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hERG Blockade by Iboga Alkaloids

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Abstract The iboga alkaloids are a class of naturally occurring and synthetic compounds, some of which modify drug self-administration and withdrawal in humans and preclinical models. Ibogaine, the prototypic iboga alkaloid that is utilized clinically to treat addictions, has been associated with QT prolongation, torsades de pointes and fatalities. hERG blockade as IKr was measured using the whole-cell patch clamp technique in HEK 293 cells. This yielded the following IC_{50} values: ibogaine manufactured by semisynthesis via voacangine (4.09 ± 0.69 μM) or by extraction from *T. iboga* (3.53 ± 0.16 μM); ibogaine's principal metabolite noribogaine (2.86 ± 0.68 μM); and voacangine (2.25 ± 0.34 μM). In contrast, the IC_{50} of 18-methoxycoronaridine, a product of rational synthesis and current focus of drug development was >50 μM. hERG blockade was voltage dependent for all of the compounds, consistent with low-affinity blockade. hERG channel binding affinities (K_i) for the entire set of compounds, including 18-MC, ranged from 0.71 to 3.89 μM, suggesting that 18-MC binds to the hERG channel with affinity similar to the other compounds, but the interaction produces substantially less hERG blockade. In view of the extended half-life of noribogaine, these results may relate to observations of persistent QT prolongation and cardiac arrhythmia at delayed intervals of days following ibogaine ingestion. The apparent structure–activity relationships regarding positions of substitutions on the ibogamine skeleton suggest that the iboga alkaloids might provide an informative paradigm for investigation of the structural biology of the hERG channel.

Keywords Toxicology · hERG · Iboga alkaloid · Ibogaine · Noribogaine · 18-Methoxycoronaridine (18-MC)

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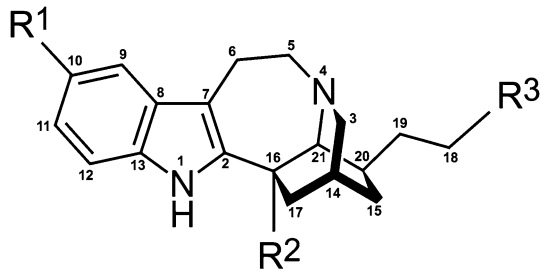
Introduction

The iboga alkaloids are a class of approximately 80 known naturally occurring and synthetic monoterpene indole alkaloids that are defined structurally on the basis of a common ibogamine skeleton (Fig. 1) [1, 2]. Some iboga alkaloids reportedly reduce the self-administration of drugs of abuse and opiate withdrawal symptoms in animal models and humans [3, 4]. Ibogaine, the prototypic iboga alkaloid is used in medical and nonmedical settings for the treatment of substance use disorders. Ibogaine is illegal in the USA and several EU countries due to its classification as a hallucinogen, and unregulated in most of the rest of the



Iboga alkaloid	R^1	R^2	R^3
Ibogaine	OCH_3	H	H
Noribogaine	OH	H	H
Voacangine	OCH_3	CO_2CH_3	H
18-Methoxycoronaridine	H	CO_2CH_3	OCH_3

Fig. 1 Chemical structures of ibogaine, noribogaine, voacangine, and 18-MC. The positions of R1, R2, and R3 on the ibogamine parent structural skeleton are numbered 10, 16, and 18, respectively, according to the Le Men and Taylor system

world, where it is neither illegal nor officially approved. The collective settings of ibogaine use have been termed a "medical subculture" [5] or a "great uncontrolled experiment" [6]. Nonetheless, in view of evidence for a novel mechanism of action, the search for targets of iboga alkaloids may be informative regarding the neurobiology of addiction and the development of fundamentally innovative treatment [3, 4, 7, 8].

Ibogaine is most often used for the specific indication of opioid detoxification, and typically administered as a large single dose in the range of 10–25 mg/kg [5, 9, 10]. Fatalities have occurred temporally related to the use of ibogaine. Nineteen such fatalities are known to have occurred between 1991 and 2009 [11], most of which were associated with commonly abused substances and preexisting medical comorbidities, particularly cardiovascular. Subsequent clinical reports have demonstrated prolongation of the QT interval and/or polymorphic ventricular tachyarrhythmias (PVTs) [12–15] including torsades de pointes (TdP) [16].

