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Iboga compounds reverse the behavioural disinhibiting and corticosterone effects of acute methamphetamine: Implications for their antiaddictive properties

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Abstract

This study investigated the effects of pretreatment with the putative antiaddictive compound, ibogaine (IBO), and its synthetic derivative, 18-methoxycoronaridine (18-MC), on the changes in behaviour in an elevated plus maze and the changes in corticosterone (CORT) produced by a low dose of methamphetamine (METH). In the elevated plus maze, the acute administration of METH (0.1 mg/kg ip, −20 min) produced an increase in both the number and the duration of open arm entries relative to saline (SAL)-treated controls. No effect of METH administration was observed on the total number of arm entries. These data indicated that METH alone produced either anxiolysis or behavioural disinhibition in this paradigm. More consistent with the latter possibility, the open arm behaviour of METH controls was associated with an increase in plasma levels of CORT, supporting a facilitatory role for CORT in this METH-induced effect. Pretreatment with both IBO and 18-MC (40 mg/kg ip, 19 h earlier) antagonized the behavioural disinhibiting effects of acute METH without altering locomotor activity. In addition, both *iboga* agents antagonized the increase in CORT produced by METH. These data provide insight into yet another potential mechanism through which *iboga* compounds may exert their antiaddictive effects, a reversal of the behavioural disinhibiting properties of stimulant drugs. Furthermore, these data indicate that this reversal is related to effects of *iboga* compounds on the stimulation of neuroendocrine systems by stimulant drugs.

Keywords: Ibogaine; Methamphetamine; Elevated plus maze; Corticosterone; Anxiety; Drug addiction

1. Introduction

The naturally occurring indole alkaloid, ibogaine (IBO), is claimed to interrupt multiple aspects of addiction to psychomotor stimulant drugs, such as cocaine and the amphetamines (Lotsof, 1986). In support of this claim, pretreatment with both IBO and a synthetic derivative, 18-methoxycoronardine (18-MC), produces a protracted (up to 24 h) decrease in the self-administration of cocaine in laboratory rodents (Cappendijk and Dzoljic, 1993; Glick and Maisonneuve, 1998; Glick et al., 1999; Popik and Skolnick, 1999; Sershen et al., 1994). Recently, 18-MC was found to decrease dose-dependently the self-administration of methamphetamine (METH) in rats (Glick et al., 2000a). Currently, the precise mechanism through which *iboga* compounds decrease the self-administration of psychomotor stimulants remains unknown.

The results of studies of the behavioural pharmacological interactions between *iboga* agents and psychomotor stimulants demonstrate that both IBO and 18-MC (40 mg/kg, 19 h earlier) increase the intensity of the locomotor and stereotypic effects of several stimulant drugs, including cocaine (Maisonneuve and Glick, 1992; Maisonneuve et al.,1997; Szumlinski et al., 1999a,b,d,e), D-amphetamine (Blackburn and Szumlinski, 1997; Maisonneuve et al., 1992), and METH (Szumlinski et al., 2000a,b). To reconcile the antiaddictive properties of *iboga* compounds with their ability to potentiate the intensity of stimulant-induced

