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Short communication

Radioligand-binding study of noribogaine, a likely metabolite of ibogaine

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Abstract

Radioligand-binding studies were performed to ascertain the actions of noribogaine, a suspected metabolite of ibogaine, on opioid receptors. Consistent with previous results, ibogaine showed highest affinity for κ opioid receptors ($K_i = 3.77 \pm 0.81$ μM), less affinity for μ receptors ($K_i = 11.04 \pm 0.66$ μM) and no affinity for δ receptors ($K_i > 100$ μM). Noribogaine showed a higher affinity than ibogaine for all of the opioid receptors: κ $K_i = 0.96 \pm 0.08$ μM, μ $K_i = 2.66 \pm 0.62$ μM and δ $K_i = 24.72 \pm 2.26$ μM. These data suggest that noribogaine is active in vivo and that it may contribute to ibogaine's pharmacological effects.

Keywords: Ibogaine; Noribogaine; Desmethyl ibogaine; Opioid receptor

Ibogaine is a naturally occurring indole alkaloid currently under investigation as an agent to treat drug addiction. In rats, ibogaine has been shown to significantly decrease morphine [8] and cocaine [2] self-administration and to prevent morphine-induced release of extracellular dopamine in several brain regions [10]. Additionally, ibogaine has been shown to significantly inhibit morphine-induced locomotor activity in rats [12] and cocaine-induced locomotor activity in mice [14] and to affect the actions of amphetamine and cocaine on the mesolimbic dopamine system [1,11].

Little is known about the mechanism of action of ibogaine. However, because of its enduring anti-addictive properties and its short half life [6], it is suspected to produce lasting effects through a long-acting active metabolite. Ibogaine researchers suspect this metabolite to be noribogaine (desmethyl ibogaine, see Fig. 1) [3] which could be formed by *N*-demethylation of ibogaine. This manuscript details the receptor-binding properties of noribogaine with regard to known binding properties of ibogaine. Previously published binding data indicate that ibogaine has highest affinity for the κ opiate receptor ($K_i = 2.08$ μM) [4,13] and no affinity ($K_i > 100$ μM) for the δ or μ opiate receptors [4]. The present study seeks to examine the binding affinities of noribogaine to determine if this potential ibogaine metabolite also binds to opioid receptors.

Radioligand-binding assays were performed in triplicate for competition studies in 2 ml volume containing 50 mM TRIS buffer, 10^{-5} naloxone (non-specific binding), radioligand, ibogaine or noribogaine and 1 ml tissue homogenate. The κ assay was performed using 1 nM [^{3}H]U69593 and calf cortex incubated for 30 min

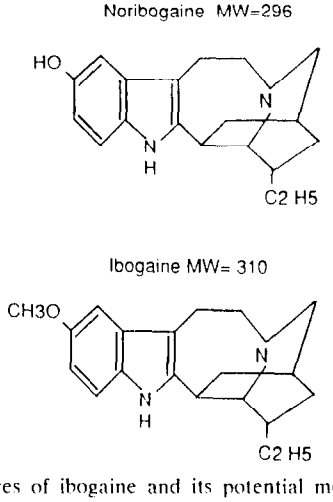

Fig. 1. Structures of ibogaine and its potential metabolite noribogaine.

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Table 1
Affinities of ibogaine and noribogaine for opiate receptors. Data are mean ± S.E.M. values of triplicate determinations from three experiments using different membrane preparations

Compound	K_i (μM) ± S.E.M. κ (^{3}H-U69593)	K_i (μM) ± S.E.M. μ (^{3}H-DAGO)	K_i (μM) ± S.E.M. δ (^{3}H-DPDPE)
Ibogaine	3.77 ± 0.81	11.04 ± 0.66	> 100
Noribogaine	0.96 ± 0.08	2.66 ± 0.62	24.72 ± 2.26

at 37°C. The δ assay was performed using 1 nM [^{3}H]DPDPE and calf caudate incubated for 4 h at 25°C. The μ assay was performed using [^{3}H]DAGO and calf cortex and was incubated for 30 min at 37°C. After incubation, tubes were filtered through Whatman GF/B glass fiber filters with 10 ml cold 50 mM Tris–HCl buffer. The filters were counted by liquid scintillation spectrometry. Compounds were considered inactive at the defined opiate receptor if there was no inhibition at 100 μM. Results were analysed using EBDA and RS1 (BBN).

Ibogaine K_i values from this experiment agree with previously published κ [4,13] and δ opioid data [4]. Previously, this laboratory has reported, using [^{3}H]carfentanil, a K_i of > 100 μM for ibogaine at the μ receptor; although the reason is obscure, we have consistently found that ibogaine does have affinity for the μ receptor when [^{3}H]DAGO is used but not when [^{3}H]carfentanil is used as the radioligand. We, therefore, report in this study, contrary to previous results [4], that ibogaine does have affinity for the μ opioid receptor (K_i = 11.04 ± 0.66 μM). Noribogaine is more active than ibogaine at both μ and κ opioid receptors and, unlike ibogaine, is active at the δ receptor. Complete binding results are summarized in Table 1 and competition curves for ibogaine and noribogaine at the κ opioid receptor are illustrated in Fig. 2.

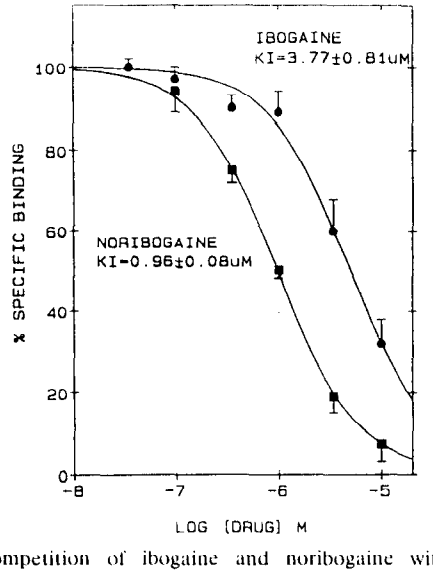

Fig. 2. Competition of ibogaine and noribogaine with 1 nM [^{3}H]U69593 for κ opioid receptor. Each data point represents triplicate determinations of three separate experiments using different membrane preparations.

The increased affinity of noribogaine at the κ opioid receptor may be of significance. κ agonists have been shown to decrease morphine- and methamphetamine-induced locomotor activity in mice [9]. κ agonists have also been shown, like ibogaine, to decrease dopamine metabolite levels in the striatum [9,5] and to decrease dopamine release in the nucleus accumbens [7]. Thus, an ibogaine metabolite, such as noribogaine, which has a higher affinity for the κ receptor than does ibogaine itself, may be capable of producing greater effects than ibogaine. Consequently, noribogaine might have anti-addictive actions at lower (and, therefore, possibly less side-effect producing) doses than ibogaine. Clearly, more studies are necessary to ascertain noribogaine's potential use as a pharmacotherapy for drug addiction.

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