Noribogaine is a G-protein biased κ-opioid receptor agonist

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ABSTRACT

Noribogaine is the long-lived human metabolite of the anti-addictive substance ibogaine. Noribogaine efficaciously reaches the brain with concentrations up to 20 μM after acute therapeutic dose of 40 mg/kg ibogaine in animals. Noribogaine displays atypical opioid-like components in vivo, anti-addictive effects and potent modulatory properties of the tolerance to opiates for which the mode of action remained uncharacterized thus far. Our binding experiments and computational simulations indicate that noribogaine may bind to the orthosteric morphinan binding site of the opioid receptors. Functional activities of noribogaine at G-protein and non G-protein pathways of the mu and kappa opioid receptors were characterized. Noribogaine was a weak mu antagonist with a functional inhibition constants (K_e) of 20 μM at the G-protein and β-arrestin signaling pathways. Conversely, noribogaine was a G-protein biased kappa agonist 75% as efficacious as dynorphin A at stimulating GDP-GTP exchange ($EC_{50} = 9$ μM) but only 12% as efficacious at recruiting β-arrestin, which could contribute to the lack of dysphoric effects of noribogaine. In turn, noribogaine functionally inhibited dynorphin-induced kappa β-arrestin recruitment and was more potent than its G-protein agonistic activity with an IC_{50} of 1 μM. This biased agonist/antagonist pharmacology is unique to noribogaine in comparison to various other ligands including ibogaine, 18-MC, nalmefene, and 6′-GNTI. We predict noribogaine to promote certain analgesic effects as well as anti-addictive effects at effective concentrations >1 μM in the brain. Because elevated levels of dynorphins are commonly observed and correlated with anxiety, dysphoric effects, and decreased dopaminergic tone, a therapeutically relevant functional inhibition bias to endogenously released dynorphins by noribogaine might be worthy of consideration for treating anxiety and substance related disorders.

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1. Introduction

Noribogaine (Fig. 1) is the primary human metabolite of ibogaine (Obach et al., 1998), an alkaloid derived from the African shrub, iboga (Tabernanthe iboga). The therapeutic and oneirophrenic properties of iboga roots are known for centuries in

Equatorial Africa where *iboga* continues to be used as natural medicine and for ceremonial purposes (Goutarel et al., 1993; Samorini, 1995). Naranjo, in collaboration with Bocher, issued a patent in 1969 based on 54 clinical cases featuring the usefulness of ibogaine for psychotherapy and anti-drug purposes (Bocher and Naranjo, 1969). A few decades later, the benefits of *iboga* (ibogaine) in the treatment of addiction for multiple drugs of abuse were highlighted by different groups (Alper et al., 1999; Mash et al., 1998; Sheppard, 1994). Preclinical studies show that ibogaine is a polypharmacological drug that can reduce self-administration to many drugs of abuse in rodents, including cocaine, morphine, heroin, alcohol, and nicotine; and further experimentation in humans supported its usefulness to treat addiction (Alper, 2001; Baumann et al., 2001a; Freedlander, 2003; Maciulaitis et al., 2008; Mash et al., 2000; Popik et al., 1995).

Noribogaine displayed a slow pharmacokinetic clearance rate in humans, being detected for several days in blood after ibogaine ingestion, and was proposed to be responsible for many of the human *in vivo* effects seen after ibogaine therapy (Mash et al., 2000). Noribogaine produced ibogaine-like anti-addictive effects in animals and the systemic administration of noribogaine induced long-lasting decrease of morphine and cocaine self-administration (Glick et al., 1996; Mash and Schenk, 1996). Noribogaine also decreased ethanol self-administration (Rezvani et al., 1995) and nicotine self-administration in rats (Chang et al., 2015). The brain levels of noribogaine in female/male rats were approximately 20/13, 10/7 and 0.8/0.1 μM at 1, 5, and 19 h after intra-peritoneal injection of 40 mg/kg ibogaine whereas plasma levels were 10–20 fold less (Pearl et al., 1997). This indicated that noribogaine had excellent drug permeability across the blood—brain barrier and reached high levels in the brain. Unlike ibogaine, noribogaine did not produce tremors and ataxia in rodents (Baumann et al., 2001b),

suggesting that it is better tolerated than its parent compound and a better drug candidate for clinical development. Recently, a study performed in healthy volunteers indicated that single oral doses of noribogaine from 3 to 60 mg were safe and well tolerated (Glue et al., 2015).

