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Short communication

Interactions between ibogaine and cocaine in rats: in vivo microdialysis and motor behavior

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To investigate a possible basis for the proposed anti-addictive property of ibogaine, the effects of an ibogaine (40 mg/kg i.p.) pretreatment on in vivo neurochemical and motor effects induced by cocaine (20 mg/kg i.p.) were studied. Ibogaine, administered 19 h earlier, potentiated the increase in extracellular dopamine levels in striatum and nucleus accumbens as well as the stimulated motor activity induced by cocaine. Although high doses of cocaine can become aversive by producing an anxiogenic reaction, it is unknown whether the potentiation of cocaine's effects by ibogaine would also cause aversion and lead to a decrease in cocaine addiction.

Ibogaine; Cocaine; Dopamine; Nucleus accumbens; Striatum; Microdialysis; Locomotor activity

1. Introduction

Two US patents (patent numbers: 4,499,096 and 4,587,243), describing the potential efficacy of an indolalkylamine, ibogaine, in treating opiate and stimulant addiction, have led to several studies investigating the possible basis for these claims. It has been reported that, in rats, ibogaine decreases i.v. morphine self-administration (Glick et al., 1991) 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 (Maisonneuve et al., 1991). In addition, it has been recently determined that ibogaine potentiates the DA release and the motor activity induced by 1.25 mg/kg of d-amphetamine (Maisonneuve et al., in press).

Since the rewarding effects of drug of abuse have been associated with their ability to increase DA release, especially in the nucleus accumbens (Di Chiara and Imperato, 1988), we explored, in the present study, whether ibogaine could alter dopaminergic responses to cocaine. By blocking the DA uptake process, cocaine increases synaptic concentrations of DA (Heikkila et al., 1975) and this might increase locomotor activity (Kuzcenski,1983).

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Using microdialysis in freely moving animals, we studied the time course of extracellular DA after i.p. injection of cocaine (20 mg/kg) in rats pretreated with ibogaine (40 mg/kg i.p.) or saline. Dialysis samples were taken from the striatum and nucleus accumbens. In addition, the effects of ibogaine pretreatment on motor activity elicited by cocaine were determined across a wide range of cocaine doses (5–40 mg/kg) in non-dialyzed rats.

2. Materials and methods

2.1. Drugs

Ibogaine HCl and cocaine HCl, obtained from Sigma Chemical Co, were dissolved in water and saline respectively and were injected i.p. in doses expressed as the salt.

2.2. Microdialysis procedures

Female Sprague-Dawley rats were implanted stereotaxically with two guide cannulas, one over the nucleus accumbens and the other over the 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) (Paxinos and Watson Atlas). At least three days after surgery,

the rats were injected i.p. with saline (2 ml/kg) or ibogaine (40 mg/kg) and then placed in a dialysis chamber where calibrated probes (3 mm probes; BAS/CMed MF-5393) were lowered into the guide cannulas. The dialysis probes were continuously perfused with a solution containing (mM) 146 NaCl, 2.7 KCl, 1.2 $CaCl_2$, 1.0 mM $MgCl_2$ and 0.05 ascorbic acid at a flow rate of 1 μl/min. On the next morning, 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). Four baseline samples were taken before i.p. injection of cocaine (20 mg/kg). The effects of cocaine were then monitored for 3 h. The interval between saline or ibogaine pretreatment and cocaine administration was 19 h. Perfusate samples were analyzed by HPLC with electrochemical detection; the HPLC consisted of a Waters pump (model 510), a WISP autosampler (model 712), an ESA CA-80 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, 50 ml/l methanol, was adjusted with HCl to pH 3.6 and was pumped at a rate of 1.2 ml/min.

2.3. Motor activity monitoring

Locomotor activity was assessed in photocell activity cages. Interruptions of any of the infrared photocells were recorded by an Apple IIe computer. Non-dialyzed rats were pretreated with saline (2 ml/kg) or ibogaine (40 mg/kg) 19 h before the administration of saline (1 ml/kg) or cocaine (5–40 mg/kg). Immediately after the cocaine injection rats were placed in activity cages and locomotion was measured for 2 h.

2.4. Statistical analysis

Repeated measure analyses of variance were done on the chemical data, expressed as percents of the respective mean basal values, and on the behavioral, non-transformed, data. Post-hoc analyses were carried out using Newman–Keuls multiple comparison tests. T-tests were performed to evaluate any differences between basal levels.

