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Ibogaine and its congeners are σ_2 receptor-selective ligands with moderate affinity

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Abstract

Ibogaine (12-methoxyibogamine) exhibited moderate affinity for σ_2 sites ($K_i = 201$ nM) and low affinity for σ_1 sites ($K_i = 8554$ nM), thus showing 43-fold selectivity for σ_2 receptors. Tabernanthine (13-methoxyibogamine) and (±)-ibogamine had σ_2 $K_i = 194$ nM and 137 nM, respectively. However, they showed 3- to 5-fold higher σ_1 affinity compared to ibogaine, resulting in about 14-fold selectivity for σ_2 sites over σ_1. A potential ibogaine metabolite, *O*-des-methyl-ibogaine, had markedly reduced σ_2 affinity relative to ibogaine ($K_i = 5{,}226$ nM) and also lacked significant affinity for σ_1 sites. (±)-Coronaridine ((±)-18-carbomethoxyibogamine) and harmaline (1-methyl-7-methoxy-3,4-dihydro-β-carboline) lacked significant affinity for either σ subtype. Thus, σ_2 receptors could play a role in the actions of ibogaine.

Keywords: σ Receptor; Ibogaine; (Subtype selectivity)

Ibogaine (12-methoxyibogamine) is one of several indole alkaloids found in the shrub *Tabernanthe iboga* of central Africa. It has been shown to have psychotropic effects, and was initially used for its hallucinogenic properties. Anecdotal reports that ibogaine decreases drug craving in addicted users have been supported in several animal studies where ibogaine has been shown to reduce self-administration of both morphine and cocaine (Glick et al., 1994). On this basis, ibogaine is currently being investigated for its potential in treating drug abuse. The mechanism of action of ibogaine is not known since this compound has been shown to lack significant affinity for all examined neurotransmitter receptors and ion channels to date, with the exception of only weak affinity ($K_i = 2080$ nM) at kappa (κ) opioid receptors (Deecher et al., 1992).

We have recently demonstrated that sigma (σ) receptors mediate morphologic and cytotoxic effects in cultured cell lines and in primary cultures of various regions of rat brain upon exposure to high doses of σ ligands (Bowen and Vilner, 1994; Vilner et al., 1995). High doses of ibogaine have also been shown to have neurotoxic effects, causing degeneration of Purkinje neurons and gliosis in the parasagittal zones of rat cerebellum (O'Hearn and Molliver, 1993). In view of this, along with reports that σ ligands can modulate the effects of cocaine (Witkin et al., 1993), we were prompted to investigate whether ibogaine and some of its congeners might have affinity for σ receptors.

σ_1 Receptors were labeled as described previously, using [^{3}H](+)-pentazocine and guinea pig brain membranes (Bowen et al., 1993). σ_2 Receptors were labeled as previously described using rat liver membranes, a rich source of σ_2 sites, and [^{3}H]DTG in the presence of 1 μM dextrallorphan to mask σ_1 receptors (Helle-

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Table 1
Affinities of ibogaine and related indole alkaloids at σ_1 and σ_2 receptors

Compound	K_i (nM)		
	σ_1 [^{3}H](+)-Pentazocine Guinea pig brain	σ_2 [^{3}H]DTG + dextrallorphan Rat liver	σ_1 K_i/σ_2 K_i
Ibogaine	8554 ± 1134	201 ± 23	42.6
Tabernanthine	2872 ± 37	194 ± 10	14.8
(±)-Ibogamine	1835 ± 131	137 ± 13	13.4
O-des-methyl-Ibogaine	15006 ± 898	5226 ± 1426	2.9
(±)-Coronaridine	35688 ± 2858	> 26000	–
Harmaline	5447 ± 65	19816 ± 675	0.27

Membranes were prepared and radioligand binding assays carried out as previously described (Bowen et al., 1993; Hellewell et al., 1994). Twelve concentrations of unlabeled test ligand ranging from 0.05 nM to 10000 nM or 0.5 nM to 100000 nM were incubated with guinea pig brain membranes and 3 nM [^{3}H](+)-pentazocine (σ_1 receptors) or with rat liver membranes and 5 nM [^{3}H]DTG in the presence of 1 μM dextrallorphan (σ_2 receptors). Non-specific binding for both assays was determined in the presence of 10 μM haloperidol. IC_{50} values were determined using the iterative curve-fitting program GraphPAD InPlot (San Diego, CA, USA). IC_{50} values were then converted to apparent K_i values using the Cheng-Prusoff equation. Values are the averages of 2–4 experiments, ±S.E.M. Each experiment was carried out in duplicate.

well et al., 1994). Ibogaine hydrochloride and harmaline hydrochloride (1-methyl-7-methoxy-3,4-dihydro-β-carboline hydrochloride) were obtained from Sigma Chemical Co. (St. Louis, MO, USA). (±)-Ibogamine, tabernanthine (13-methoxyibogamine), and (±)-coronaridine ((±)-18-carbomethoxyibogamine) were obtained as described previously (Deecher et al., 1992; Glick et al., 1994). *O*-des-methyl-Ibogaine was synthesized by demethylation of parent ibogaine using boron tribromide (C. Bertha, unpublished procedure).

