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Short communication

Time-dependent interactions between *iboga* agents and cocaine

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Abstract

The purpose of this study was to clarify the effects of *iboga* agents on cocaine-induced hyperactivity. Both inhibition and enhancement of cocaine-induced activity by ibogaine have been reported. In the present study, rats were treated with either ibogaine (40 mg/kg, i.p.), noribogaine (40 mg/kg, i.p.), 18-methoxycoronaridine (40 mg/kg, i.p.), or saline, 1 or 19 h prior to the administration of cocaine (20 mg/kg, i.p.) or saline. Motor activity was monitored thereafter for 3 h. All three *iboga* agents had acute inhibitory effects and delayed potentiating effects on cocaine-induced hyperactivity. These time-dependent effects, which could not be attributed to the motor activity induced by the *iboga* agents alone, account for divergent results reported in the literature. © 1997 Elsevier Science B.V.

Keywords: Ibogaine; Noribogaine; 18-Methoxycoronaridine; Cocaine; Motor activity

1. Introduction

Ibogaine, a natural alkaloid found in an African shrub, *Tabernanthe iboga*, has been studied for the last several years for its putative anti-addictive properties (Cappendijk and Dzoljic, 1993; Glick et al., 1994; Rezvani et al., 1995). Human anecdotal reports and preclinical studies indicate that ibogaine disrupts self-administration of opioids (Sheppard, 1994; Glick et al., 1991, 1994) and stimulants (Cappendijk and Dzoljic, 1993; Glick et al., 1994), as well as nicotine (Sheppard, 1994) and alcohol (Rezvani et al., 1995). Interactions with opioid receptors, especially agonism at kappa opioid receptors (Glick et al., 1997), blockade of NMDA ion channels (Glick et al., 1997; Popik et al., 1995), blockade of nicotinic ion channels (Badio et al., 1997), and 5-hydroxytryptamine (5-HT) uptake inhibition (Mash et al., 1995), have all been suggested as possible mechanisms for the putative anti-addictive properties of ibogaine. Ibogaine affects the dopaminergic response to various drugs of abuse, which has been linked to their rewarding effects (Wise and Bozarth, 1987; Koob, 1992). For example, ibogaine has been shown to potentiate cocaine- and amphetamine-induced increases and to attenuate morphine- and nicotine-induced increases in extracellular levels of dopamine in the nucleus accumbens (Benwell et al., 1996; Maisonneuve and Glick, 1992; Maisonneuve et al., 1991, 1992a). Ibogaine also affects motor behavior, which is presumably mediated by the dopaminergic system (Wise and Bozarth, 1987; Beninger, 1983). Contrary to the neurochemical observations, behavioral reports concerning ibogaine and locomotor activity in rats are conflicting. For example, ibogaine has been reported to either inhibit or potentiate motor activity induced by amphetamine and cocaine (Sershen et al., 1992; Maisonneuve and Glick, 1992; Maisonneuve et al., 1992a; Broderick et al., 1994). Although sex may influence the efficacy of ibogaine to modulate stimulant-induced hyperactivity (Pearl et al., 1997), we hypothesized that the interval between injections of ibogaine and the stimulant drug contributes importantly to such apparent contradictory results. For example, Broderick et al. (1994) reported that ibogaine, administered 2 h prior to cocaine, inhibited cocaine-induced motor activity, while we (Maisonneuve and Glick, 1992) showed that ibogaine, administered 19 h prior to cocaine, potentiated cocaine hyperactivity. Accordingly, in this study, we investigated whether ibogaine would differentially affect cocaine-induced hyperactivity at different times after ibogaine administration. We also included noribogaine (12-

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hydroxyibogamine), ibogaine's primary metabolite, which has many of the behavioral and pharmacological features of ibogaine (Glick et al., 1996b; Pearl et al., 1995), and a novel alkaloid, 18-methoxycoronaridine, which, like ibogaine, disrupts drug self-administration but lacks the tremorigenic and neurotoxic effects observed with ibogaine (Glick et al., 1996a).