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psychomotor activation, we proposed that one mechanism through which *iboga* compounds decrease stimulant self-administration might involve an increase in the aversive, anxiogenic properties of stimulant drugs (Maisonneuve and Glick, 1992; Szumlinski et al., 2000c). This hypothesis was based upon several lines of evidence. First, the administration of psychomotor stimulant drugs can induce anxiety in humans, an effect that is typically considered aversive (Angrist and Gershon, 1970; Cohen, 1975; Ellinwood, 1967; Jaffe, 1990). Second, in laboratory animals, stimulants can generalize to anxiogenic compounds (e.g., pentylenetetrazol; Shearman and Lal, 1981; Wood and Lal, 1987; Wood et al., 1989), an effect that is blocked by pretreatment with the prototypical anxiolytic, diazepam (Wood et al., 1989). Third, studies using various animal models of anxiety, for example, defensive withdrawal (Wood et al., 1989), elevated plus maze (Pellow et al., 1985; Yang et al., 1992 but see Olausson et al., 1999, 2000), the mouse defensive battery test (Blanchard and Blanchard, 1999), black/white two-compartmental shuttle box (Costall et al., 1989), and drinking conflict tests (Fontana and Commisaris, 1989), demonstrated that stimulant drugs can produce anxiety-like behaviours. Lastly, a number of studies demonstrate that the administration of psychomotor stimulant drugs can activate the hypothalamo–pituitary–adrenal (HPA) axis (e.g., Moldow and Fischman, 1987; Richter and Weiss, 1999; Sarnyai, 1998; Schmidt et al., 1995) and can augment plasma levels of the putative physiological index of anxiety, corticosterone (CORT; e.g., Moldow and Fischman, 1987; Richter and Weiss, 1999; Schmidt et al.,1999; Shibata et al., 1995; Yang et al., 1992 but see Mittleman et al., 1991).

To test the hypothesis that *iboga* pretreatment increases stimulant-induced anxiety, rats were pretreated (19 h earlier) with IBO, 18-MC, or vehicle (VEH) and injected acutely with a low dose of METH. The behaviour of the animals was assessed using a traditional behavioural anxiety paradigm, the elevated plus maze (Lister, 1987). To relate the behaviour of the animals to a physiological index of anxiety, plasma CORT levels were determined.

2. Methods

2.1. Animals

Subjects were female Sprague–Dawley rats (Taconic, NY) weighing 225–250 g at the beginning of the experiment. Females were selected for this study for two reasons. First, females tend to show augmented behavioural responding to psychomotor stimulant drugs, compared to males, and thus were expected to exhibit a greater degree of METH-induced open arm behaviour than would male rats. Second, as the effects of *iboga* pretreatment on METH self-administration (Glick et al., 2000a) and METH-induced motor behaviour (Szumlinski et al., 2000a,b) have been characterized only in females, consistency in the sex of the subjects was maintained to facilitate generalization across studies. Animals were housed in groups of four and allowed food and water ad libitum. The animals were maintained on a 12-h light cycle (lights on at 07:00 h) in a room carefully controlled for heat (25°C) and humidity (57%). Animals were allowed to acclimatize undisturbed to the colony room for 4–5 days prior to testing. To control for diurnal variation in plasma CORT (e.g., Kalsbeek et al., 1996), experiments began precisely at 09:00 h and blood sampling occurred between 10:30 and 11:30 h.

2.2. Drugs

IBO hydrochloride (40 mg/kg; Sigma) was dissolved in sterile water and (±)-18-MC hydrochloride (40 mg/kg; Albany Molecular Research, Albany, NY) was dissolved in a 0.01 M $NaPO_4$ buffer (pH = 6). The buffer served for pretreatment control injections (VEH). All pretreatment injections were administered at a volume of 2.0 ml/kg. METH hydrochloride (0.1 mg/kg; Sigma) was dissolved in saline (SAL) and injected at a volume of 1.0 ml/kg. SAL served for METH control injections. All injections were administered intraperitoneally (ip).

2.3. General design and procedures

Consistent with previous studies of locomotion (e.g., Maisonneuve et al., 1992; Szumlinski et al., 2000c), rats were randomly assigned to receive a pretreatment injection of IBO, 18-MC (both at 40 mg/kg ip), or VEH. Also consistent with previous locomotor studies (Szumlinski et al., 2000c), the pretreatment injections occurred in the colony room and were staggered such that pretreatment occurred 19 h prior to the test injection. On the next day (09:00 h), animals were transported in their home cages to a darkened, noncolony, experimental room, which was illuminated by a fluorescent lamp placed in the corner of the room. Animals were weighed and then allowed to habituate to the experimental room for 1 h. At this time, animals received a test injection of either METH (0.1 mg/kg ip) or SAL, such that four groups were tested in all: VEH–SAL, VEH–METH, IBO–METH, and 18-MC–METH ($n = 6$ per group). IBO–SAL and 18-MC–SAL animals were not tested in this particular study as their dose-related effects on elevated plus-maze behaviour had been characterized prior to this study under virtually identical conditions (Glick et al., 2000b). Twenty minutes following SAL/METH administration, animals were tested in the elevated plus maze (see Behavioural procedures below). Immediately following this test (approximately 30 min post-test injection), animals were sacrificed and trunk blood collected for determination of plasma CORT levels (see Plasma CORT below).