The major cause of drug-induced TdP is the blockade of a voltage-gated cardiac potassium channel [17], the pore-forming subunit of which is encoded by the human ether-a-go-go-related gene (hERG) [18]. The hERG channel conducts the efflux of potassium from the cardiac myocyte that is the basis of the rapid delayed rectifier current (IKr) during the repolarization phase of the cardiac action potential. hERG channel blockade impairs cardiac repolarization, resulting in prolongation of the QT interval and PVTs, including TdP. Consistent with observations of QT prolongation and TdP, Ibogaine blocks the hERG channel with reported IC_{50} in the low micromolar range [19, 20].

Ibogaine is most frequently used in the hydrochloride form and is produced by one of two methods. One method involves extraction from the root bark of the West African shrub *Tabernanthe iboga* Baill. (Apocynaceae family). This has been the most frequent method of manufacture in the present settings of ibogaine use [5]. The purity of this material is typically approximately 95 %, which raises the toxicological question of trace impurities as an additional possible determinant of hERG blockade. More recently, Ibogaine HCl has become available that has been produced by the route of semisynthesis via voacangine (Fig. 1), which can yield higher purity on the order of ≥99.5 %.

Noribogaine is ibogaine's principal metabolite, the product of demethylation of ibogaine (Fig. 1) via hepatic cytochrome P450 2D6 (CYP2D6). The half-life ($T_{1/2}$) of ibogaine in humans is estimated to be 4–7 h [9, 21], and the $T_{1/2}$ of noribogaine is apparently considerably longer than that of the parent compound, possibly on the order of days [22–24]. The question of hERG blockade by noribogaine is of interest in view of observations of persistent QT prolongation and arrhythmia for days following the ingestion of ibogaine [13, 15, 16].

18-Methoxycoronaridine (18-MC) is a product of rational pharmaceutical synthesis that differs from ibogaine at three of the 21 positions on the ibogamine skeleton (Fig. 1). 18-MC is reported to produce less hERG blockade than ibogaine [25]. The National Institute on Drug Abuse (NIDA) has recently committed over 6 million USD to support preclinical testing and chemical manufacturing and control work intended to eventually enable clinical trials for the development of 18-MC [8]. However, ibogaine is the iboga alkaloid that has been commonly used for the treatment of addiction.

In the present study, we evaluated hERG blockade and binding affinities for the hERG channel of iboga alkaloids. We evaluated blockade of the hERG channel by noribogaine, and compared ibogaine produced by extraction from *T. iboga* versus a sample of higher purity produced by semisynthesis via voacangine. Collectively, the data from this set of compounds appear to allow some tentative structural hypotheses regarding positions on the ibogamine structural skeleton in relation to the effect of hERG blockade.

Methods

Chemicals

Ibogaine HCl (purity = 95 %) produced by extraction of *T. iboga* root bark was obtained from Slater & Frith Ltd, Wroxham Norwich, UK. Ibogamine was the major impurity in this sample, with lesser amounts of tabernanthine and ibogaline. Ibogaine HCl (purity = 99.5 %) obtained by conversion from voacangine, and voacangine (purity >99 %) were obtained from Phytostan Enterprises, Inc., Montreal, Quebec. Noribogaine (purity = 99.2 %) was

obtained from Slater & Frith Ltd. 18-MC HCl (purity >99 %) was from Obiter Research LLC, Champaign, IL. The purities of iboga alkaloids are stated on certificates of analyses and verified by the available manufacturer's HPLC documentation and/or HPLC–MS or GC–MS in the laboratory of Martin Kuehne, Department of Chemistry, University of Vermont, Burlington, Vermont [7].

Transfection in HEK Cells

hERG cDNA was subcloned into the pcDNA3.1 vector (Invitrogen, Carlsbad, USA). Human embryonic kidney 293 (HEK293) cells were cultured in minimum essential medium (MEM) supplemented with 10 % fetal bovine serum, 1 mM sodium pyruvate, 0.1 mM non-essential amino acid solution, 100 U/ml penicillin, and 100 mg/ml streptomycin sulfate in 5 % CO_2 incubator at 37 °C. HEK293 cells were transiently transfected with 0.9 μg of WT-hERG using Lipofectamine according to the manufacture's instruction (Invitrogen, California, USA). 0.15 μg of eGFP plasmid was co-transfected to monitor transfection efficacy. To examine the blocking effect of ibogaine and its derivatives on hERG channel, HEK293 cells were harvested at 36 h after transfection and seeded onto a glass coverslip. After 12–24 h, the cell-attached coverslips were used for electrophysiological recordings.

