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The Effect of Ibogaine on κ-Opioid- and 5-HT$_3$-Induced Changes in Stimulation-evoked Dopamine Release In Vitro from Striatum of C57BL/6By Mice

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ABSTRACT: Ibogaine is an indole alkaloid that has been suggested to have potential efficacy for interrupting dependency on stimulant drugs. The κ-opioid and serotonin 5-HT$_3$ systems may be involved in the action of ibogaine, related to their modulation of dopaminergic transmission. The κ-opioid agonist U 62066 attenuated the in vitro stimulation-evoked efflux of tritium label from striatal tissue prelabeled with [$_3$H]dopamine. In mice pretreated with ibogaine·HCl (40 mg/kg IP given 2 h prior or 2 × 40 mg/kg and animals killed 18 h later), the inhibitory effect of U 62066 on stimulation-evoked release of tritium was eliminated. The 5-HT$_3$ agonist phenylbiguanide had a biphasic effect on stimulation-evoked release of tritium; at 10^{-6} M phenylbiguanide, stimulation-evoked release was attenuated. At 10^{-5} M the basal outflow of tritium was increased. Ibogaine pretreatment had no effect on basal or stimulation-evoked release in the presence of 10^{-6} M phenylbiguanide, but increased the stimulation-evoked outflow of tritium in the presence of 10^{-5} M phenylbiguanide. Cocaine (10^{-6} M), a dopamine uptake blocker, increased the electrically-evoked release of dopamine; ibogaine pretreatment did not affect the enhanced electrically-induced release of [^{3}H]dopamine by in vitro cocaine. The effects of ibogaine on the κ-opioid and 5-HT$_3$ receptors, located presynaptically on striatal dopamine terminals, modulating dopamine release may partly underlie its putative antiaddictive properties.

KEY WORDS: Key Words: Ibogaine, κ-opioid receptor, U 62066, 5-HT$_3$, Phenylbiguanide, Dopamine, Cocaine.

INTRODUCTION

Ibogaine (NIH 10567, Endabuse™) is an indole alkaloid that has been shown to antagonize cocaine-induced locomotor stimulation [25], preference for cocaine consumption in C57BL/6By mice [27], and cocaine-self-administration in rats [5]. Ibogaine has complex effects on neurotransmitter systems, affecting noradrenergic [8], dopaminergic [16,25,26], cholinergic [20], and serotonergic receptors [28]. A recent radioligand screen conducted in bovine and rat brain tissue found the affinity of ibogaine to be in the μM range for the voltage-dependent sodium channel ([^{3}H]BTX-B) and the κ-opiate receptor ([^{3}H]U-69593 binding site) [7]. Because it has been proposed that the κ-opioid activity of ibogaine, on the basis of its affinity to the [^{3}H]U-69593 binding site, may be responsible for its putative anti-addictive properties, we wanted to examine further the effect of ibogaine on κ-opioid receptor modulation of dopamine release, and whether other receptor sites are involved.

Initial studies with ibogaine, noting its structural similarity to serotonin, support an interaction with this system. Our data, indicating effects of ibogaine on the serotonin system [25], suggest that this could be relevant in its antiaddiction action, possibly through modulating dopamine release. Studies of cocaine habituation found that the cocaine binding site(s) associated with the dopamine and with the serotonin reuptake carriers [21] are involved in cocaine-induced locomotor activity, reward, and the reinforcing effects of cocaine. Recent studies indicate that presynaptic serotonin sites can modulate dopamine release; for example, serotonergic innervation of the anterior striatum may exert a facilitatory influence on dopamine release [2,3]. Presynaptic mechanisms (inhibition of reuptake) may mediate the discriminative stimulus, in addition to the reinforcing effects of cocaine [13]. Acute effects of ibogaine may be related to its action on the cytoplasmic pool of transmitter; for example, the stimulation of dopamine release, in the absence of Ca^{2+}, in the presence of inhibition of the voltage-sensitive Na^+ channels, and also in striata from reserpine-pretreated mice, would indicate release of transmitter primarily from the cytoplasmic pool [9]. Ibogaine's effect may relate also to alteration of stimulant drug-induced release of transmitter (dopamine). Ibogaine may alter the interaction and modulation of releasable pools of neurotransmitters [26] or alter modulation of dopamine release via interaction at other receptor sites, for example, the κ-opioid and serotonin receptors that are located presynaptically on dopamine terminals in the striatum.

Some interactions of these neurotransmitter systems, and their alteration by ibogaine, were examined in the present study, undertaken to determine whether ibogaine altered the κ-opioid- and 5-HT$_3$-induced modulation of stimulation-evoked release of striatal dopamine.

