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Ibogaine and the inhibition of acetylcholinesterase

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ABSTRACT

Ethnopharmacological relevance: Ibogaine is a psychoactive monoterpine indole alkaloid extracted from the root bark of *Tabernanthe iboga* Baill. that is used globally in medical and nonmedical settings to treat drug and alcohol addiction, and is of interest as an ethnopharmacological prototype for experimental investigation and pharmaceutical development. The question of whether ibogaine inhibits acetylcholinesterase (AChE) is of pharmacological and toxicological significance.
Materials and methods: AChE activity was evaluated utilizing reaction with Ellman's reagent with physostigmine as a control.
Results: Ibogaine inhibited AChE with an IC_{50} of $520 \pm 40\,\mu M$.
Conclusions: Ibogaine's inhibition of AChE is physiologically negligible, and does not appear to account for observations of functional effects in animals and humans that might otherwise suggest the possible involvement of pathways linked to muscarinic acetylcholine transmission.

1. Introduction

The iboga alkaloids are a group of naturally occurring and synthetic monoterpine indole alkaloids, some of which reportedly reduce the self-administration of drugs of abuse and opiate withdrawal symptoms in animal models and humans (Alper, 2001; Glick et al., 2001; Alper et al., 2008). Ibogaine (Fig. 1) is the most abundant iboga alkaloid in the root bark of *Tabernanthe iboga* Baill., which grows in West Africa where eboga, the shavings of *T. iboga* root bark, has been used as a psychopharmacological sacrament in the Bwiti religion for several centuries (Fernandez, 1982). Outside of Africa ibogaine has been used with increasing frequency over the last 25 years, most often for detoxification from opiates (Alper et al., 1999, 2008).

The inhibition of acetylcholinesterase (AChE) could explain some functional effects of ibogaine that appear consistent with increased muscarinic cholinergic transmission. Ciba Pharmaceutical patented ibogaine for the indication of reducing tolerance to opioid analgesics (Schneider and McArthur, 1956; Schneider, 1957) and specifically suggested that AChE inhibition might mediate

the potentiation of morphine analgesia by ibogaine. Bradycardia, which can result from increased muscarinic cholinergic transmission among a variety of other causes, was observed in 6 of a series of 39 patients following single oral dose administrations of ibogaine (Mash et al., 1998), and has been reported anecdotally in medical (Kamlet, 2009) and nonmedical (Samorini, 1998) settings and in some preclinical studies (Schneider and Rinehart, 1957; Dhahir, 1971; Glick et al., 1999; Binienda et al., 2002). The apparently significant role of pre-existing cardiovascular medical comorbidities in deaths temporally associated with the use of ibogaine (Alper et al., in press) indicates the medical and toxicological relevance of bradycardia, which heightens the risk for fatal cardiac arrhythmia (Cubeddu, 2009). Ibogaine produces an atropine-sensitive EEG rhythm in animals (Depoortere, 1987; Schneider and Sigg, 1957) that has been attributed to muscarinic cholinergic input from the ascending reticular activating system (ARAS) on the basis of ablation experiments and suggested to involve the inhibition of AChE (Schneider and Sigg, 1957). The enhancement of spatial memory by ibogaine in preclinical models (Popik, 1996; Helsley et al., 1997) is another functional effect that could possibly relate to the inhibition of AChE in view of the use of AChE inhibitors to treat memory impairment in dementias (Birks, 2009).

Studies performed in the 1940s found that ibogaine obtained by crystallization from extract of *T. iboga* root bark inhibited AChE from horse serum, sheep brain, and dog pancreas with an IC_{50} of approximately $150\,\mu M$ (Vincent and Sero, 1942; Vincent and Lagreu, 1949). These early studies utilized a manometer for gasometric

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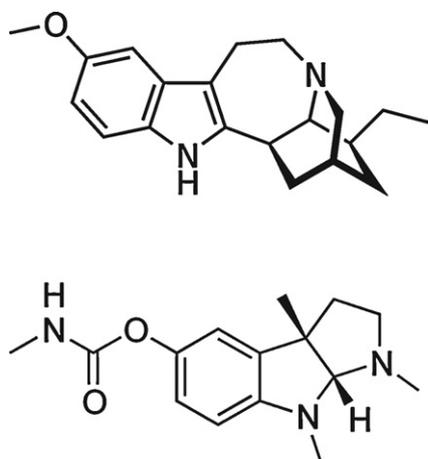E-mail address: kra1@nyu.edu (K. Alper).

Fig. 1. Chemical structures of ibogaine (top) and physostigmine (bottom).

