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Main targets of ibogaine and noribogaine associated with its putative anti-addictive effects: A mechanistic overview

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Abstract

Background: There is a growing interest in studying ibogaine (IBO) as a potential treatment for substance use disorders (SUDs). However, its clinical use has been hindered for mainly two reasons: First, the lack of randomized, controlled studies informing about its safety and efficacy. And second, IBO's mechanisms of action remain obscure. It has been challenging to elucidate a predominant mechanism of action responsible for its anti-addictive effects. **Objective:** To describe the main targets of IBO and its main metabolite, noribogaine (NOR), in relation to their putative anti-addictive effects, reviewing the updated literature available. **Methods:** A comprehensive search involving MEDLINE and Google Scholar was undertaken, selecting papers published until July 2022. The inclusion criteria were both theoretical and experimental studies about the pharmacology of IBO. Additional publications were identified in the references of the initial papers. **Results:** IBO and its main metabolite, NOR, can modulate several targets associated with SUDs. Instead of identifying key targets, the action of IBO should be understood as a complex modulation of multiple receptor systems, leading to potential synergies. The elucidation of IBO's pharmacology could be enhanced through the application of methodologies rooted in the polypharmacology paradigm. Such approaches possess the capability to describe multifaceted patterns within multi-target drugs. **Conclusion:** IBO displays complex effects through multiple targets. The information detailed here should guide future research on both mechanistic and therapeutic studies.

Keywords

Iboga, ibogaine, noribogaine, substance use disorders, anti-addictive, hallucinogen, psychedelic

Introduction

Ibogaine (IBO) is the main alkaloid of the shrub *Tabernanthe iboga* (Lavaud and Massiot, 2017). While traditionally part of West Central African medicine (Faura and Langlois, 2022), IBO is now gaining recognition as a potential treatment for Substance Use Disorders (SUDs) (Belgers et al., 2016; dos Santos et al., 2016). A substantial body of preclinical research supports IBO's effectiveness in reducing drug self-administration and decreasing the likelihood of drug relapse involving cocaine, ethanol, nicotine, and opioids (Belgers et al., 2016). The reported effects in preclinical models are in line with those reported in humans.

Two studies have assessed the pharmacokinetics of IBO in humans. In healthy volunteers, IBO administered at a single dose of 20 mg (0.285 mg/kg) has a half-life of 2–5 h (Glue et al., 2015a). In comparison, IBO administered to heroin users at a higher dose (10 mg/kg) has a half-life of 7.45 h (Mash, 2001). Remarkably, the active metabolite noribogaine (NOR) has a longer half-life than IBO and may be implicated in its anti-addictive effects. Indeed, it has been described that the half-life after a single administration of NOR in healthy volunteers (0.14 mg/kg) is about 49 h, whereas higher doses (0.85 or 2.33 mg/kg) had a shorter half-life between 27 and 29 h (Glue et al., 2015b).

Both preclinical and clinical studies have reported noteworthy effects that surpass the half-life of either IBO or NOR. These findings suggest long-lasting changes in the reward or stress systems linked to withdrawal states.

Notwithstanding, no randomized and controlled clinical trials have explicitly addressed the “anti-addictive” properties of IBO in humans. However, there is promising evidence from case reports and observational research (Brown and Alper, 2018; Köch et al., 2022; Malcolm et al., 2018; Noller et al., 2018). There is only one randomized and placebo-controlled study that assessed the efficacy of a *T. iboga* extract (1800 mg, single dose) in the treatment of cocaine dependence (Prior and Prior, 2014).

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These authors report that the extract elicited powerful psychoactive effects for patients in the IBO group that lasted 72 h after administration. No cardiac monitoring was done, or at least was not reported. It seems that cravings and dependence associated with cocaine use disorder were drastically reduced over a period of 24 weeks.

In spite of the dearth of randomized and controlled studies, IBO is offered as a treatment for SUDs in several countries around the world, often without medical supervision. This phenomenon has been described as a “vast, uncontrolled experiment” (Vastag, 2005). A systematic review of these studies supports IBO’s therapeutic potential to significantly reduce drug withdrawals, cravings, and self-administration in patients with SUDs (dos Santos et al., 2016). The duration of the therapeutic effect varies highly between studies, ranging from 24 h to weeks or months (dos Santos et al., 2016).

Despite this encouraging scenario, a number of safety concerns have hindered the clinical development of IBO. Three systematic reviews reported that IBO poses certain risks (i.e., QT prolongation), and fatalities have occurred in rare cases (Alper et al., 2012; Koenig and Hilber, 2015; Ona et al., 2021). The most common situations include QT (electrocardiogram parameter) prolongation, gastrointestinal symptoms (vomiting, nausea), or physical symptoms (ataxia, muscle tension, and weakness) (Corkery, 2018; Ona et al., 2021). The QT prolongation is regarded as one of IBO’s most dangerous effects. Koenig et al. (2015) described how IBO inhibits the hERG (human Ether-a-go-go-Related Gene) channels, which play an important role in the repolarization of the action potential. This inhibition delays repolarization, producing a prolongation of the QT interval and, consequently, inducing arrhythmias and sudden death. Koenig et al. (2015) also demonstrated that IBO inhibits sodium and calcium flow in the ventricular cardiomyocyte (Koenig et al., 2013). Notably, it appears that NOR blocks the hERG channel with a potency comparable to its parent compound IBO (Alper et al., 2016). Given the longer half-life of NOR, this might explain the persistent QT prolongations observed in several case reports (Alper et al., 2012; Koenig and Hilber, 2015; Ona et al., 2021). Innovative methodologies have been implemented in that regard to predict NOR-induced cardiotoxicity (Shi et al., 2021). In addition, a recently published open-label trial stated that this substance can induce a clinically relevant QT prolongation (50% of patients reached QT above 500 ms) and severe ataxia (Knuijver et al., 2022). However, a valuable contribution by Luz and Mash (2022) noted that this report had several limitations and could be potentially flawed technically. Specifically, it underscores inappropriate methods of QT correction or the co-administration of drugs (metoclopramide) inhibiting CYP2D6, the main enzyme responsible for IBO metabolism.