The results are shown in Table 1. Ibogaine had low affinity for σ_1 receptors but exhibited moderate affinity for σ_2 sites, having 43-fold selectivity for the latter. Tabernanthine differs from ibogaine in the position of the methoxy group on the indole phenyl ring (C-13 vs. C-12), whereas ibogamine lacks phenyl ring substitution. Tabernanthine and (±)-ibogamine showed similar affinity for σ_2 sites as ibogaine, but slightly higher affinity for σ_1 sites. These results show that the methoxy group is not critical for σ_2 binding activity. However, *O*-des-methyl-ibogaine, a probable ibogaine metabolite, had greatly reduced (24-fold lower) affinity for the σ_2 site compared to ibogaine itself. This suggests that compared to the methoxy group, the more polar phenolic hydroxy group may not be well tolerated in the σ_2 binding site. (±)-Coronaridine and harmaline, a structurally related β-carboline, lacked σ affinity, indicating a role of the ibogaine saturated ring system in σ binding.

These results show that ibogaine and two of its congeners, tabernanthine and (±)-ibogamine, are relatively selective σ_2 receptor ligands, with moderate σ_2 affinity (K_i = 137–201 nM). Ibogaine's σ_2 affinity is higher than at any other receptor reported to date. In addition, results with the potential ibogaine metabolite, *O*-des-methyl-ibogaine, suggest that demethylation in vivo would eliminate σ binding activity and therefore would terminate any actions of ibogaine which might be mediated by σ_2 sites. As previously observed with other σ receptor ligands (Bowen and Vilner, 1994; Vilner et al., 1995), initial studies have shown that micromolar concentrations of ibogaine produce morphological changes and cell death in rat C6 glioma, human SK-N-SH neuroblastoma, and mixed primary culture of rat cerebellum (in preparation). Thus, the possible role of σ_2 receptors in the behavioral and/or neurotoxic effects of ibogaine in vivo deserve further investigation. These data also suggest that ibogaine congeners may be good leads in the development of better σ_2-selective ligands.

References

Bowen, W.D. and B.J Vilner, 1994, Sigma receptor-mediated morphological and cytotoxic effects on primary cultures of rat central and peripheral nervous system, Soc. Neurosci. Abstr. 20, No. 314.10, 747.

Bowen, W.D., B.R. De Costa, S.B. Hellewell, J.M. Walker and K.C. Rice, 1993, [^{3}H](+)-Pentazocine: a potent and highly selective benzomorphan-based probe for sigma-1 receptors, Mol. Neuropharmacol. 3, 117.

Deecher, D.C., M. Teitler, D.M. Soderlund, W.G. Bornmann, M.E. Kuehne and S.D. Glick, 1992, Mechanisms of action of ibogaine and harmaline congeners based on radioligand binding studies, Brain Res. 571, 242.

Glick, S.D., M.E. Kuehne, J. Raucci, T.E. Wilson, D. Larson, R.W. Keller, Jr. and J.N. Carlson, 1994, Effects of *iboga* alkaloids on morphine and cocaine self-administration in rats: relationship to tremorigenic effects and to effects on dopamine release in nucleus accumbens and striatum, Brain Res. 657, 14.

Hellewell, S.B., A. Bruce, G. Feinstein, J. Orringer, W. Williams and W.D. Bowen, 1994, Rat liver and kidney contain high densities of σ_1 and σ_2 receptors: characterization by ligand binding and photoaffinity labeling, Eur. J. Pharmacol. Mol. Pharmacol. 268, 9.

O'Hearn, E. and M.E. Molliver, 1993, Degeneration of Purkinje cells

in the parasagittal zones of the cerebellar vermis after treatment with ibogaine or harmaline, Neuroscience 55, 303.

Vilner, B.J., B.R. De Costa and W.D. Bowen, 1995, Cytotoxic effects of sigma ligands: sigma receptor-mediated alterations in cellular morphology and viability, J. Neurosci. 15, 117.

Witkin, J.M., P. Terry, M. Menkel, P. Hickey, M. Pontecorvo, J. Ferkany and J.L. Katz, 1993, Effects of the selective sigma receptor ligand, 6-[6-(4-hydroxypiperidinyl)hexyloxy]-3-methylflavone (NPC 16377), on behavioral and toxic effects of cocaine, J. Pharmacol. Exp. Ther. 266, 473.