MATERIALS AND METHODS

Materials

Ibogaine HCl was purchased from Sigma Chemical Co. (St. Louis, MO). The kappa agonist (U 62066) and 5-HT$_3$ agonist

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TABLE 1

EFFECT OF IBOGAINE PRETREATMENT ON COCAINE, KAPPA-OPIOID, AND 5-HT_3-AGONIST-INDUCED MODULATION OF STIMULATION-EVOKED RELEASE OF TRITIUM FROM STRIATAL TISSUE PRELABELED IN VITRO WITH [^{3}H] DOPAMINE

Agonist	S1	S2	S2/S1
Control	2.55 ± 0.22	2.40 ± 0.22	0.94 ± 0.03 [6]
Ibogaine (2 h)	2.74 ± 0.31	3.24 ± 0.59	1.14 ± 0.12 [5]
Ibogaine (18 h)	1.45 ± 0.15	1.82 ± 0.28	1.25 ± 0.16 [6]
Dopamine Uptake Blocker			
Cocaine (10^{-6} M)	1.37 ± 0.31	2.86 ± 0.55	2.40 ± 0.59 [5]*
Ibogaine (2 h) + Cocaine (10^{-6} M)	2.04 ± 0.31	3.78 ± 0.37	2.02 ± 0.27 [6]*
Kappa Agonist			
U 62066 (10^{-6} M)	1.74 ± 0.29	0.84 ± 0.17	0.57 ± 0.09 [10]*
Ibogaine (2 h) + U 62066 (10^{-6} M)	2.13 ± 0.27	1.75 ± 0.27	0.90 ± 0.13 [10]†
U 62066 (10^{-6} M)	1.85 ± 0.27	1.03 ± 0.28	0.60 ± 0.19 [6]*
Ibogaine (18 h) + U 62066 (10^{-6} M)	1.89 ± 0.25	2.02 ± 0.20	1.10 ± 0.11 [6]†
5-HT_3 Agonist			
Phenylbiguanide (10^{-6} M)	2.59 ± 0.54	1.40 ± 0.33	0.55 ± 0.08 [6]*
Ibogaine (2 h) + Phenylbiguanide (10^{-6} M)	2.74 ± 0.65	1.59 ± 0.47	0.54 ± 0.12 [6]*

Mice were treated either with ibogaine·HCl (40 mg/kg, IP) and killed 2 h later or 2 times 40 mg/kg ibogaine (6 h apart) and killed 18 h later. Striata were dissected and incubated with [^{3}H]dopamine for 1 h. After a 1 h pre perfusion time, release of tritium was measured. The tissue was stimulated electrically during the 3rd (S1) and 13th (S2) collection period. Agonists were added during the 10th collection and remained until the end of the experiment. Release was expressed as the fractional release, for example, as the percentage release of radioactivity in the tissue at the time the release was determined, and the ratio of fractional release S2 over fractional release S1 (S2/S1) was calculated. Values are means ± SEM (Student's t-test, $p < 0.01$ * versus control, † versus agonist drug control).

phenylbiguanide were from Research Biochemicals Inc. (Natick, MA).

Animals and Treatment With Ibogaine

C57BL/6By adult male mice (25–30 g) were used. In the experimental group, mice were treated 2 h previously with ibogaine·HCl (40 mg/kg SC; Sigma Chemical Co., MO), or given two injections of ibogaine (40 mg/kg IP, spaced 6 h apart) and killed 18 h after the last injection. The mice were decapitated and striatal tissue was dissected and incubated for 60 min at 37°C in 0.5 ml of Krebs-bicarbonate buffer (in mM: NaCl 118, KCl 4.7, $CaCl_2$ 2.5, KH_2PO_4 1.2, $MgCl_2$ 1.2, $NaHCO_3$ 25, glucose 11.5, Na_2EDTA 0.03, ascorbic acid 0.3; pH 7.4) containing 1.25 μCi [^{3}H]dopamine (specific activity 26.7 Ci/mmol (Dupont, NEN). The reaction mixture was continuously gassed with an O_2/CO_2 mixture (95%/5%).