This complicated scenario has led researchers to develop non-hallucinogenic, non-toxic analogs of IBO. This challenging research is currently emerging and starting to bear fruit (Cameron et al., 2021; Gassaway et al., 2016). For instance, tabernanthalog showed promise in preliminary research due to its pharmacokinetics and lack of hallucinogenic effects. It has thus been proposed as an IBO alternative with therapeutic potential (Lu et al., 2021).

Given IBO’s supposed “anti-addictive” potential and its unclear safety profile, it is crucial to understand the central mechanisms of this substance. The atypical multi-target profile of IBO

(see Figure 1) poses a challenge to elucidate the primary mechanism of action responsible for its anti-addictive potential. The most comprehensive review of IBO’s mechanisms was published more than 25 years ago (Popik et al., 1995). It is therefore necessary to update the description of the main targets of IBO and its metabolite. The aim of this manuscript is to provide an overview of the pharmacological targets of IBO/NOR and discuss the most recent advances. Because the relevance of the target may depend on the drug (e.g., opioids, amphetamines, etc.), each target’s relevance for different drugs will be discussed when necessary.

Main receptors/targets

Opioid receptors. Early radioligand binding analyses (Sweetnam et al., 1995) and preclinical studies (Codd, 1995) suggested that both IBO and its metabolite NOR bind to the mu opioid receptor (MOR) with affinities in the low micromolar (μM) range. It has therefore been suggested that the anti-craving and detoxification mechanisms of IBO share similarities with other effective treatments for opioid dependence, such as buprenorphine (a partial agonist of MOR; Lutfy et al., 2003) and methadone (a MOR agonist; Kreek et al., 2011).

The hypothesis that IBO and NOR could act as MOR agonists was suggested on the basis of naloxone-sensitive stimulation of guanosine-5'-O-(γ -thio)-triphosphate ([35S]GTP γ S) binding (Pablo and Mash, 1998). However, a seminal study by Alper in 2013 demonstrated unequivocally that neither IBO nor NOR act as partial or full agonists at MOR (Antonio et al., 2013). In this study, the authors examined the effects of IBO and NOR by measuring the activation of MOR using [35S]GTP γ S in cell cultures that overexpressed the recombinant MOR. Additionally, they evaluated MOR activity in rat thalamic membranes and performed autoradiography on the brain slices. Both IBO and NOR displayed MOR antagonists features with K_i (equilibrium dissociation constant) values of $3\mu\text{M}$ (IBO) and $13\mu\text{M}$ (NOR) (Antonio et al., 2013). Based on the above details, both IBO and NOR should be considered weak MOR antagonists. MOR antagonists have been used to mitigate the abuse potential of opioid drugs and treat non-opioid drug dependence and addictive behaviors (Goodman et al., 2007).

Both IBO and NOR interact with the kappa opioid receptor (KOR) (Maillet et al., 2015; Staley et al., 1996). Both act on this receptor as agonists, but NOR exerts a stronger effect on KOR (Staley et al., 1996). In the study conducted by Maillet et al. (2015), it was shown that NOR is a partial G-protein-biased kappa agonist. KOR agonists display analgesic, antidepressant, and neuroprotective effects. But clinical use has been limited due to their side effects, consisting mainly of dysphoria and psychotomimetic effects (Stein, 2016). Indeed, the psychoactive effects of IBO may be related to KOR agonism to some extent, taking into account that salvinorin-A, another “atypical psychedelic,” acts as a highly selective KOR agonist that produces powerful hallucinogenic effects (Ona et al., 2022; Roth et al., 2002).