Electrophysiology

Membrane currents were measured using whole-cell patch clamp procedures with Axopatch 200B amplifiers (Axon Instruments, Foster City, CA, USA). Internal pipette solution contained 130 mM KCl, 1 mM $MgCl_2$, 5 mM EGTA, 5 mM MgATP, and 10 mM HEPES with pH 7.2 adjusted with KOH. External solutions consisted of 137 mM NaCl, 4 mM KCl, 1.8 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM glucose, and 10 mM HEPES with pH 7.4 adjusted with NaOH. Recordings were made at room temperature.

Concentration–response curves were tested for iboga alkaloids. The IKr current was elicited from a holding potential of −80 mV by a depolarizing pulse to 20 mV for 4 s and then followed by a repolarization step to −50 mV for 4 s to evoke tail current (Itail). The IKr current was first recorded when superfused with extracellular solution without drug (control condition), then the same cell was superfused with extracellular solution containing a giving concentration of the tested drug, and current was recorded after steady state was achieved in the presence of drug. The tail current recorded in the presence of drug is compared with the current recorded without drug, and the decreased percentage is marked as the blocking effect of the tested drug. Concentration–response curves were fitted with the following equation: $I/Imax = 1/1 + [(drug)/IC_{50}]^n$.

The current–voltage relationships of IKr were tested after depolarizations from −60 to 50 mV in 10 mV increments from a holding potential of −80 mV in the absence or presence of the iboga alkaloids. Ibogaine from either source, and noribogaine and voacangine was all evaluated at a concentration of 3 μM. Because the effect on IKr of 18-MC at a concentration of 3 μM was negligible, we tested the effect of 18-MC at a concentration of 10 μM.

Radioligand Binding Assays

The radioligand binding assay methodology has been described elsewhere [26, 27]. Briefly, membrane pellets for radioligand binding assays were prepared from HEK 293 cells stably expressing hERG channels. Inhibition of [^{3}H]Dofetilide (2 nM) binding to the hERG channel was carried out in the absence (total binding) and presence of increasing concentrations of iboga alkaloids (0.1–10,000 nM) in 96-well plates, with final volume of 125 ml per well-binding buffer (10 mM HEPES, 135 mM NaCl, 5 mM KCl, 0.8 mM $MgCl_2$, 1 mM EGTA, 1 mg/ml BSA, pH 7.4). Bound radioligand was captured by filtration onto glass fiber filter paper, and radioactivity retained on the filter was counted in a MicroBeta TriLux plate counter. Results were analyzed in GraphPad Prism with the built-in one-site inhibition binding function to obtain binding affinity (K_i). Affinity values are presented as mean from a minimum of two independent assays, each in triplicate.

Statistical Analysis

Pclamp9.2 (Axon Instruments) and Excel (Microsoft, Seattle, Wash) were used for data acquisition and analysis. Data are presented as mean ± SE. An unpaired Student *t* test and one-way ANOVA were used to compare means. Values of $p < 0.05$ were considered statistically significant.

Results

Concentration–Response Relationships

99.5 % ibogaine manufactured by semisynthesis via voacangine blocked hERG with IC_{50} 4.09 ± 0.69 μM ($n = 14$) (Figs. 2a, 3a). IC_{50} for hERG blockade by 95 % ibogaine manufactured by extraction from *T. iboga* was 3.53 ± 0.16 μM ($n = 10$) (Fig. 3b). There was no difference for IC_{50} of ibogaine produced by the two respective methods of manufacturing ($t = 0.67$, $df = 23$; $p = .51$).

Noribogaine blocked the hERG channel with an IC_{50} of 2.86 ± 0.68 μM ($n = 11$, Figs. 2b, 3c). Similar to ibogaine and noribogaine, voacangine blocked the hERG channel with an IC_{50} of 2.25 ± 0.34 μM ($n = 6$) (Fig. 3d), IC_{50}