2. Material and methods

Ibogaine HCl and cocaine HCl were obtained from Sigma (St Louis, MO, USA), 12-hydroxyibogamine HCl was provided by NIDA and 18-methoxycoronaridine HCl was synthesized by Martin Kuehne and Upul Bandarage (University of Vermont, Burlington, VT, USA). Ibogaine and noribogaine were dissolved in sterile water, 18-methoxycoronaridine in phosphate buffer and cocaine in sterile saline.

Naive female Sprague–Dawley rats (Taconic, Germantown, NY, USA), weighing between 250–275 g, were treated with either ibogaine (40 mg/kg, i.p.), noribogaine (40 mg/kg, i.p.), 18-methoxycoronaridine (40 mg/kg, i.p.) or saline either 1 or 19 h prior to the administration of cocaine (20 mg/kg, i.p.) or saline, which always occurred at 11.00 am. Immediately following the cocaine injection the rats were placed, for the first and only time, in cylindrical photocell activity cages (diameter 60 cm, three crossing beams). Interruptions of light beams were recorded with the software Med-PC (MED Associate, St. Albans, VT, USA) for 3 h (from 11.00 am to 2.00 pm) in intervals of 1 h. In order to avoid using an excessive number of rats, saline was used as the control for all treatments; previous studies in our laboratory have shown that saline, sterile water, or phosphate buffer administration produce similar effects. For all experiments the 'Principles of Laboratory Animal Care' (NIH publication No. 85-23, revised 1985) were followed.

The behavioral data were analyzed using an analysis of variance (ANOVA) with repeated measures followed by Newman–Keuls tests for post-hoc comparisons when appropriate.

3. Results

When administered 1 h prior to saline (Fig. 1, inset), noribogaine significantly prevented the usual habituation observed during the second and third hour after saline administration ($P < 0.02$ and 0.005 for the second and third hour, respectively). The same trend was observed with ibogaine, but did not reach significance. 18-Methoxycoronaridine had no effect. When administered 19 h prior to saline (Fig. 2, inset), ibogaine, but not noribo-