3. Results

3.1. Effects of cocaine on DA and its metabolites

Injection of cocaine (20 mg/kg) in control rats led to an immediate increase in extracellular dopamine (fig. 1) (time effect, $P < 0.0001$) that peaked during the second sampling period and remained elevated up to 100 min postinjection ($P < 0.05$). The response to cocaine was not different in the two regions studied. 3,4-Dihydroxyphenylacetic (DOPAC) values (data not shown) decreased from 20 min to the end of the experiment ($P < 0.0002$), reaching a value of about 70% of basal levels. Homovanillic acid (HVA) values (data not shown) also decreased during the same period (20–180 min, $P < 0.005$), reaching a value of 78% of basal levels.

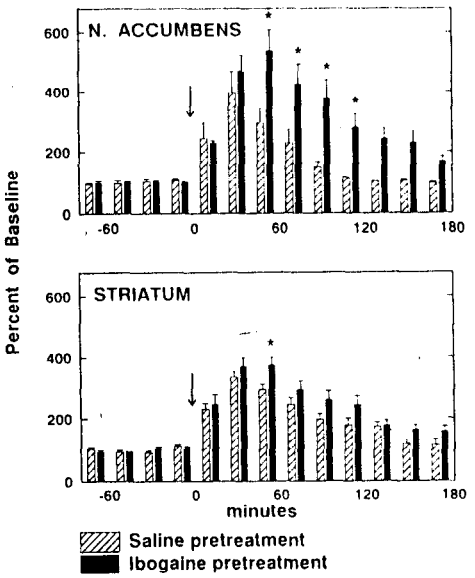

Fig. 1. Time course of extracellular DA in the nucleus accumbens (top panel) and in the striatum (bottom panel) before and after administration of cocaine (20 mg/kg i.p.) in rats pretreated with saline ($n = 6$) or ibogaine (40 mg/kg i.p., $n = 6$) 19 h earlier. Samples were collected at 20-min intervals. Data are expressed as a percent of baseline values (± S.E.). * $P < 0.05$ as compared to saline pretreatment at the same time.

3.2. Effects of ibogaine on DA and metabolite changes induced by cocaine

In both regions ibogaine pretreatment (40 mg/kg i.p.) had no significant effects on basal DA, DOPAC or HVA levels, although all values tended to be lower. Estimated extracellular basal levels, in saline versus ibogaine-pretreated groups were as follows: in nucleus accumbens, DA 10.02 ± 1.45 versus 7.81 ± 0.36 nM, DOPAC 4.46 ± 0.48 versus 3.67 ± 0.61 μM, HVA 2.03 ± 0.24 versus 1.70 ± 0.21 μM; and in striatum, DA 14.49 ± 1.9 versus 13.84 ± 1.76 nM, DOPAC 5.27 ± 0.85 versus 4.49 ± 0.70 μM and HVA 3.55 ± 0.72 versus 2.86 ± 0.37 μM. These levels, corrected for probe recovery, were based on four basal samples taken at about 16–17 h after probe insertion and prior to cocaine administration.

Administration of ibogaine 19 h prior to a cocaine challenge potentiated the rise in extracellular DA in

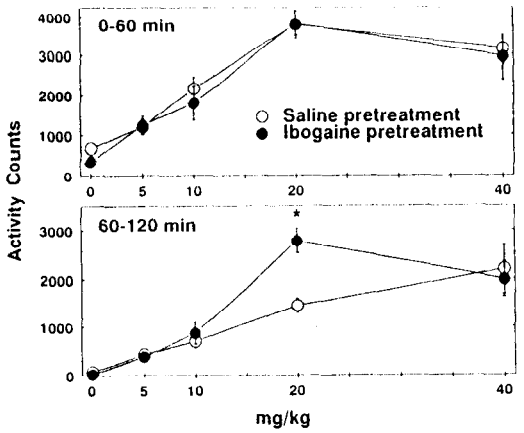

Fig. 2. Effects of a saline or ibogaine pretreatment (40 mg/kg i.p.) on the motor effects induced by several doses of cocaine (5–40 mg/kg i.p.). Cocaine was administered at time zero and the pretreatments 19 h earlier. Each point represents the average activity counts (±S.E.) of six rats (11 rats for 20 mg/kg) for a period of 1 h. * $P < 0.05$ as compared to saline pretreatment at the same time.

both regions (fig. 1), but this effect was not as pronounced in the striatum (pretreatment × region × time $P < 0.01$). While this potentiation was present in the nucleus accumbens from 40 to 120 min ($P < 0.01$), it lasted only from 40 to 60 min in the striatum ($P < 0.01$). Ibogaine pretreatment had no significant effects on cocaine-induced decreases in DOPAC and HVA levels (data not shown).