2.4. Behavioural procedures

The elevated plus maze was a black, Plexiglas, plus-formed maze, elevated 50 cm from the floor. The arms of the plus maze were 40 cm long and 10 cm wide. Two opposing arms were surrounded by 10-cm high black walls (closed arms), while the other arms were devoid of walls (open arms). An experimenter who was blind to the pretreatment of the animals conducted the testing. For testing, rats were placed in the center of the elevated plus maze, facing a closed arm (-20 min post-test injection; -19 h and 20-min post-pretreatment injection). Animals were allowed to explore the elevated plus maze for 5 min, undisturbed. The behaviour of the animals was videotaped using a camera located above the center of the maze, permitting visualization of approximately 10 cm into each arm. Upon completion of the test, the animal was removed from the maze, placed in an unfamiliar cage, and removed from the room. The maze was cleaned with 70% ethanol between tests. The videotapes were subsequently scored for the number of open and closed arm entries and the percent of time the animals spent in the open arms. The total number of arm entries served as an index of locomotor hyperactivity. An arm entry was counted only when the entire length of the rat's body (from nose to base of tail) entered into an arm.

2.5. Plasma CORT

Immediately following elevated plus-maze testing, animals were sacrificed by decapitation and the trunk blood was collected into a beaker, which was rinsed with 500 μl of 1000 USP porcine heparin. Blood was then transferred to chilled centrifuge tubes containing 10 μl of 1000 USP porcine heparin. Samples were centrifuged at 10 000 rpm in a refrigerated (4°C) table-top centrifuge for 20 min. Plasma was decanted and stored at -80°C until analysis. Plasma CORT levels were determined using an Immunochem double antibody CORT radioimmunoassay (RIA) kit (ICN Pharmaceuticals, Costa Mesa, CA). Data were expressed as μg CORT/dl plasma.

2.6. Statistical analysis

The data were examined using a one-way analysis of variance (ANOVA) followed by Duncan's multiple range post hoc tests. All analyses were two-tailed.

3. Results

3.1. Elevated plus maze

Statistical analysis revealed a significant Group effect for both the percent of time in the open arm [$F(3,24)=4.77$, $P<.01$] and the number of open arm entries [$F(3,24)=3.33$, $P<.04$]. As can be observed in Fig. 1, the acute administration of METH (0.1 mg/kg) increased both the duration and number of open arm entries (post hoc tests). Inspection of Fig. 1 suggested that both IBO and 18-MC pretreatment (40 mg/kg, 19 h earlier) reversed the effect of METH on open arm behaviour. Post hoc analysis revealed that the effect of *iboga* pretreatment was statistically significant for the percent of time in the open arm (for IBO, $P<.008$; for 18-MC, $P=.05$) but was only marginal for the number of open arm entries (for IBO, $P<.09$; for 18-MC, $P<.07$). No difference in the total number of arm entries was observed between any of the groups tested [$F(3,24)=1.10$, $P=.37$].