In Vitro Stimulation-evoked Release of ^{3}H-labeled Outflow

After prelabeling with [^{3}H]dopamine, the tissue (whole striatum, one side, 5 mg wet weight) was transferred to a superfusion chamber (0.3-ml reaction chamber, Brandel Superfusion 1200, MD) and pre-perfused at a rate of 0.4 ml/min for 60 min. Effluent was discarded during this period and thereafter 4-min fractions were collected for an additional 80 min. Release was induced by electrical field stimulation (40 V, 2 Hz frequency, 2 ms impulse, duration 1 min) applied in the 3rd (1st stimulation, S1) and 13th (2nd stimulation, S2) collection periods. Cocaine (10^{-6} M), the κ-opioid agonist U 62066 (10^{-6} M), or the 5-HT_3 agonist, phenylbiguanide (10^{-5}-10^{-6} M) was added starting with the 10th collection period for the remainder of the perfusion. The release of tritium was expressed as fractional release, as the percentage release of the radioactivity content above base line in the tissue at the time the release was determined, and as the ratio of fractional release S2 over fractional release S1 (S2/S1) was calculated. Since phenylbiguanide also increased resting (basal) release, data were given as means of the fractional release at each collection period.

In previous studies [4,9,25], [^{3}H]dopamine was separated from its main ^{3}H-labeled metabolites. Enhanced tritium efflux evoked by electrical stimulation was mainly due to the increase in the outflow of [^{3}H]dopamine. Nevertheless, for accuracy release is expressed as ^{3}H-labeled outflow.

RESULTS

Under control conditions, no drugs added in vitro, the S2/S1 ratio was 0.94 ± 0.03. Ibogaine pretreatment did not affect the stimulation-evoked release of tritium in the absence of drug in the perfusion fluid (Table 1).

Effect of Ibogaine on Cocaine-induced Dopamine Outflow

Cocaine increased the stimulation-evoked release of tritium (Table 1). Ibogaine pretreatment did not alter the cocaine-induced response.

Effect of Ibogaine on κ-opioid Agonist (U 62066)-induced Dopamine Outflow

Striatal tissue were superfused continuously and stimulated two times with U 62066 present during the second stimulation. The κ agonist U 62066 inhibited the stimulation-evoked release of tritium by approximately 40% (S2/S1, $p < 0.01$) (Table 1). No effect on basal release was observed. When the mice were first pretreated with ibogaine (2 or 18 h prior), the effect of U 62066 on stimulation-evoked release of tritium was abolished.

Effect of Ibogaine on 5-HT_3 Agonist-induced Dopamine Outflow

With 10^{-6}M phenylbiguanide present during the second stimulation, no effect was seen on basal release. However, stimulat

tion-evoked release of tritium was reduced by about 40% (S2/S1, $p < 0.01$) (Table 1). In striata from ibogaine-pretreated mice, the reduction of evoked release of tritium by 10^{-6} M phenylbiguanide was unchanged (Table 1).

At 10^{-5}M phenylbiguanide, basal release of tritium was enhanced (Fig. 1, upper panel—1 electrical stimulation), with no effect on stimulation-evoked release (data not shown). Ibogaine pretreatment had no effect on the increase in basal release (upper panel without stimulation). The stimulation-evoked release of tritium from ibogaine pretreated striata was increased and prolonged (Fig. 1, lower panel).

DISCUSSION

This study further investigated the mechanism of action of ibogaine related to its attenuation of behavioral responses to cocaine administration. Based on ibogaine's affinity to the κ-opioid receptors and similarity to serotonin, to cocaine's action on dopamine reuptake blockade, and to κ-opioid and serotonin modulation of dopamine release, the effect of ibogaine on their presynaptic modulation of dopamine release was examined in striatal tissue utilizing in vitro perfusion electrically-evoked release techniques.

Ibogaine itself shows weak affinity to the dopamine transporter site in striatal tissue labeled with [^{3}H]WIN 35, 248 (cocaine analog) or [^{3}H]GBR-12935, and ibogaine did not alter [^{3}H]WIN 35, 248 binding after prior treatment in vivo [25]. Consonant with the lack of effect of ibogaine on the dopamine transporter was the absence of an effect of ibogaine on the enhancement of electrically-induced [^{3}H]dopamine release by in vitro cocaine (10 μM). This does not necessarily imply that the release process was not affected, since decreased uptake of [^{3}H]dopamine has been observed in the striatum after repeated treatment with amphetamine [30] in the absence of changes in [^{3}H]GBR-12935 binding [1]. Ibogaine added acutely in vitro has been shown to release dopamine, primarily from the cytoplasmic pool [9]. These acute effects may relate to the hallucinogenic action of ibogaine. The present study therefore examined the addition of ibogaine in vivo to evaluate both its long-term action and characterize its possible action at other sites. Since ibogaine pretreatment did not influence the stimulated dopamine release in the presence of cocaine, it is likely that the dopamine uptake blockade by cocaine was not affected by ibogaine. This would suggest an action of ibogaine and cocaine at other sites in addition to the reuptake transporter. Release of dopamine under control conditions was not influenced by pretreatment with ibogaine, suggesting also that the action of ibogaine must act on some modulatory site that will show a response only after activation with, for example, with stimulant drugs.