3.3. Effect of ibogaine on behavioral response to cocaine

Statistical analysis showed that the only significant effect of ibogaine pretreatment (fig. 2) was for the 20 mg/kg dose of cocaine during the second hour ($P < 0.0002$).

4. Discussion

In this study, cocaine induced an immediate increase in extracellular DA levels in nucleus accumbens and striatum. By inhibiting the uptake of DA (Heikkila et al., 1975), the primary means of inactivation of extracellular DA, cocaine causes an accumulation of basal DA outflow. The moderate decreases in DA metabolites induced by cocaine confirms that the spontaneous exocitotic DA release contributes modestly to the formation of DOPAC and HVA (Zetterström et al., 1988). In contrast to the findings of Di Chiara and Imperato (1988), the magnitude of cocaine response was similar in the nucleus accumbens and striatum. Sampling of different subregions, as well as the use of different types of probes (transversal versus concentric), might possibly explain this divergence.

Pretreatment with ibogaine potentiated the increase in extracellular DA levels induced by cocaine in the nucleus accumbens and to a lesser extent in the striatum. This phenomenon occurred when ibogaine should have no longer been present in the body (half-life = 1 h in rodents, Dhahir, 1971). It is possible that ibogaine administration results in the formation of an active metabolite with a long half-life and/or that a persistent change in neuronal activity occurs.

Ibogaine, or an active metabolite, could potentiate cocaine's effects by increasing brain cocaine levels (e.g. interfering with its metabolism or its bound fraction). However, this possibility seems unlikely since the magnitude of the potentiation was not the same in the two regions studied. A more plausible explanation may involve an element that differs in these two regions. Although controversial, there are reports suggesting that DA uptake sites in the striatum and in the nucleus accumbens are dissimilar (Missale et al., 1985; Lew et al., 1991). It is unclear how ibogaine administration would lead 19 h later to a potentiation of the DA uptake blockade induced by cocaine. Ibogaine, as a potential weak Na^+ channel agonist (Deecher et al., in press), could induce a carrier-mediated DA release, but cocaine, as a local anesthetic, would block the necessary inward Na^+ movement. In addition, since ibogaine pretreatment did not potentiate the cocaine-induced decrease in DA metabolites, a vesicular origin of the excess extracellular DA is likely.

Although somewhat different in the time course, motor effects of 20 mg/kg cocaine were also enhanced. The lack of behavioral potentiation during the first hour after cocaine administration could be due to a combination of factors. Ibogaine pretreatment, by itself, produces some motor inhibition during the first hour after its administration (Maisonneuve et al., in press) and this could have masked a potentiation of cocaine's stimulatory effects. In addition, it is logical to infer that behavioral potentiation should have followed neurochemical enhancement, which began 40 min after cocaine injection, and it is possible that 20 min of enhancement may have been 'lost' in the 60-min period. It is also unclear why only the locomotor effect induced by 20 mg/kg of cocaine was potentiated by ibogaine. This selectivity was so surprising that we repeated the 20 mg/kg experiment: the same result occurred. The increase in motor activity induced by a dose of 40 mg/kg of cocaine is a combination of increased locomotion and stereotypy, and stereotypy can actually reduce photocell activity counts (Glick, 1972). Perhaps ibogaine did indeed potentiate the effect of the 40 mg/kg dose of cocaine but this might have resulted in increased stereotypic behavior as well and consequently lower activity counts.

The mesolimbic and mesocortical DA systems are thought to mediate the potent rewarding effects and

abuse potential of cocaine (Wise and Bozarth, 1987). Our results suggest that ibogaine may increase the reinforcing efficacy of cocaine. However, it has been reported that high doses of cocaine can become aversive by producing an anxiogenic reaction (e.g. Cohen, 1975). Whether the potentiation of cocaine's effects by ibogaine can cause aversion, and a subsequent decrease in cocaine addiction, is unknown.

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