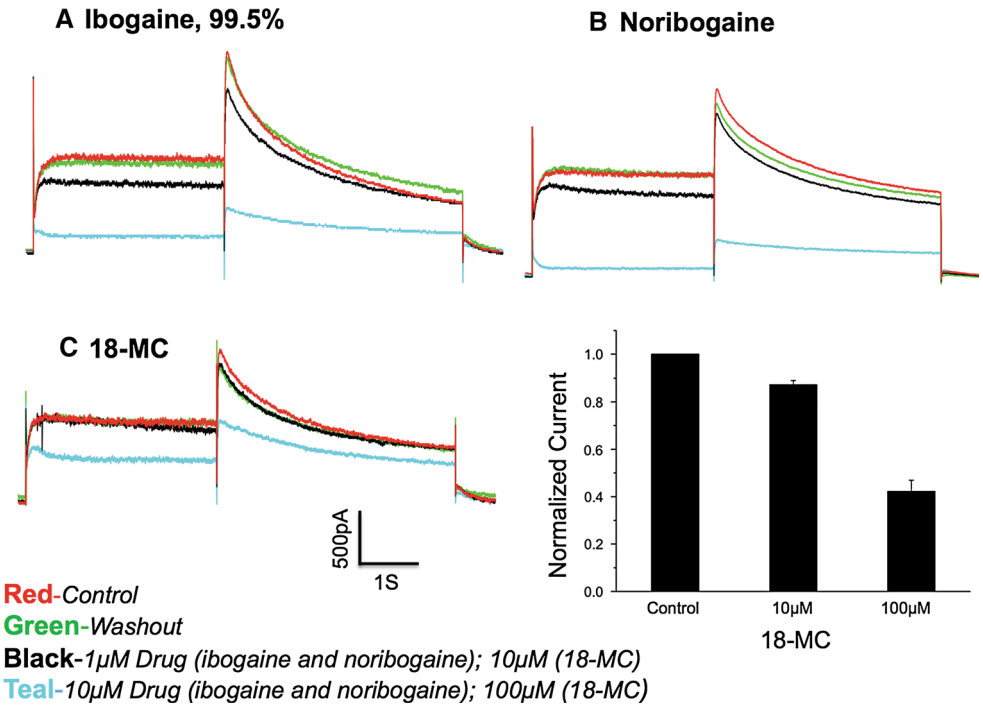


Fig. 2 Effect on hERG blockade of: **a** ibogaine (99.5 % purity), and **b** noribogaine. Original current recording in the same cell with control (*red*), 1 μM (black), 10 μM (*blue*), and after washout (*green*). **c** Effect of 18-MC on hERG blockade: (*left*) original current recording in the same cell with control (*red*), 10 μM (*black*), 100 μM (*teal*), and after washout (*green*); (*right*) 18-MC at concentrations of 10 and 100 μM reduced IKr by 12.8 ± 1.8 and 57.8 ± 4.7 %, respectively (Color figure online)