Further complicating the understanding of the mechanism of action of ibogaine, we showed that ibogaine was able to attenuate the locomotor stimulation in mice induced by cocaine [25], preference for cocaine consumption [27], and to attenuate or stimulate the locomotor activity induced by amphetamine in mice and rats, respectively [26]. These behavioral differences may relate to the strain dependent alteration by ibogaine of the stimulation-evoked release of [^{3}H]dopamine induced by amphetamine, with stimulation-evoked release attenuated in mice and increased in rats.

It has been shown that inhibitory κ-opioid receptors are located presynaptically on dopamine terminals and can modulate transmitter release [12,17]. The stimulation-evoked tritium overflow from slices preloaded with [^{3}H]dopamine was significantly reduced by the κ-agonist U-50,488, but not by μ- or δ-opioid receptor selective drugs [17]. The κ agonist U-69593 was also

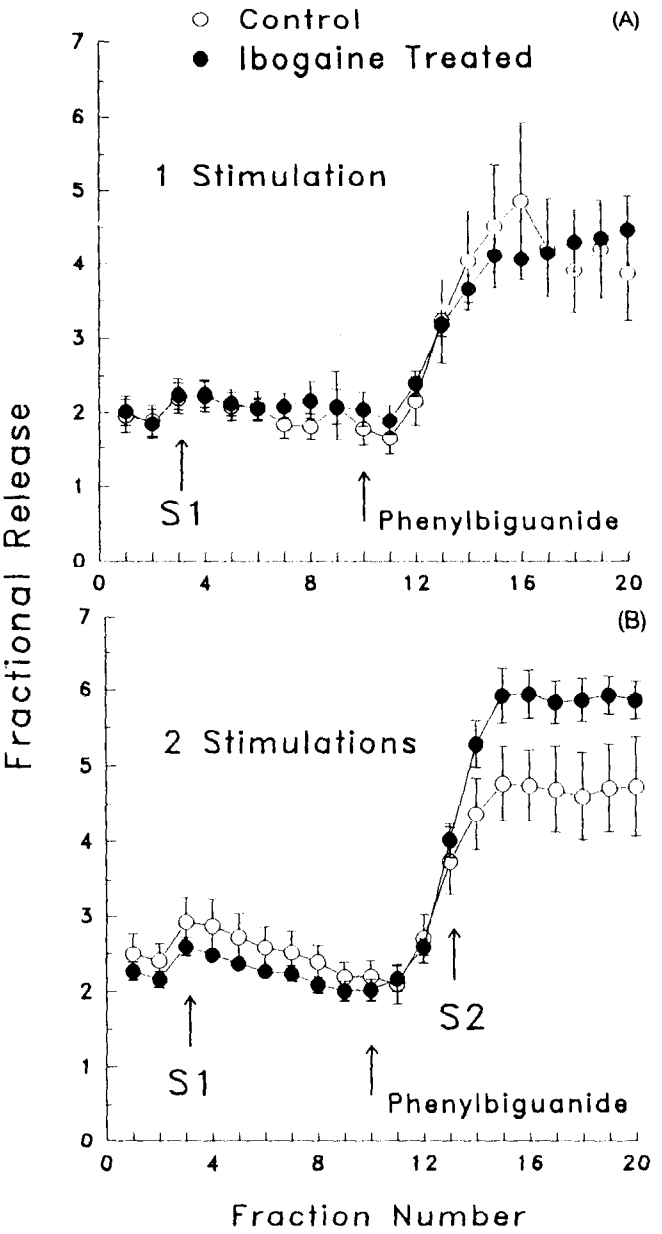

FIG. 1. Effect of ibogaine on phenylbiguanide-induced changes in basal and stimulation-evoked release of tritium from striatal tissue prelabeled with [^{3}H]dopamine. In the upper panel (A) the tissue was stimulated electrically (40 volts, 2 Hz, 2 ms pulse duration for 1 min) at the 3rd collection period. Phenylbiguanide (10^{-5} M) was added during the 10th collection period and remained until the end of the experiment. Solid circles represent tissue from ibogaine-pretreated mice (40 mg/kg IP, 2 h prior to killing). In the lower panel (B), two electrical stimulations were given. Phenylbiguanide was added as above. Values are the mean ± SEM of fractional release for each collection period (mean average of fractions 13 to 20 for control (4.54 ± 0.12) versus ibogaine treated (5.58 ± 0.24), $p < 0.01$, $n = 8$).