KOR agonists have also attracted attention for the treatment of SUDs (Butelman et al., 2012; dos Santos et al., 2014) since they prevent both behavioral and neurochemical responses evoked by drug dependency. Furthermore, it has been proposed that the dynorphin/KOR system may function as an anti-reward

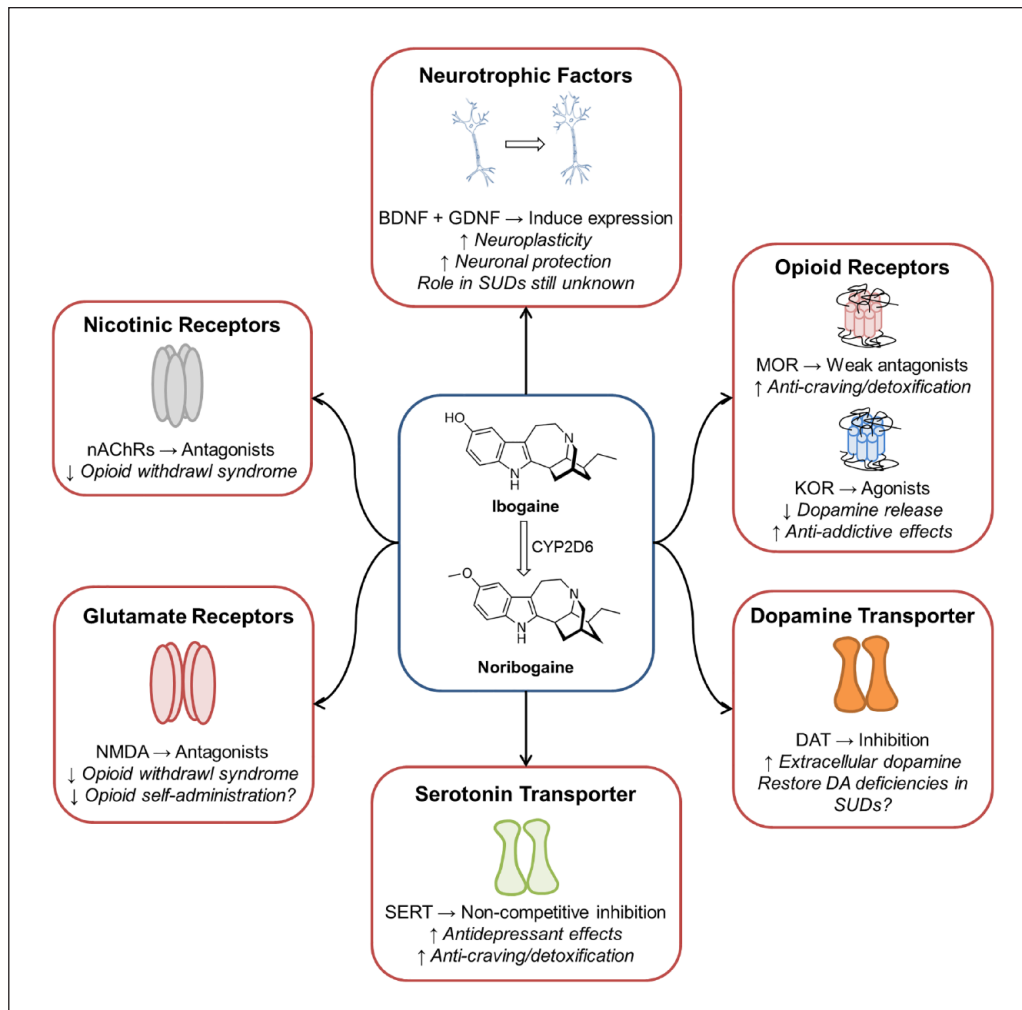


Figure 1. Main targets of ibogaine and noribogaine related to the treatment of substance use disorders and the respective effects they convey (in italics).

BDNF: brain-derived neurotrophic factor; GDNF: glial cell-derived neurotrophic factor; DA: dopamine; DAT: dopamine transporter; KOR: kappa opioid receptor; MOR: mu opioid receptor; nAChRs: nicotinic acetylcholine receptors; NMDA: N-methyl-D-aspartate receptor; SERT: serotonin transporter; SUDs: substance use disorders.

system after acute drug use (Tejeda and Bonci, 2019). However, chronic drug users might present with a dysregulated dynorphin/KOR system, which can promote negative affective states and a higher sensitivity to stress (Tejeda and Bonci, 2019). In this regard, it is possible to speculate that IBO/NOR regulates KOR function by inducing distinct dynamics in KOR signaling pathways. In fact, it has been observed that in the presence of dynorphin, NOR is able to modulate the functional selectivity of dynorphin (Maillet et al., 2015). According to the authors of the study, this mechanism could potentially contribute to the antagonism of negative affective states triggered by an excessively active dynorphin-KOR system (Maillet et al., 2015).

DA transporter. Early preclinical studies demonstrated the effects of IBO on DA depends on the brain region involved (Maisonneuve et al., 1991) and the dose of IBO administered. These studies examined the biphasic effects on DA levels depending on the IBO concentration used (Reid et al., 1996). It has also been reported that IBO blocks DA uptake through the inhibition of the

DA transporter (DAT), potentially increasing extracellular DA levels (Wells et al., 1999). However, later studies found that IBO has a low affinity for DAT, resulting in a weak inhibition of DA uptake (Baumann et al., 2001a). In addition, IBO induces marked and sustained decreases in DA concentrations, in conjunction with elevations in the metabolites 3,4-dihydroxyphenylacetic acid and homovanillic acid (Ali et al., 1996; Baumann et al., 1998). These effects of IBO are specific to the dopamine system and are consistent with disruption of synaptic vesicle storage via inhibition of VMAT2 (Staley et al., 1996).