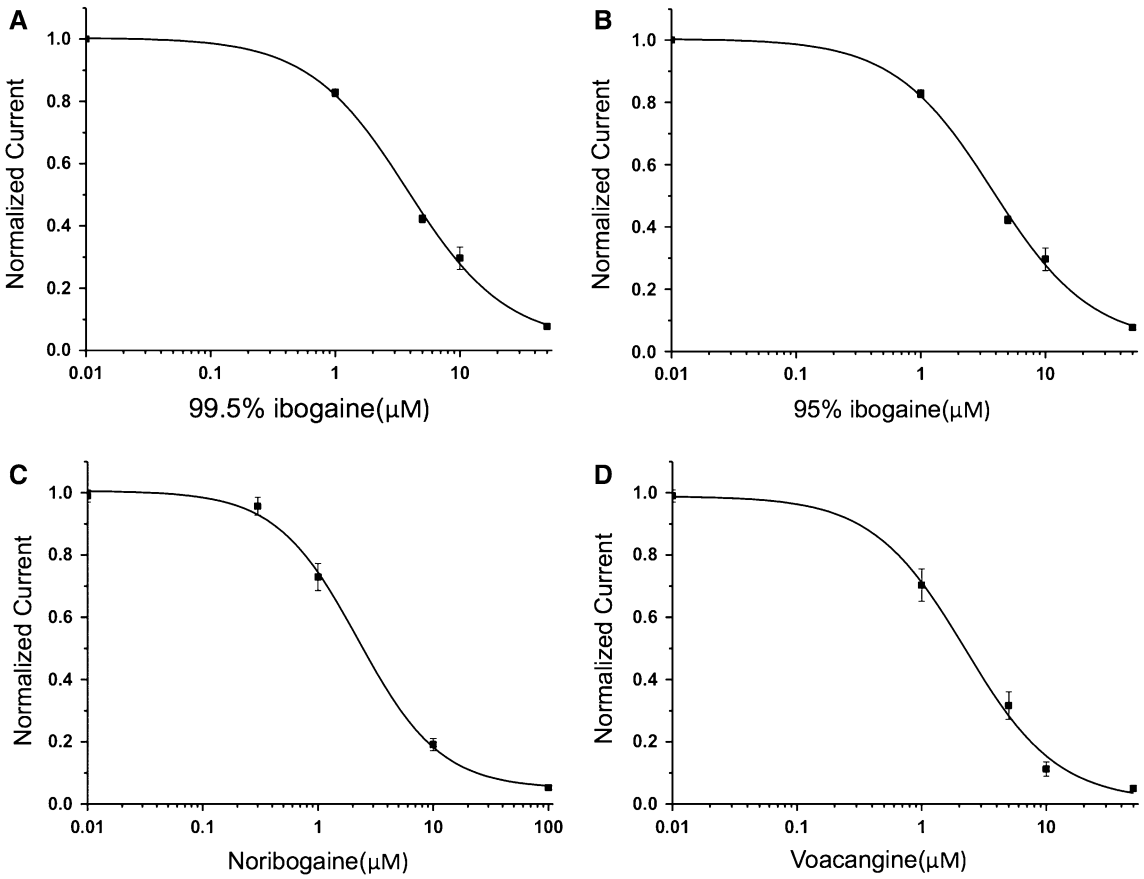


Fig. 3 Concentration-response curves for hERG blockade by iboga alkaloids: **a** ibogaine 99.5 % purity produced by semisynthesis via voacangine, **b** ibogaine 95 % purity produced by extraction from *T. iboga* root bark, **c** noribogaine, and **d** vocangaine

did not differ among ibogaine produced by either manufacturing method, noribogaine, and voacangine (one-way ANOVA, $F_{3,27} = 1.53$; $p = .22$).

In contrast to the other compounds, 18-MC showed much less potent hERG blockade. Concentrations of 10 and 100 μM decreased IKr current by 12.8 ± 1.8 and 57.8 ± 4.7 %, respectively ($n = 9$) (Fig. 2c). We observed precipitation with higher concentrations of 18-MC in Tyrode solution, which limited the accuracy of the measurement of IC_{50}. We estimate that the IC_{50} of 18-MC is between 50 and 100 μM.

Current–Voltage Relationships

hERG blockade was studied across the range of voltages between −60 mV and 50 mV in 10 mV increments (Fig. 4). Tail current density did not differ significantly among control and drug-treated conditions at any voltages below 10 mV. Tail current density differed significantly among control and drug-treated conditions at 10 mV (one-way ANOVA, $F_{5,56} = 2.78$; $p = 0.025$), and differences were all highly significant at voltages of 20 mV or greater ($p < 0.001$).

hERG blockade was voltage dependent for all of the compounds. However, there was no significant difference between the control and 10 μM 18-MC at any voltage. The values for blockade of tail current at 20 mV by 99.5 % ibogaine, and 95 % ibogaine were 42 ± 5.2 % ($n = 6$) and 45 ± 5.6 % ($n = 4$), respectively. Noribogaine, voacangine, and 18-MC blocked of tail current at 20 mV with respective values of 52 ± 6.4 % ($n = 5$), 54 ± 2.7 % ($n = 9$) and 13 ± 3.0 % ($n = 7$).

Radioligand Binding Assays

K_i values (μM) were as follows: ibogaine (99.5 % purity) = 0.71 ± 0.13; noribogaine = 1.96 ± 0.36; voacangine = 3.89 ± 0.69; and 18-MC = 3.12 ± 0.60.

Discussion

In the present study, we evaluated hERG blockade by ibogaine, 18-MC, noribogaine, and voacangine utilizing the whole-cell patch clamp technique. Noribogaine blocked the hERG channel with potency comparable to that of its parent compound. Ibogaine produced by extraction from *T. iboga* root bark or as a purer product of semisynthesis via voacangine produced similar hERG blockade. Collectively, the set of compounds suggests possible structure–function inferences regarding the relatively less hERG blockade associated with 18-MC.