3.2. Plasma CORT

Statistical analysis revealed a significant Group effect on plasma CORT levels [$F(3,24)=2.8$, $P<.03$]. As can be observed from Fig. 2, the acute administration of METH (0.1 mg/kg) to control rats produced a modest increase in plasma CORT relative to their SAL-treated counterparts ($P=.05$, post hoc tests). Pretreatment with both IBO and 18-MC (40 mg/kg) reversed the effects of

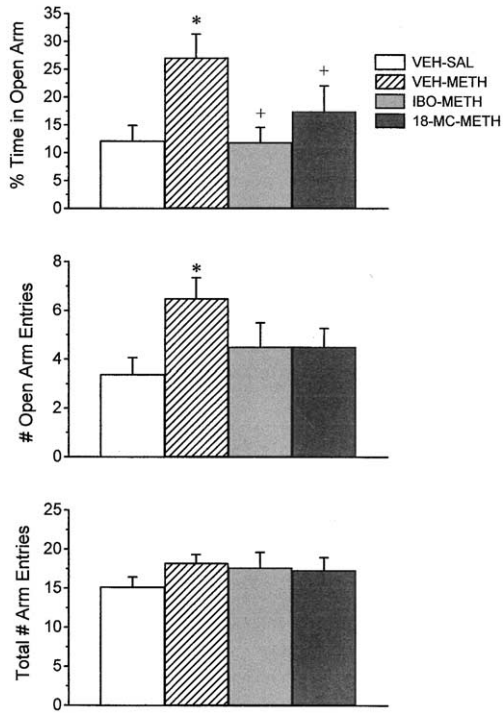

Fig. 1. Effects of pretreatment with IBO, 18-MC (both at 40 mg/kg), or VEH on the behaviour of rats treated acutely with METH (0.1 mg/kg) or SAL in the 5-min elevated plus-maze test ($n=6$ per group). *Iboga* pretreatment injections occurred 19 h prior to METH/SAL injection and animals were tested 20 min following METH/SAL administration. Acute METH administration increased significantly both the percent of time in (top) and the number of entries into (middle) the open arm of the plus maze (* $P<.05$ vs. VEH–SAL, post hoc tests). These effects were reversed by both IBO and 18-MC pretreatment ($^{+}P<.05$ vs. VEH–METH, post hoc tests). No difference in the total number of arm entries was observed between the test groups (one-way ANOVA, $P>.05$).

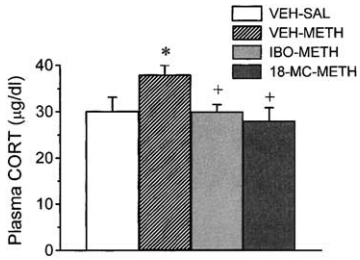

Fig. 2. Effects of pretreatment with IBO, 18-MC (both at 40 mg/kg), or VEH on the plasma levels of CORT of rats treated acutely with METH (0.1 mg/kg) or SAL in an elevated plus-maze test ($n=6$ per group). Sampling occurred immediately following the elevated plus-maze test. Acute METH administration increased plasma levels of CORT (* $P<.05$ vs. VEH–SAL, post hoc tests) and this effect was reversed by both IBO and 18-MC pretreatment ($^{+}P<.05$ vs. VEH–METH, post hoc tests).

METH on plasma CORT (for IBO, $P=.05$; for 18-MC, $P=1.04$, post hoc tests).

4. Discussion

The present study aimed to investigate the effects of pretreatment with the putative antiaddictive drug, IBO, and its synthetic derivative, 18-MC, on METH-induced anxiety using a traditional animal model of anxiety, the elevated plus maze. To probe a potential mechanism mediating any changes in anxiety-related behaviour, the effects of pretreatment with *iboga* compounds on the changes in plasma CORT produced by METH administration were assessed. Based, in part, upon the results of previous studies of stimulant-induced motor behaviour (for review, see Szumlinski et al., 2000c), it was hypothesized that pretreatment with *iboga* compounds would increase METH-induced anxiety and this would be reflected both at the behavioural and the physiological level.