This finding holds particular significance in the context of SUDs involving psychostimulants like cocaine and methylphenidate, as these drugs inhibit DAT, leading to increased synaptic DA levels, particularly in the ventral tegmental area (VTA) and nucleus accumbens (NAc) (Zahniser and Sorkin, 2004). More recently, several studies utilizing in vitro and *Drosophila* models have provided additional evidence that both IBO and NOR, along with IBO analogs, interact with DAT and restore functional activity in DAT mutations. These effects are due to the influence on

transporter folding (Beerepoot et al., 2016; Bhat et al., 2021; Kasture et al., 2016). The implications of these findings regarding SUDs are not yet clear. But the authors suggested that both IBO and NOR can exert additional non-described effects on DAT, which might be relevant in the context of SUDs.

However, it is challenging to predict the eventual effects of IBO/NOR on DA neurotransmission, due to both of these molecules inhibiting DAT and being KOR agonists, as noted in the previous section. Acute activation of KOR inhibits DA release specifically at the NAc and dorsal striatum (Escobar et al., 2020). In this sense, two preclinical studies reported that IBO decreases drug-induced DA efflux in the NAc and striatum after chronic cocaine or morphine use (Pearl et al., 1996; Szumlinski et al., 2000).

The influence of IBO/NOR on dopamine signaling is unquestionable given the evidence provided in the literature. It is plausible that both mechanisms, DAT inhibition and KOR activation, counteract each other. Depending on the dose of IBO/NOR administered, DA levels could either be increased or decreased. Therefore, further research should be performed with the equivalent of standardized clinical doses to assess the implications of IBO-associated DAT inhibition in the context of SUDs.

5-HT transporter. Unlike other hallucinogens, IBO/NOR have weak affinities for serotonin (5-HT) receptors, including the 5-HT_{2A} receptor, which is the main target of classic hallucinogens such as LSD, psilocybin, and DMT (Kyzar et al., 2017). Acute IBO administration to rats does not elicit the characteristic head twitch response typically associated with the administration of psychedelics (González et al., 2018). IBO therefore produces psychedelic effects through a different biological mechanism, which has not yet been elucidated. Recently, researchers suggested that IBO induces psychedelic effects by altering gamma oscillations in rats (González et al., 2021).

IBO is an inhibitor of the 5-HT transporter (SERT; Toll et al., 1998; Repke et al., 1994). NOR is an SERT inhibitor approximately 10 times stronger than IBO (Baumann et al., 2001a) and increases in 5-HT levels have been observed in different *in vivo* studies (Baumann et al., 2001a, 2001b). Recently, IBO has been categorized as an active-site-binding inhibitor that demonstrates non-competitive inhibition (Coleman et al., 2019). This is an exception in enzymology, since inhibitors that bind to the active site tend to do so by competition (Blat, 2010).

The inhibition of SERT can be associated with antidepressant effects, which can be useful in the context of drug detoxification. For instance, a preclinical study found antidepressant effects after a single administration of IBO to rats (Rodríguez et al., 2020). This finding is consistent with IBO's antidepressant effects reported in an uncontrolled human study (Mash et al., 2018). The regulation of 5-HT levels through SERT inhibition is a mechanism that may be directly involved in the anti-addictive properties of IBO/NOR, especially in the case of opioids. Indeed, withdrawal from chronic MOR agonist exposure is associated with reduced 5-HT levels, which are partially responsible for withdrawal syndrome (Kirby et al., 2011). Thus, the inhibition of SERT by IBO/NOR would sustain 5-HT levels and soften the detox process.

N-methyl-D-aspartate. IBO is a competitive N-methyl-D-aspartate (NMDA) receptor antagonist, as demonstrated by both

in vitro and *in vivo* studies (Chen et al., 1996; Popik et al., 1994). However, NOR shows a lower affinity for that target (Maillet et al., 2015). In rats, the systemic administration of NMDA receptor antagonists tends to attenuate the rewarding effects of drugs (Allen et al., 2005; Shelton and Balster, 1997). However, divergent results have been observed with opioids. In certain studies, NMDA receptor antagonists like dizocilpine and ketamine increased heroin self-administration in rats when administered systemically (Xi and Stein, 2002). In others, NMDA receptor antagonists (memantine) diminished opioid withdrawal syndrome (OWS) in humans (Bisaga et al., 2001). Notably, when ketamine and AP5 (d-(−)-2-amino-5-phosphonopentanoic acid, a competitive NMDA receptor antagonist) were administered directly to the VTA of rats, heroin self-administration was effectively blocked (Bisaga et al., 2001).

More direct evidence on the relationship between NMDA and OWS was first provided by Zhu and Ho (1998). Following chronic exposure to morphine, OWS was induced in rats through naloxone administration. Subsequently, a ventricular administration of an antisense oligonucleotide was used to knockdown the NMDA-R1 (NR1) subunit. The observed results indicated a significant attenuation of OWS, suggesting that functional NMDA receptors are necessary for full OWS expression (Zhu and Ho, 1998).

The mechanisms through which functional NMDA receptors allow the expression of OWS are highly complex. It appears that NMDA signaling plays a crucial role in plasticity processes associated with neural adaptation or the regulation of both DA release and Δ FosB expression, which are linked to OWS via NMDA antagonists (Glass, 2011).