The values for IC_{50} of ibogaine and noribogaine appear clinically relevant. The IC_{50} values for 99.5 %, 95 % ibogaine, and noribogaine were 4.09, 3.53, and 2.86 μM, respectively. In a sample of 24 subjects that were orally administered ibogaine dosages of 10 mg/kg, mean peak blood levels for ibogaine and noribogaine, respectively,

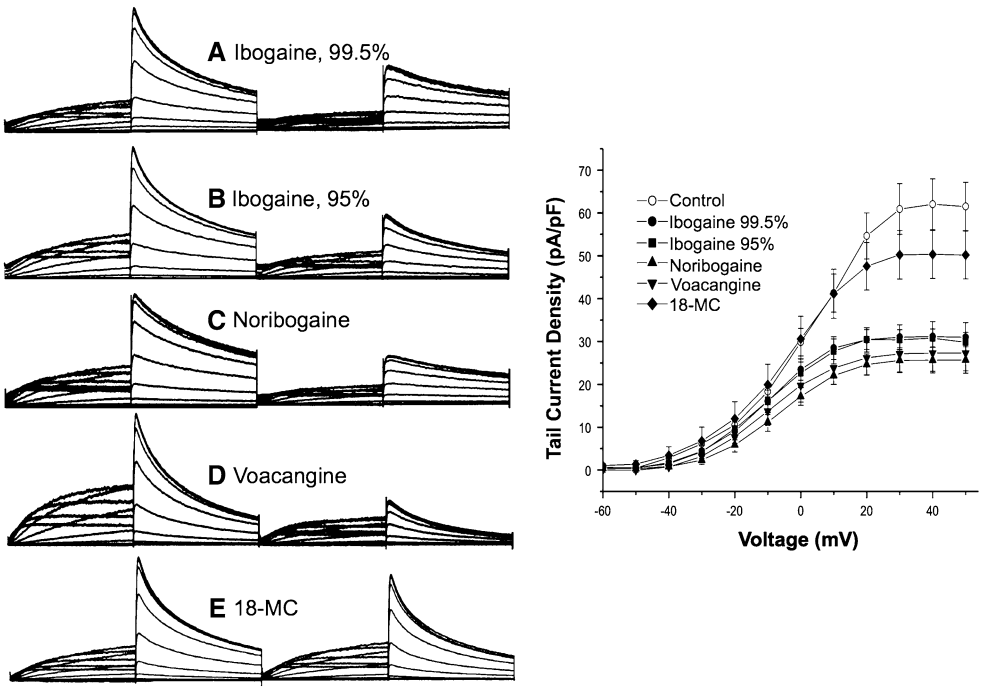


Fig. 4 Current–voltage relationships for hERG blockade by iboga alkaloids. *Left* original recordings of IKr under control conditions (for each compound, the control recording is to the left of the test compound recording) with extracellular solution containing 3 μM ibogaine 99.5 % purity (**a**), ibogaine 95 % purity (**b**), noribogaine (**c**), and vocangaine (**d**); and 10 μM 18-MC (**e**). *Right* the current–voltage curve of the tail currents under control conditions (*empty symbol*) and with 3 μM ibogaine 99.5 %, ibogaine 95 %, noribogaine, and voacangine; and 10 μM 18-MC. $n = 4$ to 9 cells

were 2.4 and 3.2 μM [9]. A protocol consisting of single large orally administered dose is clinically representative; ibogaine is commonly administered for opiate detoxification as a single dose in the range of 10–25 mg/kg [5, 10, 11]. From a postmortem series of 19 fatalities, the subset of 10 cases in which blood ibogaine levels was available, the mean was 7.6 μM (range 0.77–30 μM), and in the two cases for which they were available, noribogaine levels were 13.4 and 18.8 μM [11]. Although the interpretation of levels from postmortem studies may be complicated by redistribution, and taking into account that ibogaine is 65 % protein bound [25], ibogaine or noribogaine may produce significant hERG channel blockade at clinically relevant concentrations [25]. There is apparently no published data regarding the fraction of noribogaine that is protein bound.

The clearance of noribogaine is prolonged relative to ibogaine. A study on 24 human volunteers that excluded CYP2D6 slow metabolizers found ibogaine $T_{1/2} = 7.45$ h following the administration of a fixed dose of 800 mg ibogaine HCl [9]. In this same sample, the half-life of noribogaine was reported as not quantifiable, but individual 24 h blood versus concentration curves published separately appear to indicate $T_{1/2}$ well beyond one day [22, 23]. In a subsequent study in which human volunteers received single doses of noribogaine ranging from 3 to 60 mg, $T_{1/2}$ for noribogaine ranged from 28 to 49 h [24]. A single dose of 60 mg noribogaine produced a mean peak blood level of 0.39 μM [24], and repeated administration would be expected to produce higher steady state levels in view of the extended $T_{1/2}$ of noribogaine.