Consistent with the results of the majority of studies using the elevated plus maze (for reviews, see Pellow, 1986; Pellow et al., 1985), the SAL control rats in the present study spent approximately 12.5% of their time in the open arms. These data indicate that the exploratory behaviour of the control animals in the plus maze was inhibited (for discussion, see File et al., 1993; Ouagazzal et al., 1999; Pellow et al., 1985). In contrast, animals treated acutely with a low dose of METH (0.1 mg/kg ip) spent a greater amount of time in the open arms (approximately 27%) and entered the open arms approximately twice as often (6.5 vs. 3.5 entries). These data indicate that METH disinhibited normal closed arm behaviour, an effect indicative of anxiolysis, rather than anxiogenesis (see below for further discussion of this matter). This observation is, in fact, consistent with several other reports in which either the acute or the repeated administration of stimulant drugs increased open arm behaviour of rats (e.g., Dawson et al., 1995; Olausson et al., 2000; Weiss et al., 1998).

Interestingly, pretreatment with either IBO or 18-MC (19 h earlier) decreased significantly the amount of time and decreased marginally the number of entries in the open arms of the plus maze produced by METH. These findings are consistent with the results of the factor analysis and correlational studies of File et al., indicating that percent time in the open arm is a more sensitive variable to drug effects than the number of open arm entries (e.g., File et al.,1993; Ouagazzal et al., 1999; Pellow et al., 1985). Importantly, these data indicate that pretreatment with *iboga* compounds can produce a protracted (19 h) reversal of the behavioural disinhibiting effects of METH. These data for METH are particularly interesting in light of recent observations that, when administered alone, IBO produces effects on elevated place maze behaviour that are opposite to those produced by 18-MC. Compared to VEH-treated animals, IBO dose-dependently decreases, while 18-MC increases, the open arm behaviour of rats (Glick et al., 2000b). Based on these previous data, it does not appear likely that the ability of *both* IBO and 18-MC to reverse the effects of METH on elevated plus-maze behaviour can be attributed to their direct effects on anxiety. As is apparent in Fig. 1, the open arm behaviour of *iboga*-pretreated rats was virtually identical to but not greater or less than that of the VEH–SAL control.

In contrast to other reports of stimulant-induced behaviour in an elevated plus maze (e.g., Dawson et al., 1995; Olausson et al., 2000; Weiss et al., 1998), the low dose of METH administered in the present study did not increase the total locomotor activity of VEH-pretreated rats, as indexed by the total number of arm entries (see Fig. 1). Thus, the increase in open arm behaviour of the SAL–METH controls cannot be attributed to a nonspecific increase in hyperactivity. This observation is consistent with the results of File et al., demonstrating that measures of behavioural inhibition/disinhibition (i.e., percent time and percent entries in the open arms) and the total number of arm entries during the first exposure to the elevated plus maze are independent variables (e.g., File et al., 1993; Ouagazzal et al., 1999; Pellow et al., 1985). In further support of this, both IBO and 18-MC decreased the open arm behaviour of METH-treated rats without affecting the total number of arm entries. This finding is also consistent with the results of a recent locomotor activity study, which demonstrated that 18-MC pretreatment does not alter the motor behavioural effects of lower (<2.0 mg/kg) doses of METH in acutely treated animals (Szumlinski et al., 2000a). Thus, these data indicate that at a dose, which is supermaximal for attenuating METH self-administration (Glick et al., 2000a), *iboga* compounds exerted effects on open arm behaviour.

Compared to all other groups, the plasma levels of CORT were elevated in METH-injected animals when sacrificed 5 min following elevated plus-maze testing. These data are consistent with a large literature indicating that psychomotor stimulant administration activates the