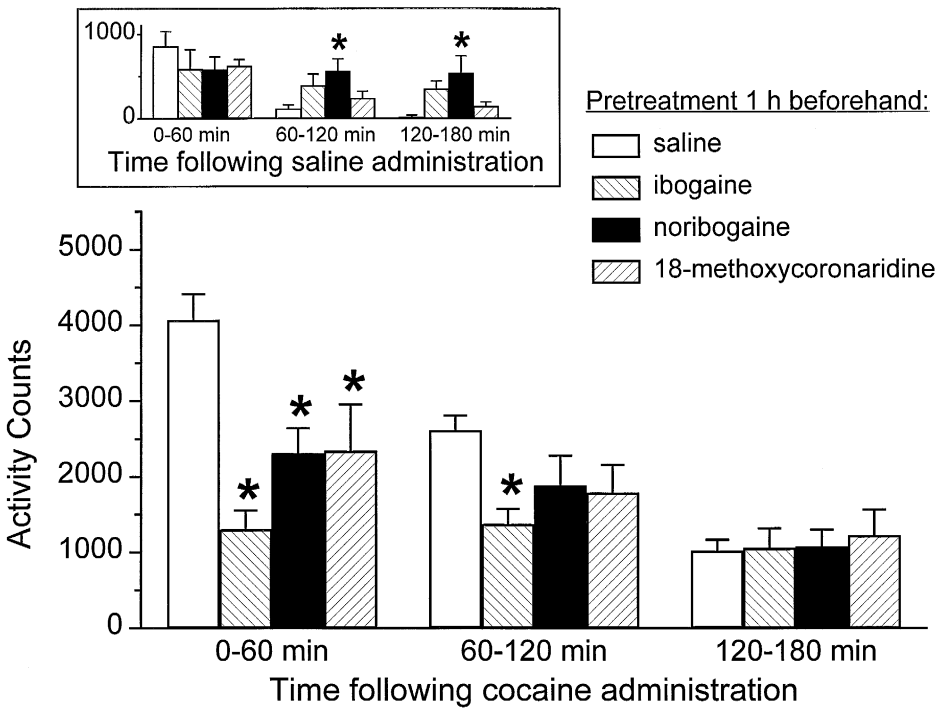

Fig. 1. Locomotor activity (mean activity counts per hour ± S.E.M.) induced by cocaine (20 mg/kg, i.p.) or saline (insert) in rats pretreated 1 h beforehand with either ibogaine (40 mg/kg, i.p.; $n = 8$ (cocaine), 6 (saline)), noribogaine (40 mg/kg, i.p.; $n = 8$ (cocaine), 6 (saline)), 18-methoxycoronaridine (40 mg/kg, i.p.; $n = 6$ (cocaine), 6 (saline)), or saline (n = 11 (cocaine), 6 (saline)). * $P < 0.05$ as compared to saline pretreatment.

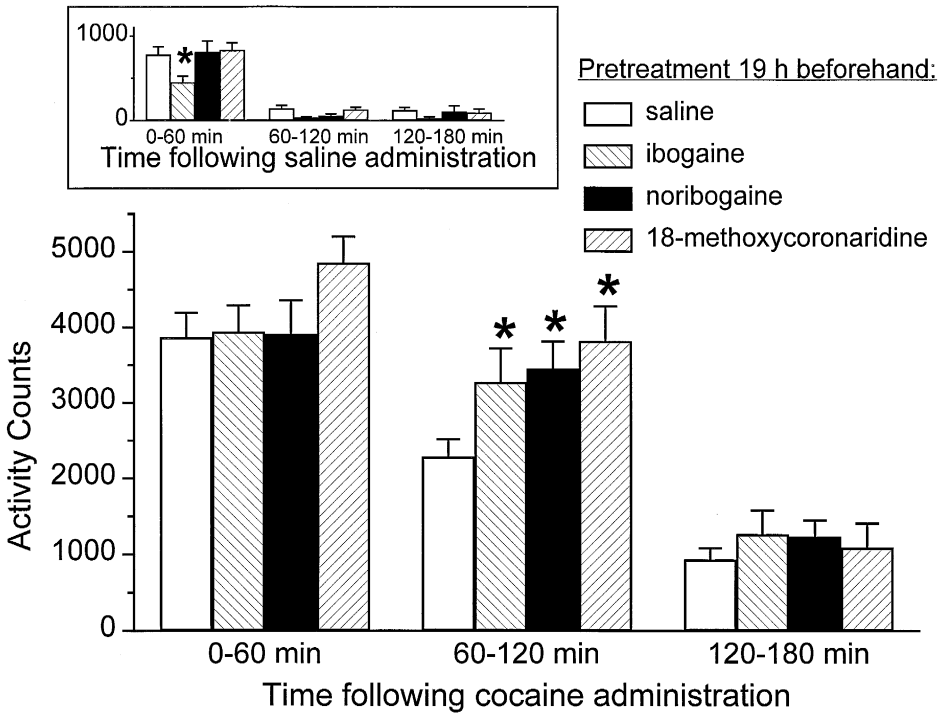

Fig. 2. Locomotor activity (mean activity counts per hour ± S.E.M.) induced by cocaine (20 mg/kg, i.p.) or saline (insert) in rats pretreated 19 h beforehand with either ibogaine (40 mg/kg, i.p.; $n = 8$ (cocaine), 6 (saline)), noribogaine (40 mg/kg, i.p.; $n = 8$ (cocaine), 6 (saline)), 18-methoxycoronaridine (40 mg/kg, i.p.; $n = 6$ (cocaine), 6 (saline)), or saline ($n = 11$ (cocaine), 6 (saline)). * $P < 0.05$ as compared to saline pretreatment.

gaine or 18-methoxycoronaridine, reduced the novelty-induced hyperlocomotion observed during the first hour following saline administration ($P < 0.001$).