Additionally, there seem to be critical brain regions where NMDA antagonism might be more related to anti-addictive effects. For instance, the blockade of NMDA receptors at the NAc and VTA was associated with the inhibition of OWS (Glass, 2011; Wang et al., 2005). Therefore, future human neuroimaging studies with IBO to describe its specific neuropharmacological effects would help better understand its anti-addictive attributes.

It is important to highlight that the NMDA antagonistic properties exhibited primarily by IBO, and to a lesser extent by NOR, may have implications for potential antidepressant effects similar to ketamine. This is indicated by the overall psychoactive effects of IBO/NOR, due to similarities recently being found in the cortical activity between ketamine and IBO-treated animals (González et al., 2021).

Nicotinic receptors. A prominent theory that has emerged to explain the IBO's anti-addictive effects is its ability to modulate nicotinic acetylcholine receptors (nAChRs), particularly the $\alpha 3 \beta 4$ subtype, by functioning as a noncompetitive antagonist (Popik et al., 1995).

In recent decades, it has been increasingly accepted that nicotinic receptors are crucial for OWS. Preclinical evidence has shown that nicotinic antagonists attenuate naloxone-precipitated morphine withdrawal (Hall et al., 2011; Taraschenko et al., 2005). In humans, two datasets have shown that variants of the CHRNA3 gene (which is coding for the $\alpha 5$, $\alpha 3$, and $\beta 4$ nAChRs subunits) are associated with opioid dependence and withdrawal (Muldoon et al., 2014). In addition, a recent study suggested that IBO inhibits ($\pm$)-epibatidine-induced Ca^{2+} influx in the $\alpha 3 \beta 4$ receptor with an estimated potency nine times stronger than phencyclidine

(PCP). Both IBO and PCP bind to overlapping sites located between the serine and valine/phenylalanine rings, blocking the nAChR ion channel (Arias et al., 2010). In the case of IBO, it maintained nAChR in a desensitized state for a longer period of time (Arias et al., 2010). A putative explanation for the relevance of nAChRs to IBO's anti-addictive effects is their connection to the VTA. This brain region is critical for behavioral activation and sensitization by morphine, and its activity is mostly regulated by nAChRs (Vezina and Stewart, 1984). Notably, nAChRs also mediate the rewarding effects of morphine (Rezayof et al., 2007). Additionally, cholinergic activation at VTA modulates dopamine release in the NAc and extends midbrain dopaminergic systems (Bajic et al., 2015; Mansvelder and McGehee, 2002), making it a highly relevant target in the context of SUDs.

IBO as well as other well-known nAChRs antagonists, like dextromethorphan and 18-methoxycoronaridine (18-MC), have low selectivity for the $\alpha 3\beta 4$ subtype. Variable levels of attenuation of OWS have thus been observed (Muldoon et al., 2014). However, later studies using highly selective $\alpha 3\beta 4$ antagonists, like α -conotoxin AuIB (AuIB), have confirmed the role of this target to attenuate the somatic signs of opioid withdrawal (Bajic et al., 2015).

Neurotrophic factors. Both IBO and NOR induce the expression of glial cell-derived neurotrophic factors (GDNF) and brain-derived neurotrophic factors (BDNF) in both cell cultures and in vivo rat studies (Carnicella et al., 2010; Marton et al., 2019). Neurotrophic factors (NTFs) are proteins that regulate neuronal survival and the differentiation and the migration of neuroprogenitor cells. In addition, they are reported to protect neurons from toxins and injury (Koskela et al., 2017).

BDNF binds to tropomyosin-related kinase B (TrkB), initiating downstream signaling via the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), phospholipase C γ (PLC γ), and phosphoinositol 3-kinase (PI3K) pathways (Huang and Reichardt, 2003; Liran et al., 2020). BDNF and TrkB are widely expressed in the brain, especially in the cortex, hippocampus, and cerebellum (Hofer et al., 1990; Liran et al., 2020). GDNF is expressed in multiple brain regions, notably the striatum, thalamus, cortex, and hippocampus (Pochon et al., 1997; Liran et al., 2020). GDNF exerts its signaling effects through the receptor tyrosine kinase RET (Durbec et al., 1996; Liran et al., 2020).

The relationship between NTFs and SUDs is highly complex. Most of the effects of NTFs on the central nervous system are still not well understood. According to a review conducted by Ghitza et al. (2010), both GDNF and BDNF can either facilitate or inhibit drug-taking behaviors. The outcome depends on various factors such as the specific type of drug, the brain region where NTFs are induced, the addiction phase, and the timing between NTF manipulations and behavioral assessments related to reward and relapse (Ghitza et al., 2010). For example, the administration of both BDNF and GDNF in the mesocorticolimbic system of rats has been shown to enhance cravings for cocaine and heroin (Airavaara et al., 2011). Conversely, when a GDNF infusion is administered in the VTA of rats, it exhibits a dose-dependent reduction in ethanol operant self-administration (Carnicella et al., 2008).

The roles of GDNF and BDNF are also not clear in regards to opioid dependence and withdrawal. While in some studies,

heterozygous GDNF $\pm$ mice displayed enhanced conditioned place preference (CPP) for morphine (Niwa et al., 2007), others reported a similar CPP between GDNF $\pm$ and wild-type mice (Koo et al., 2012). In studies examining heroin cravings, it was found that direct injections of GDNF into the NAc, but not the VTA, resulted in an increased extinction response following withdrawal.