Fig. 2. Inhibitory effects of physostigmine and ibogaine on cholinesterase activity measured in vitro utilizing the acetylcholine pseudo-substrate ACTI and Ellman's reagent in the presence of enzyme (AChE, 0.19 U).

determination of rates of AChE inhibition, which predated the contemporary colorimetric approach (Ellman et al., 1961; Järvinen et al., 2010), and raises questions regarding the accuracy of their estimates. In these early studies *T. iboga* root bark extract produced a greater degree of AChE inhibition than the crystallisate, suggesting an effect due to additional alkaloids other than ibogaine in the root bark. Other studies have evaluated the inhibition of AChE by crude extracts that included various iboga alkaloids from *Tabernaemontana australis* (Müell. Arg) Miers (Andrade et al., 2005) or *Tabernaemontana divaricata* R.Br. ex Roem. & Schult (Ingkaninan et al., 2006; Chattipakorn et al., 2007; Nakdook et al., 2010; Pratchayasakul et al., 2010). In view of the need for a contemporary laboratory investigation focused specifically on ibogaine with its purity established by current chemical analytical techniques, this present study utilized ibogaine in the HCl form, and an assay based on reaction with Ellman's reagent to evaluate the inhibition of AChE (Ellman et al., 1961; Järvinen et al., 2010).

2. Methods

2.1. Materials

Chemicals were purchased from Sigma–Aldrich (St. Louis, MO): 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB – D218200), acetylthiocholine iodide (ACTI – A5751), – acetylcholinesterase from Electrophorus electricus, (AChE – C3389-2KU, ~236 U/mg), physostigmine (Fig. 1) (E8375). Ibogaine HCl was obtained from Slater & Frith Ltd, UK (assay analysis 95%) (Slater and Frith LTD., 2008). Most of the remaining 5% was ibogamine with lesser amounts of ibogaline and tabernanthine (Martin Kuehne, personal communication) (Slater and Frith LTD., 2008).

2.2. AChE assay and analysis

AChE activity was measured in vitro based on a reaction with Ellman's reagent (Ellman et al., 1961) and as recently described (Järvinen et al., 2010). AChE catalyses the hydrolysis of the substrate ACTI to form thiocholine, which reacts with 5,5′-dithio-bis(2-nitrobenzoic acid) (DTNB, Ellman's reagent) to produce a colored anion. The final concentration of the reagents in the reaction cuvette was 1.36 mM DTNB, 2.7 mM ATCI, and 0.19 U AChE, and the addition of inhibitor in a 4 ml final volume. Reagents/inhibitors were dissolved in 50 mM Tris–HCL buffer (pH 8). The reaction was started with addition of the substrate (ACTI) and detected with a Shimadzu UV-VIS recording spectrophotometer (Model UV-160) at 412 nm wavelength. After addition of substrate, absorbance
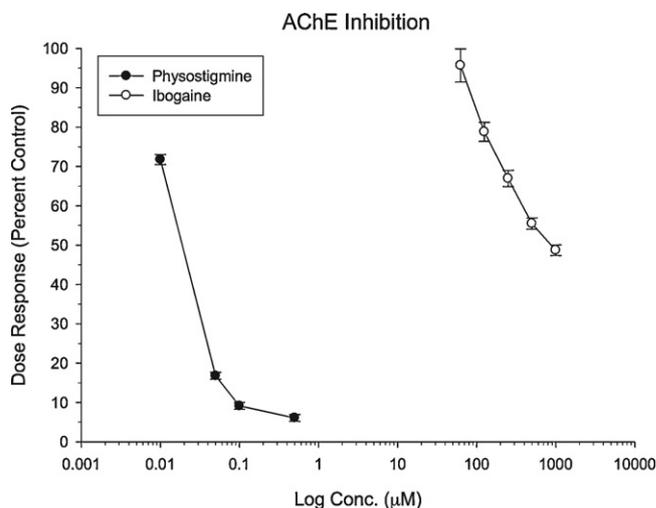
recordings were taken for 6 min. Ibogaine and physostigmine were initially tested at 1, 10, and 100 µM concentrations to determine inhibition–dose range; subsequent assays were conducted at the dose–inhibition range shown in Fig. 2. Two control curves were collected in the absence of inhibiting compound, one at the beginning of the experiment prior to testing varying concentrations of compound, and a second at the end after compound testing. The two control curves were almost identical and were averaged for subsequent analysis. AChE activity per minute was computed for control and drug concentrations, and IC_{50} values were estimated by nonlinear computer curve-fitting procedures. Specifically, the ALLFIT equation for drug inhibition (DeLean et al., 1978) was used, which equals the logistic model in the Origin software (Origin-Lab Corp., Northampton, MA, USA). Analysis of the multiple drug concentration inhibition data by computer fitting with the ALLFIT equation provided the standard deviations given in the text.