When administered 1 h prior to cocaine (Fig. 1), all three *iboga* agents decreased the hyperactivity induced by cocaine (pretreatment × time interaction, $F(6,58) = 8.26$, $P < 0.0001$). With all pretreatments the effect was significant during the first hour following cocaine administration ($P < 0.0002$); only ibogaine pretreatment was significant during the second hour ($P < 0.004$). In contrast, when administered 19 h prior to cocaine (Fig. 2), all three *iboga* agents potentiated the motor activity induced by cocaine (pretreatment × time interaction, $F(6,58) = 1.88$, $P < 0.05$ one-tailed; we considered the P value being significant using a one-tailed test since we had predicted the outcome based on previous results (Maisonneuve and Glick, 1992)). This effect was significant for all the *iboga* agents during the second hour following cocaine administration (ibogaine and noribogaine, $P < 0.02$; 18-methoxycoronaridine, $P < 0.002$).

4. Discussion

As predicted ibogaine had an opposite effect on cocaine-induced activity depending on the time of its administration in relation to the cocaine challenge. The observed decrease in cocaine hyperactivity induced by ibogaine, shortly after its administration, is in agreement with the report published by Broderick et al. (1994). This result cannot be explained by motor impairment since neither ibogaine nor the other *iboga* agents produced a deficit in motor activity following saline administration (see Fig. 1 inset). On the contrary, noribogaine, and ibogaine to a lesser extent, prevented habituation or enhanced the effect of novelty; the same trend was observed by Broderick et al. (1994). The decrease in cocaine hyperactivity induced by ibogaine may be correlated with a decrease in cocaine-induced dopamine effects (Broderick et al., 1994).

The potentiation of cocaine hyperactivity by ibogaine reported in this study is very similar to the result published by our laboratory in 1992 (Maisonneuve and Glick, 1992); that is, the potentiation was limited to the second hour following cocaine administration. The same effect was observed after noribogaine and 18-methoxycoronaridine. This effect is puzzling since, 19 h after its administration, ibogaine, alone, still has a small inhibitory effect on motor activity (Kesner et al., 1995; Maisonneuve et al., 1992b). Several explanations are possible. (1) 19 h after its administration ibogaine is still present in whole brain tissue (0.7 μM), coexisting with similar levels of noribogaine (Pearl et al., 1997). These low brain levels allow interaction with a more restricted variety of receptors than higher brain levels, observed immediately after ibogaine administration (at 1 h: 10 μM (Pearl et al., 1997)). Effective interactions with 5-HT transporters (Mash et al., 1995), nicotinic receptors (Badio et al., 1997) and $\sigma 2$ receptors (Mach et al., 1995) may occur while interactions with kappa opioid

receptors (Deecher et al., 1992) and NMDA channels (Popik et al., 1994) may be limited. Therefore, it is likely that low and high brain concentrations of ibogaine have different pharmacological profiles, possibly causing dissimilar alterations of cocaine's effects. In addition, it is conceivable that another metabolite, besides or beyond noribogaine, is produced. Long-lasting metabolites with their own pharmacological activities could explain the present results. (2) It is possible that acute administration of *iboga* agents induces permanent pharmacological changes that are observable at later times. For example a change in cocaine pharmacokinetics (i.e., decrease metabolism) could overcome the decrease in activity induced by ibogaine alone to the point of observing a limited potentiation. Such a phenomenon has been reported with amphetamine (Glick et al., 1992).

Time-dependent interactions may also be involved in other behavioral effects of *iboga* agents and explain yet other divergent results reported in the literature (for review, see Sershen et al., 1997). The relevance of the delayed potentiating effects of *iboga* agents on cocaine-induced hyperactivity to the putative anti-addictive effects of these agents is unclear. It is possible that by enhancing the cocaine response, *iboga* agents render cocaine aversive (Cohen, 1975) and thus decrease its self-administration.

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