BDNF has been identified as a negative modulator of morphine action (Koo et al., 2012). Chronic administration of morphine to mice has been found to suppress BDNF expression in the VTA. This allows for the enhancement of rewarding and locomotor responses to morphine by increasing the excitability of DA neurons. In this context, when BDNF is administered to VTA, morphine CPP is extinguished (Koskela et al., 2017). Moreover, it has been reported that morphine suppresses the binding of phospho- cAMP response element-binding protein (CREB) and nuclear receptor related-1 (NURR1) to *Bdnf* gene promoters in the VTA, resulting in the decreased expression of BDNF. Overexpression of NURR1 in the VTA decreased morphine CPP, whereas a local knockout of *Bdnf* halted this effect (Koo et al., 2015; Koskela et al., 2017). In contrast, repeated exposure to heroin in rats has been shown to elevate BDNF levels in the VTA. Furthermore, infusions of BDNF into the VTA induce a shift from a DA-dependent opiate reward system to a DA-independent one (Vargas-Pérez et al., 2009).

In conclusion, the role of GDNF and BDNF in opioid dependence and withdrawal remains largely unknown. IBO induces the gene expression of BDNF in the prefrontal cortex (PFC) and upregulates GDNF levels, especially in the VTA (Marton et al., 2019). Given that the GDNF pathway has been proposed as a potential strategy for the treatment of SUDs, and both the PFC and the VTA are critical brain areas involved in this disorder, further research should elucidate IBO's potential NTF-related mechanisms in this context.

Significantly, when assessing the structural and functional plasticity of both IBO and NOR, it was found that NOR, rather than IBO, induces neural plasticity. NOR specifically increases dendritic arbor complexity with an EC₅₀ value comparable to ketamine (Ly et al., 2018). Despite a weak binding affinity, this effect seems to be at least partially mediated by the 5-HT_{2A} receptor, since ketanserin, a selective 5-HT₂ serotonin receptor antagonist, blocked this effect (Ly et al., 2018).

Other targets of IBO

The targets that have been discussed in previous sections are not only those closely related to SUD treatment, but also those that IBO has shown greater binding affinity for. Besides these targets, IBO has also demonstrated minor to moderate affinity for various targets potentially associated with SUDs. Low-affinity binding interactions are not necessarily unproductive (Csermely et al., 2005). They should therefore not be overlooked when seeking a comprehensive understanding of IBO's anti-addictive effects.

ATP-binding cassette transporters

One potential mechanism underlying IBO's anti-addictive effects may be related to its inhibitory effects on P-glycoprotein (P-gp) and the breast cancer resistance protein (BCRP) (Martins et al.,

2022; Tournier et al., 2010). This hypothesis has not yet been mentioned in the literature, but it deserves further attention.

Both P-gp and BCRP belong to the ATP-binding cassette (ABC) transporter subfamily. They are responsible for the drug efflux from the cell and are therefore highly involved in the processes of multidrug resistance (MDR) and tolerance. They are present in a myriad of structures, such as the blood–brain barrier (BBB), the blood–cerebrospinal fluid barrier, intestinal epithelial cells, the bile canaliculi membrane, and kidney tubules. Importantly, animals that have developed tolerance to drugs, including opioids, exhibit elevated levels of P-gp and BCRP (Mercer and Coop, 2011). This occurs because a greater number of P-gp and BCRP transporters are recruited to facilitate the efflux of the drugs. Inhibiting P-gp or BCRP would effectively impede the development of tolerance.

Dexamethasone, morphine, and methadone are recognized as P-gp substrates (DrugBank, 2020). Regarding methadone, in vivo studies performed with P-gp KO mice or rats exposed to P-gp inhibitors showed that brain concentrations of methadone were greater, and its analgesic effect was higher when P-gp was absent or inhibited (Rodríguez et al., 2004; Wang et al., 2004). These findings are especially relevant considering the recent interest in IBO for methadone detoxification [NCT04003948]. This is because a decrease in tolerance may allow for effective dose tapering in a much faster manner than usual protocols.

IBO's potential ability to inhibit P-gp and BCRP could be associated with the reduced tolerance to drugs reported by pre-clinical studies (Bhargava and Cao, 1997; Sunder Sharma and Bhargava, 1998). This complements other IBO-related mechanisms that lower tolerance, such as the inhibition of β -arrestin-2 recruitment (Maillet et al., 2015). However, further studies are needed. The relevance of ABC transporters and BBB transport at this juncture is speculative.

Sigma receptors

Radioligand binding assays have shown that IBO has moderate affinity for sigma-2 (σ_2) and a slight affinity for sigma-1 (σ_1) receptors (Bowen et al., 1995; Mach et al., 1995). NOR shows less affinity for sigma receptors (Maillet et al., 2015). These receptors were initially described as subtypes of opioid receptors, but they are currently considered a distinct orphan class. There are a few known endogenous compounds for σ receptors (*N,N*-dimethyltryptamine or DMT, a powerful hallucinogenic compound, neuroactive steroids, and choline) (Hidalgo-Jiménez and Bouso, 2022). The development of σ receptor ligands is currently a high interest area given their involvement in cancer, pain, neuropsychiatric disorders, and SUDs (Rousseaux and Greene, 2016).