shown to attenuate cocaine-induced behavioral sensitization [10], and the agonist U50-488H may be involved in cocaine-induced conditioned place preference [29]. In the present study, the κ agonist U 62066 like U50488 reduced stimulation-evoked release of dopamine. Kappa agonists may decrease the effects of cocaine

by restricting cocaine's ability to enhance dopaminergic transmission [10]. Kappa receptors appear to mediate inhibition of evoked [^{3}H]dopamine release from nucleus accumbens via a decrease in Ca^{2+} conductance, an effect that may be modulated by ibogaine via its affinity to the kappa receptor. Activation of μ and δ opioid receptors enhance K^+ conductance resulting in inhibition of [^{3}H]ACh release [11]. The lack of effect of the kappa agonist on dopamine release after ibogaine pretreatment may relate to loss of modulatory or feedback control of dopamine release via this system.

Additionally, ibogaine has structural similarities to serotonin and in particular to 5-HT$_3$ antagonists. The 5-HT$_3$ system also has a modulatory role in dopaminergic activity. Recent studies indicate that presynaptic serotonin sites can modulate dopamine release; for example, serotonergic innervation of the anterior striatum may exert a facilitatory influence on dopamine release [2]. Presynaptic mechanisms (inhibition of reuptake) may mediate the discriminative stimulus, in addition to the reinforcing effects of cocaine [13].

Effects of ibogaine vary regionally; ibogaine (40 mg/kg) decreased the extracellular level of DA in nucleus accumbens and striatum and increased it in the prefrontal cortex [15]. Long and Lerrin [14] have shown that ibogaine is a reversible competitive inhibitor of the active transport of serotonin into blood platelets similar to cocaine, amphetamine, and imipramine. Potentiation of the hexobarbital hypnosis produced by serotonin and reserpine was blocked by ibogaine [23].

The dopamine releasing effect of 5-HT$_3$ agonists has been suggested to be due to their action at the site of 5-HT transport into dopaminergic terminals, rather than to activation of 5-HT$_3$ receptors [4,31] and release of vesicular dopamine into the cytoplasmic pool [4]. The effect of phenylbiguanide at 10^{-5} M on basal release of tritium may occur through a similar mechanism. The attenuation of stimulation-evoked release at lower concentrations (10^{-6} M), not reported by others, suggests a multiphasic mode of action. A bell-shaped dose-response curve has been reported for the attenuating effects of 5-HT$_3$ antagonists [6]. The role of the serotonin system becomes more apparent when the dopamine system is activated [18]. Similarly, differences in response to the 5-HT$_3$ agonist after ibogaine treatment were seen when the dopamine system was activated by electrical stimulation.

A number of neurotransmitter systems interact and function to modulate transmitter release; for example, the kappa and 5-HT receptors can modulate dopamine release. It was reported that kappa agonists [10] and 5-HT$_3$ antagonists [21,24] (or other 5-HT subtypes may be involved [19]) attenuate cocaine and amphetamine responses, suggesting that the modulation (feedback control) of these system can alter dopamine responses and can also be involved in the action of drugs of abuse. We think that ibogaine may alter cocaine responses, by interacting with 5-HT$_3$ and kappa receptor sites, thus altering subsequent dopaminergic responses to drugs of abuse. Alternatively, ibogaine may act on the kappa-opioid and serotonin receptors located presynaptically on striatal dopamine terminal altering their responsiveness, and subsequently modulation of dopamine release. How ibogaine effects the kappa and 5-HT$_3$ receptor sites is not known, although it has affinity to these sites [7,28]. The effects are long lasting, which also agrees with our behavioral studies. Whether the effect of ibogaine is also related to changes in the releasable pools of dopamine to stimulant drugs needs further study.

A number of studies showed that neurotransmitter systems interact and regulate each other's function. Although many of the locomotor stimulant effects of drugs are thought to be mediated via dopamine release, and several hypotheses associated the dopaminergic system with the reinforcing effects of drugs, it is important to recognize that many neurotransmitter systems interact to produce their effects, and this should be considered in the long-term evaluation of the mechanism of action of ibogaine. As shown here, long-term ibogaine effects on the serotonergic and kappa-opioid receptor systems may underlie its modulation of stimulant drug-induced changes in dopaminergic receptor functioning. The understanding of the neurotransmitter system and its relationship to behavior will require understanding these interactions and their functional consequences, which also has relevance to the action of ibogaine in antagonizing drug abuse.

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