3. Results and discussion

The IC_{50} for the inhibition of AChE by ibogaine was 520 ± 40 µM (Fig. 2). The IC_{50} of physostigmine at a substrate concentration of 2.7 nM ACTI with AChE from electric eel was 18.4 ± 1.8 nM, which is comparable to recently reported values for IC_{50} for inhibition of AChE by physostigmine of 40 nM with AChE from electric eel (Järvinen et al., 2010), and 40 nM and 20 nM in rat and human neocortex respectively (Jackisch et al., 2009). In this study the activity of physostigmine's inhibition of AChE was greater than that of ibogaine by a factor of 2.8×10^4, whereas Vincent et al. found that physostigmine was more active than ibogaine obtained by crystallization of *T. iboga* root bark extract by a factor of approximately 3×10^3 (Vincent and Sero, 1942; Vincent and Lagreu, 1949). The relative AChE inhibition activity of ibogaine compared to physostigmine observed in this study is approximately an order of magnitude less than the earlier results reported by Vincent et al., and suggests that the crystallisate in their study may have contained other compounds that inhibit AChE. Voacangine has been isolated from *T. iboga* root bark (Dickel et al., 1958) and reportedly inhibits AChE at the same concentration as the reference compounds physostigmine and galantamine (Andrade et al., 2005). Ibogaine co-occurs with voacangine in *T. divaricata* (Kam et al., 2004), a species that produces particularly strong AChE inhibition among plants used in Thai traditional medicine (Ingkaninan et al., 2003), and other alkaloid and non-alkaloid constituents of *T. divaricata* that could

inhibit AChE (Chattipakorn et al., 2007) might possibly co-occur with ibogaine in *T. iboga* as well.

The results reported here indicate that the effect of ibogaine on the inhibition AChE is likely physiologically negligible. Reported observations of ibogaine levels in the human brain are limited to two autopsied cases. One case involved an individual who took an estimated dose of 16–20 mg/kg of ibogaine HCl taken orally (Alper et al., in press), which is within the dosage range often used for opioid detoxification. The half-life of ibogaine in humans is reportedly approximately 4–7.5 h (Mash et al., 2000; Kontrimavičiūtė et al., 2006). This individual died 8–9 h following ingestion with a brain level of 18.6 mg/kg (60.0 μM). In the other case, the brain ibogaine level obtained an estimated 53 h following the ingestion of dried root bark was 12.5 mg/kg (40.3 μM) (Kontrimavičiūtė et al., 2006). The possible effect of a post-mortem artifact regarding concentrations of ibogaine in human brain tissue is unknown, however even the largest reported postmortem human brain concentration, which is 60 μM (Alper et al., in press) would correspond to a level of inhibition of AChE of only 8% based on the ALLFIT equation for drug inhibition applied to the data shown in Fig. 2 (DeLean et al., 1978). In the cases described above, the concentrations of ibogaine in postmortem peripheral blood were lower than in brain tissue. In the rat, the dosage of ibogaine that is most commonly utilized and consistently produces reductions in the self-administration of drugs and alcohol and signs of opioid withdrawal is 40 mg/kg administered intraperitoneally (Alper, 2001; Glick et al., 2001), and the reported half-life of ibogaine is in the range of approximately 1–2 h (Dhahir, 1971; Baumann et al., 2001). The concentration of ibogaine in the rat brain after 1 h following intraperitoneal administration is 10 μM (Hough et al., 1996), and the peak blood concentration reported in rats is 12.4 μM (Baumann et al., 2001).

To put these results into a clinical context, the IC$_{50}$ in human brain tissue of rivastigmine, which is the least potent among AChE inhibitors approved in the United States for the treatment of Alzheimer's dementia, is 9.1 μM (Jackisch et al., 2009), which is still well over an order of magnitude more potent than ibogaine. Rivastigmine administered to human subjects produced a maximum inhibition of cerebrospinal fluid (CSF) AChE activity of 60% when administered as a single unit dose (Novartis Pharmaceuticals Corporation, 2006), and 36% after treatment for 12 months (Darreh-Shori et al., 2002). The prescribing information indicates that bradycardia did not occur in clinical trials at a rate greater than that observed with placebo in with patients receiving rivastigmine therapy over time intervals on the order of months (Novartis Pharmaceuticals Corporation, 2006). The apparently low incidence of bradycardia with a substantially more potent AChE inhibitor than ibogaine argues against AChE inhibition as a mechanism accounting for bradycardia associated with ibogaine. An alternative explanation could involve ibogaine's low micromolar affinity for sodium channels (Deecher et al., 1992; Sweetnam et al., 1995; Glick et al., 2001), in view of the association of sodium channel blockade with bradycardia (Kolecki and Curry, 1997).

This study did not evaluate AChE inhibition with regard to noribogaine, the principal metabolite of ibogaine (Staley et al., 1996). Both ibogaine and noribogaine bind weakly to M1 or M2 muscarinic cholinergic receptors (mAChRs) with reported affinities generally in the range of approximately 5–30 μM (Repke et al., 1994; Sweetnam et al., 1995; Staley et al., 1996; Glick et al., 2001), although the functional effect of this interaction has not apparently been investigated. The association of ibogaine with an atropine-sensitive EEG rhythm is not necessarily conclusive evidence for an agonist effect at mAChRs per se, because some electrical or pharmacological manipulations of the ARAS can produce an atropine-sensitive EEG rhythm without the administration of cholinergic agents (Bradley and Key, 1958; White and Daigneault, 1959).

In conclusion, Ibogaine inhibits AChE with an IC$_{50}$ = 520 $\pm$ 40 μM. This result suggests that the inhibition of AChE by ibogaine physiologically is negligible, and is unlikely to account for functional effects that might otherwise be viewed as suggesting the possible involvement of pathways linked to muscarinic acetylcholine transmission.

Acknowledgment

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