It is not clear from the literature whether IBO acts as an agonist or an antagonist at these receptors. It has been challenging for researchers to define other σ receptor ligands as either agonists or antagonists (Sambo et al., 2018).

Although the affinity on the σ_2 receptor has been linked to IBO's neurotoxic effects (Vilner et al., 1998), the modulation of this receptor can also play a role in IBO's anti-addictive effects. Preclinical research with cocaine, amphetamine (Matsumoto, 2009), and alcohol (Quadir et al., 2019) has demonstrated the recruitment of sigma receptors is necessary to establish SUDs.

Accordingly, σ_1 receptor antagonists are able to interrupt addictive behaviors in animal models (Matsumoto et al., 2002, 2008).

It is noteworthy that drugs like cocaine and methamphetamine interact primarily with the σ_1 receptor (Matsumoto et al., 2003; Nguyen et al., 2005), whereas IBO has 43-fold selectivity for the σ_2 receptor (Bowen et al., 1995). Further research should define the exact role of IBO/NOR at σ sites and its putative implications for its anti-addictive effects.

Serotonin receptors

Although the affinity of IBO for serotonin receptors is weak ($K_i > 10,000$ nM for 5-HT_{2A}, 5-HT_{2C}, 5-HT_{1A}; $> 100,000$ nM for 5-HT_{1B}, 5-HT_{1D}) (Ray, 2010), it might be enough to achieve relevant modifications or at least enhance the effects of IBO on other targets, as stated above (Csermely et al., 2005). The non-selective, low-binding affinity of IBO/NOR for multiple serotonin receptors would thus be especially relevant for the antidepressant effects exerted via SERT inhibition. It has been recently demonstrated that serotonin receptors (5-HT_{1A}) are involved in some of IBO's effects in mice (González-Trujano et al., 2022). Preliminary evidence suggests that the low-binding affinities found in IBO/NOR may play a potential role, supporting the assertions derived from the polypharmacology paradigm.

Muscarinic receptors

It has been observed that both IBO and NOR bind to muscarinic receptors (M_1 , M_2 , and M_3) at similar affinities (7.6–16 μ M for M_1 and 5.9–31 μ M for M_2) (Glick et al., 1999; Ray, 2010; Sweetnam et al., 1995). Indeed, its agonistic action on those receptors might be responsible for IBO-induced bradycardia (Glick et al., 1999).

Relatively little research has focused on the involvement of these receptors in the overall anti-addictive effects of IBO, yet muscarinic agonists reduce psychostimulant self-administration in mice (Thomsen et al., 2010). Therefore, it has been suggested that M_1 agonists may become useful for treating SUDs, especially in the case of psychostimulants (Dencker et al., 2012). The involvement of muscarinic receptors in the anti-addictive effects of IBO therefore cannot be ruled out.

Potential synergistic effects

One of the main mechanisms through which synergy can be produced is the display of multi-target effects, since binding to distinct targets can produce stronger effects on certain complex systems (Ona and Bouso, 2021). The modulation of different targets by IBO/NOR (see Table 1 for the K_i of IBO in its main targets) can therefore potentially result in synergistic effects. Considering the previous discussion, there is speculation about potential synergistic effects that could contribute to IBO's anti-addictive properties. These effects should be appropriately evaluated through specifically designed studies.

The first area in which potential synergistic effects are produced by IBO/NOR is the modulation of the dopaminergic system. IBO/NOR may increase extracellular DA levels by DAT

Table 1. Binding affinities of IBO and NOR to the main targets related to SUDs.

Target	Affinity	Action	References
MOR	IBO: 2–3 μ M; NOR: 0.68–13 μ M	Weak antagonists	Antonio et al. (2013), Glick et al. (1999)
KOR	IBO: 2.1–13.8 μ M; NOR: 0.61–0.96 μ M	Agonists	Glick et al. (1999), Pearl et al. (1996), Popik and Skolnick (1999)
DAT	IBO: 2–4.11 μ M; NOR: 2.05–3.35 μ M	Inhibitory	Popik and Skolnick (1999), Ray (2010), Staley et al. (1996), Sweetnam et al. (1995)
SERT	IBO: 0.59 μ M; NOR: 0.04 μ M	Inhibitory	Staley et al. (1996)
NMDA	IBO: 1–5.6 μ M; NOR: 15–31.4 μ M	Antagonists	Glick et al. (1999), Popik and Skolnick (1999), Sweetnam et al. (1995)
nAChR (α 3 β 4 subtype)	IBO: 0.22 μ M; NOR: 6.2 μ M	Antagonists	Arias et al. (2010)
ABC transporters	—	Inhibitory	Tournier et al. (2010)
NTFs	—	Increased expression	Marton et al. (2019)

MOR=mu opioid receptor; KOR=kappa opioid receptor; DAT=dopamine transporter; SERT=serotonin transporter; NMDA=N-Methyl-d-aspartate; nAChR=nicotinic acetylcholine receptor; ABC transporters=ATP-binding cassette transporters; NTFs=neurotrophic factors; IBO=ibogaine; NOR=noribogaine.

inhibition. However, indirect effects related to KOR agonism might counteract this effect since acute KOR agonism decreases DA levels. On the other hand, chronic activation (possibly induced by NOR) facilitates DA neurotransmission (Escobar et al., 2020). The available preclinical evidence suggests that DA efflux related to different drugs decreases rather than being potentiated (Pearl et al., 1996; Szumlinski et al., 2000). One additional pathway through which dopaminergic neurotransmission can be modulated is through IBO's reported NMDA antagonism. As with other NMDA antagonists, IBO/NOR would diminish the DA release associated with OWS as well as the acute reinforcing effects of drugs (Glass, 2011). The DA-related rewarding effects could therefore be attenuated, and the associated neuronal pathways could adapt to less pathological functioning.