Clinically, hERG blockade by noribogaine, in view of its extended $T_{1/2}$ may relate to the occurrence of arrhythmias or fatalities at an extended interval following the ingestion of ibogaine. Deaths at intervals of days after ingestion of ibogaine occur at a time when it would be expected that most ibogaine would be metabolized to noribogaine. For example, in a recent case report, QTc remained >500 ms for 4 days following administration of ibogaine [15]. In another case of well-characterized TdP and pause-dependent PVT, runs of PVT persisted into the fifth hospital day [16]. In the series of 19 fatalities, the interval between ingestion and death ranged from 1.5 to 76 h, with a mean of 24 h [11].

Ibogaine HCl 95 % produced by extraction from *T. iboga* root bark is the purity and method of manufacture that has been most commonly used clinically [5]. This 95 % ibogaine and the 99.5 % ibogaine produced by semisynthesis via voacangine produced similar levels of hERG blockade. From a toxicological perspective, the very similar hERG blockade by either ibogaine sample appears to indicate that the observed hERG blockade is due to ibogaine itself and not to a trace impurity. Ibogaine hydrochloride form either source utilized in this study is relatively pure in contrast to crude alkaloid extracts or dried root bark from *T. iboga* [5, 11]. The frequency of fatalities [5, 11, 28, 29] or serious cardiac arrhythmias [12–14] in cases involving the use of alkaloid extracts or dried *T. iboga* root bark suggests the possibility that these crude forms may contain toxicologically relevant compounds in addition to ibogaine.

Our findings of IC_{50} values of 4.09 μM and 3.53 μM, respectively, for 99.5 % ibogaine and 95 % ibogaine agree well with a previous study that reported an IC_{50} value for ibogaine of 4 μM in TSA-201 cells heterologously expressing hERG [19]. However, our finding of an 18-MC IC_{50} value >50 μM differs somewhat from a previously reported value of 14.9 μM [25]. This previously published value for the IC_{50} of 18-MC was reportedly determined as in the prior study that had reported on ibogaine [19]. However, the more salient feature may be the apparent general agreement of our present findings with the previously published data indicating that 18-MC produces substantially less hERG blockade than ibogaine [19, 25].

The concept of "repolarization reserve" [30] clinically contextualizes hERG blockade to multifactorial determinants of cardiac rhythm instability. Typically, drug-induced TdP occurs in the clinical setting of multiple factors in addition to hERG blockade that diminish cardiac stability [17]. Among fatalities temporally related to ingestion of ibogaine, factors in addition to hERG blockade that diminish repolarization reserve are frequently present. Hypokalemia appears to be particularly important, as in a case involving severe depletion of potassium due to very aggressive use of cathartics as part of a "cleansing" regimen prior to treatment, an example that also illustrates the idiosyncratic hazards associated with the unconventional settings in which ibogaine is often administered [16].

Additional factors that commonly diminish repolarization reserve in chronic substance-related disorders include various co-ingestants, cardiac disease, and systemic medical conditions such as liver or respiratory disease, seizures, hypomagnesemia, or withdrawal from cocaine or alcohol [17, 31–33]. These factors are frequently present in cases of arrhythmia or fatalities associated with the ingestion of ibogaine [11–13, 16]. Additional case reports have involved other significant, diverse comorbidities, such as a patient with an automatic implantable cardioverter defibrillator [28, 29], or Marfan's syndrome [14]. A recent case of a cardiac arrest with postanoxic encephalopathy in a previously healthy 26-year-old man who ingested a very high dose of 32 mg/kg [34] appears to be an exception from the general association of ibogaine-related deaths or severe cardiac adverse events with medical co-morbidities and co-ingestants, and may indicate a dose-related effect.