Of particular interest with regards to their acknowledged roles in modulating opiate dependence are ibogaine and noribogaine's effects on the opioid system. In addition to effects on the pursuit and administration of drug of abuse, these drugs were shown to modulate the analgesic power and the development of physical tolerance to morphine. Pre-administration of noribogaine (40 mg/kg, 19 h) had a moderate but detectable effect of potentiation on both basal nociception and morphine-induced analgesia (Bagal et al., 1996). When noribogaine (40 mg/kg) was co-administered with 4 mg/kg morphine, it amplified the duration of morphine-induced analgesia (Bagal et al., 1996). Noribogaine (40 mg/kg) enhanced anti-nociception when added to morphine but did not enhance anti-nociception when combined with U50,488 (kappa opioid agonist) or DPDPE (delta opioid agonist) (Bhargava et al., 1997). At lower doses of 10–20 mg/kg, noribogaine has also been shown to greatly potentiate (or restore) morphine anti-nociceptive activity in morphine-tolerant mice but remained inactive in naïve mice (Sunder Sharma and Bhargava, 1998). Finally, noribogaine was shown to prevent the development of tolerance to the analgesic effects of morphine (Bhargava and Cao, 1997). The mode of action for these effects, as well as the anti-addictive effects, remained largely uncharacterized thus far.

Noribogaine has principal known binding affinities to the opioid receptors, the nicotinic acetylcholine receptors (Maillet et al., submitted manuscript), and the SERT and DAT transporters, but marginal affinities to NMDA, sigma 2 and 5-HT2 receptors in comparison to the parent compound ibogaine (Baumann et al.,
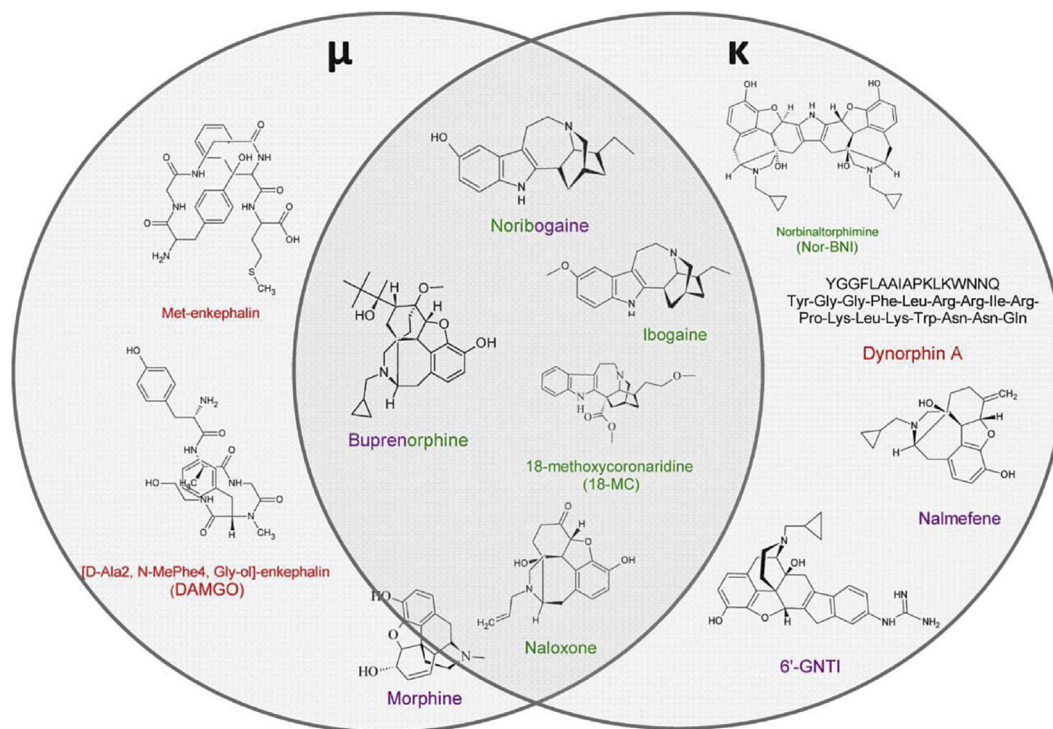

Fig. 1. Structures of noribogaine, and other mu and kappa opioids ligands tested in this study. [Met]-enkephalin, [D-Ala2, N-MePhe4, Gly-ol]-enkephalin (DAMGO), buprenorphine, naloxone, noribogaine, ibogaine, morphine, norbinaltorphimine (nor-BNI), 18-methoxycoronaridine (18-MC), dynorphin A, nalmefene, 6'-guanidinonaltrindole (6'-GNTI). Agonists (red), partial agonists (purple), and antagonists (green) are arranged in the diagram according to their affinities for either the μ or κ opioid receptor. Structures in the overlapping region have affinity for both subtypes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)