptors (O'Dell and Christensen 1988); these two molecules are open channel blockers (Varanda et al. 1985; Javitt and Zukin 1989; Banerjee et al. 1990). It is possible that ibogaine exerts its antinicotinic effects directly by blocking the nicotinic open channel. Earlier studies which had reported that ibogaine did not interact with nicotinic receptors had used a ligand ([^{3}H]methylcarbamylcholine) that binds to the nicotinic site and is not a non-competitive blocker (Deecher et al. 1992). In support of this hypothesis, both ibogaine and mecamylamine decreased the dopamine, DOPAC and HVA responses to nicotine, although the effects of mecamylamine were greater than those of ibogaine. These differences could be simply due to differences in dosage. Additional actions of ibogaine which affect primarily the release of dopamine (i.e., kappa opioid activation) could explain the greater ability of ibogaine to affect the nicotine induced increase in dopamine as compared to DOPAC and HVA.

In the present study, inhibition of nicotinic effects by ibogaine occurred 19 h after its administration. Although ibogaine has a reported half-life of 1 h in rodents (Dhahir 1971), this prolonged effect of ibogaine is not surprising. Pharmacologically active concentrations of ibogaine (Glick et al. 1993) have been detected in plasma and brain a day after its administration (Gallagher et al. 1995). Ibogaine, due to its lipophilic nature, concentrates in fat where it could be slowly released in the systemic circulation, maintaining prolonged low levels of ibogaine (Hough et al. 1996). In addition, recent evidence suggests that the primary metabolite of ibogaine, noribogaine, persists in the plasma for more than a day (Mash et al. 1995a) and shares several of ibogaine's biochemical actions (Mash et al. 1995b; Pearl et al. 1995).

Further studies are warranted to explore possible mechanisms of the ibogaine-nicotine interaction as well as to determine the effects of ibogaine after chronic administration of nicotine.

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