Bradycardia importantly potentiates the risk of drug-induced TdP [17, 30]. It has been observed in association

with ibogaine in both animal models [35–38] and humans [11, 16, 39, 40]. The mechanism by which ibogaine causes bradycardia remains unknown, and is an interesting and clinically significant toxicological question for future study. Although an older literature suggested inhibition of acetylcholinesterase as a basis for bradycardia, this is not supported by contemporary assay techniques [41]. Ibogaine binds to sodium channels in animal brain tissue with low micromolar affinity [4], and there is an association of sodium channel blockade with bradycardia [42]. However, in human, $Na_v1.5$ sodium channels heterologously expressed in TSA-201 cells both ibogaine and 18-MC produce minimal blockade (>100 μM) [25].

hERG channel blockade was voltage dependent for all of the compounds tested. Blockade of hERG channels by low-affinity ligands tends to be voltage dependent [43], in contrast to the little or no voltage-dependence commonly exhibited by high-affinity hERG channel blockers.

The data appear to indicate structure–activity relationships regarding positions of substitutions on the ibogamine skeleton and hERG blockade. As indicated in Fig. 1, there are only three positions on the iboga alkaloid structural skeleton that distinguish among the set of iboga alkaloids evaluated in this study. Utilizing the LeMen and Taylor system for numbering the ibogamine skeleton [44, 45], voacangine differs from ibogaine with regard to the carbomethoxy group at the 16 position (R^2 in the figure). Voacangine and ibogaine show an equivalent effect of hERG antagonism, suggesting that the carbomethoxy group of 18-MC at position 16 is not protective regarding hERG blockade. Ibogaine and voacangine have a methoxy group, and noribogaine has a hydroxyl group at position 10 (R^1 in the figure), and all have comparable hERG antagonism. An oxygen atom could form a noncovalent electrostatic interaction, or in the case of noribogaine, a hydrogen bond with a polar amino acid residue in the binding site of the channel, raising the possibility that oxygen-containing substitutions at position 10 might be a mediator of hERG blockade. 18-MC, in contrast to the other compounds has only a hydrogen at position 10. The methoxy group at position 18 (R^3 in the figure) is another possible structural determinant of the substantially smaller effect of 18-MC on hERG blockade.

The hERG channel binding affinities for the entire set of compounds, including 18-MC fell into a relatively restricted range from 0.71 to 3.89 μM. Nonetheless, there is a fivefold difference between the top and bottom of this approximately 3 μM range. The two compounds at the upper end of this range, voacangine and 18-MC have similar values of K_i of 3.89 and 3.12 μM, respectively, and share the common attribute of a carbomethoxy group at the same position 16 (R^2 in the figure), suggesting that this specific substitution might be a determinant of decreased binding affinity. Interestingly, although this substitution might influence binding affinity, it is not apparently a critical determinant of the effect of hERG blockade, as indicated by the widely divergent values of IC50 for voacangine and 18-MC of 2.25 and >50 μM respectively. 18-MC binds to the hERG channel with an affinity that is within a comparable range to that of the other compounds, but the interaction apparently produces substantially less hERG blockade.

The question of the modulation of hERG blockade by substitutions on the ibogamine skeleton should be addressed further by expanding the query to additional iboga alkaloids in future studies. The apparent structure–activity relationships observed in this study suggest that it may be productive to apply computational biological approaches to investigation of the iboga alkaloid "toxicophore," including in silico modeling of the iboga alkaloid interaction with the hERG channel [46].

In the present study, we used whole-cell patch clamp technique to investigate the potency of hERG blockade by iboga alkaloids. The effect of iboga alkaloids on the gating properties of the hERG channel should be a focus for future study. Future research should extend the model beyond single cells to include interactions among cardiac myocytes using a myocardial wedge preparation, which allows simultaneous recordings of endocardial and epicardial transmembrane action potential in order to evaluate transmural dispersion [47]. The whole animal heart model [48, 49] may be useful approach to the investigation of ibogaine's clinically salient effect of bradycardia, which appears to substantially potentiate the risk of TdP.

Conclusions

The low micromolar IC_{50} values of ibogaine and noribogaine appear clinically relevant regarding levels that have been associated with QT prolongation, arrhythmia, and/or fatalities. The prolonged clearance of noribogaine may be a mediating factor in persistent QTc prolongation, arrhythmia, and fatalities at delayed intervals following the ingestion of ibogaine on the order several days. Collectively, the set of iboga alkaloids investigated in this study indicates structure–activity relationships regarding positions on the ibogamine skeleton and hERG blockade, and suggest that this alkaloid class might provide an informative paradigm for investigation of the structural biology of the hERG channel.

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