Another potential synergy could occur in the case of decreased tolerance to drugs, especially opioids. The main mechanisms attributed to IBO's tolerance-decreasing effect are related to the inhibition of β -arrestin-2 recruitment for MOR and KOR agonists, as well as its agonist activity at KOR (Maillet et al., 2015). However, this decrease in tolerance might be enhanced by IBO/NOR's NMDA antagonism since NMDA receptor antagonists are known to block opioid tolerance (Inturrisi, 1997). Furthermore, the previously mentioned inhibition of P-gp and BCRP may potentiate tolerance reduction. Consequently, the combined action of these mechanisms can lead to a sensitization to drugs, particularly opioids, which can attenuate the occurrence of withdrawal syndrome if the drug is still present in plasma concentrations. This effect also enables an effective tapering of the drug's dose during the detoxification processes.

IBO also modulates different targets that can reduce withdrawal symptoms. For instance, it has been demonstrated that NMDA antagonism attenuates OWS (Glass, 2011; Wang et al., 2005). Additionally, withdrawal from chronic exposure to MOR agonists is highly associated with reduced 5-HT levels, which would be partially counteracted by the SERT inhibition produced by IBO/NOR. Finally, the antagonist effect of IBO/NOR on nicotinic receptors could also attenuate withdrawal symptoms, since preclinical evidence suggests nicotinic antagonists attenuate OWS (Hall et al., 2011; Taraschenko et al., 2005). Closely linked to that would be an antidepressant effect obtained via different receptors. IBO/NOR inhibit SERT, are NMDA antagonists, and

induce the expression of NTFs, which are mechanisms associated with antidepressant effects.

Closing remarks

As previously described, both IBO and NOR display multitarget effects on several sites related to SUDs directly or indirectly. Most of the previous literature that tried to discuss the mechanisms of action underlying IBO's anti-addictive effects was focused on finding the "key target." This approach used either highly selective ligands or specific antagonists to either confirm or refute the relevance of those targets. This procedure is in line with the classical paradigm in drug design, focused on the development of "magic bullets." As emerging techniques such as "omics" (Caesar et al., 2021) and paradigms like polypharmacology (Hopkins, 2008) gain prominence, there is a need to adopt a more comprehensive perspective when studying IBO's anti-addictive effects. Studies using omics or complex approaches have not yet been performed with IBO. Instead of focusing on certain targets or receptors, omics techniques allow researchers to discover the entire molecular landscape affected by drugs. Several other examples in highly complex natural products research demonstrate groundbreaking results in recent literature (Liu et al., 2022; Wang et al., 2020; Xue et al., 2022).

IBO's anti-addictive effects could be better understood as resulting from its complex polypharmacology, which is able to modulate a high number of relevant targets, rather than simply modulating certain key targets. As Luccock stated, a symphony cannot be whistled, it takes an orchestra to play it (Pike and Krumm, 1954). The anti-addictive effects demonstrated by the multi-target effects of IBO and its metabolite should not be oversimplified. The polypharmacology paradigm offers us an opportunity to gain a deeper understanding of these complex effects. IBO/NOR serves as an illustrative example of how multiple, weak perturbations at various targets can produce a notable impact on the complex patterns involved in SUDs.

However, this complex approach does not prevent us from needing to perform more preclinical research to fully understand the pharmacology of IBO/NOR. The complex landscape of treating SUDs, where IBO exhibits its complex effects amidst neural adaptations to different drugs, should be replicated and carefully

characterized in preclinical models using omics and other recently developed techniques. This would support the rational design of multi-target drugs that might be safer than IBO. Also, a detailed description of receptor binding and affinity, as well as the pharmacokinetics of IBO when using therapeutic doses, should be investigated.

In addition, human studies have demonstrated that IBO's psychoactive effects can play a role in the psychological impacts of SUDs and provide personal insights that can produce changes in behavior (Kohek et al., 2020; Rodriguez-Cano et al., 2022). Regrettably, there is limited research on the subjective experience elicited by IBO, especially with contemporary methods involving specific psychometric questionnaires or visual analog scales. However, anecdotal reports have mentioned various subjective effects such as synesthesia, visions of spirit beings, cosmic experiences, or representations of the iboga plant (Brown et al., 2019; Kohek et al., 2020). Additionally, individuals commonly report reviewing their life and experiencing the retrieval of multiple past memories during IBO sessions (Brown et al., 2019; Schenberg et al., 2017). The intricate interplay between the pharmacological properties of IBO and its subjective effects underscores the complex nature of this compound.

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