HPA axis (e.g., Moldow and Fischman, 1987; Richter and Weiss, 1999; Sarnyai, 1998; Schmidt et al., 1995, 1999; Shibata et al., 1995; Yang et al., 1992), an action presumed to mediate their anxiogenic properties. Consistent with the results of preliminary work in our laboratory (Szumlinski et al., 2000b), *iboga* pretreatment reversed the changes in CORT produced by METH. However, in contrast to previous observations that increased plasma levels of CORT are associated typically with a decrease in open arm behaviour in the plus maze (Yang et al., 1992), increased plasma levels of CORT were associated with an increase in open arm behaviour (VEH–METH group). One interpretation of this data is that the behavioural disinhibiting effects of low doses of METH, and perhaps other stimulant drugs, masks or overrides their anxiogenic properties. Evidence in support of this interpretation can be derived from studies of addicted humans where it is clear that despite an increase in anxiety, be it drug-induced (e.g., Gawin and Kleber, 1985) or circumstance-related (i.e., fear of the financial, legal, or social repercussions resulting from their addiction; e.g., Falk et al., 1987), addicted individuals still display a loss of inhibitory control of their drug-taking behaviour (e.g., Goeders et al., 1998; Robbins and Everitt, 1999).

Alternatively, CORT may act as the substrate mediating the behavioural disinhibitory effects of METH administration. Despite evidence that the intracerebral administration of corticotrophin-releasing factor (CRF) can induce anxiety-like behaviours in defensive withdrawal paradigms (e.g., Butler et al., 1990), many reports have demonstrated that the administration of either CRF or CORT can increase exploratory behaviours in the center of an open field (e.g., Butler et al., 1990; Oitzl et al., 1994; Song et al., 1995, 1997). These data indicate that, in certain circumstances, activation of the HPA axis can induce a disinhibition of normal behaviour. Relating CORT and behavioural disinhibition to drug-addicted behaviours, a series of studies conducted by Piazza et al. demonstrated a positive relationship between behavioural disinhibition in locomotor activity paradigms, plasma CORT, and the propensity of rats to self-administer drugs of abuse (for reviews, see Piazza and Le Moal, 1996, 1998). Consistent with this relationship, manipulations that increase basal levels of CORT increase the tendency of laboratory animals to engage in drug-seeking behaviours (e.g., Deroche et al., 1997; Piazza et al., 1991); conversely, manipulations that decrease basal levels of CORT decrease drug-seeking behaviours (e.g., Goeders and Guerin, 2000; Goeders et al., 2000; Piazza and Le Moal, 1996; Piazza et al., 1994). Also consistent with these findings, a study of cocaine self-administration demonstrated that, compared to unstressed controls, stressed rats maintain higher levels of bar-pressing behaviour during time-out periods (i.e., times when responding on the lever does not produce a drug infusion; Miczek and Mutschler, 1996). From these data, it has been suggested that stress (and presumably the elevation in CORT associated with stress) can increase the behavioural disinhibition or "impulsivity" (Miczek and Mutschler, 1996) of animals in a drug self-administration setting. The present data are consistent with these findings in that two "antiaddictive" compounds, IBO and 18-MC, reversed the behavioural disinhibiting and CORT effects of METH. Thus, the possibility exists that the ability of *iboga* compounds to reverse the behavioural disinhibiting effects of METH are related to a suppression of HPA activation.

Lastly, in addition to its facilitation of drug self-administration behaviour, CORT itself can serve as a positive reinforcer in self-administration paradigms (Deroche et al., 1993; Piazza et al., 1993). In light of such findings, the present data raise the possibility of yet another mechanism through which *iboga* compounds decrease the self-administration of stimulant drugs, namely an attenuation of the reinforcing properties of stimulants via a suppression of CORT secretion.

The data in the present study provide the first evidence that *iboga* pretreatment can alter drug-induced changes in behaviour in the elevated plus maze, an effect associated with circulating plasma levels of CORT. Despite the debates surrounding interpretation of elevated plus-maze behaviour, these data provide evidence that *iboga* pretreatment alters the psychological consequences of drug administration (be it anxiety and/or a reduction in inhibitory control), effects that may prove to contribute to their unique ability to reduce the self-administration of a wide variety of drugs of abuse. Furthermore, these data raise the possibility that the effects of *iboga* compounds on stimulant-induced behavioural disinhibition, and perhaps also reinforcement, might be related to their ability to reverse the neuroendocrine response to stimulant drugs.

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