Original Paper

Noribogaine reduces nicotine self-administration in rats

Qing Chang[1], Taleen Hanania[1], Deborah C Mash[2,3] and Emeline L Maillet[2]

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Abstract

Noribogaine, a polypharmacological drug with activities at opioid receptors, ionotropic nicotinic receptors, and serotonin reuptake transporters, has been investigated for treatment of substance abuse-related disorders. Smoking cessation has major benefits for both individuals and society, therefore the aim of this study was to evaluate the potential of noribogaine for use as a treatment for nicotine dependence. Adult male Sprague-Dawley rats were trained to self-administer nicotine intravenous. After initial food pellet training, followed by 26 sessions of nicotine self-administration training, the rats were administered noribogaine (12.5, 25 or 50 mg/kg orally), noribogaine vehicle, varenicline or saline using a within-subject design with a Latin square test schedule. Noribogaine dose-dependently decreased nicotine self-administration by up to 64% of saline-treated rats' levels and was equi-effective to 1.7 mg/kg intraperitoneal varenicline. Noribogaine was less efficient at reducing food pellets self-administration than at nicotine self-administration, inhibiting the nondrug reinforcing effects of palatable pellets by 23% at the highest dose. These results suggest that noribogaine dose-dependently attenuates drug-taking behavior for nicotine, attenuates the reinforcing effects of nicotine and is comparable to varenicline power in that regard. The findings from the present study hold promise for a new therapy to aid smoking cessation.

Keywords

Food self-administration, α3β4 nicotinic acetylcholine receptor antagonist, α7 nicotinic acetylcholine receptor antagonist, addiction

Introduction

Noribogaine (Figure 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, 1993; Samorini, 1995). Naranjo, in collaboration with Bocher, issued a patent in 1969 based on 54 clinical cases featuring ibogaine usefulness for psychotherapy and anti-drug purposes (Bocher and Naranjo, 1969). A few decades later, the benefits of *iboga* (ibogaine) in the treatment of human addiction for multiple drugs of abuse were highlighted by different groups (Alper et al., 1999; Mash et al., 1998).

Preclinical studies have shown that ibogaine is a polypharmacological drug and can reduce self-administration to many drugs of abuse, including cocaine, morphine, heroin, alcohol, and nicotine, and further experimentation in humans supported its usefulness to treat addiction (Baumann et al., 2001a; Freedlander, 2003; Maciulaitis et al., 2008; Mash et al., 2000). Noribogaine displays a slow pharmacokinetic clearance rate in humans and was proposed to be responsible for many of the human in vivo effects seen after ibogaine therapy (Mash et al., 2000). Proof-of-concept studies demonstrated that systemic administration of noribogaine induced long-lasting decrease of morphine and cocaine self-administration in rodents (Glick et al., 1996; Mash and Schenk, 1996). Noribogaine also decreased ethanol self-administration in rats (Rezvani et al., 1995a). Ibogaine itself appeared more active at blocking ethanol consumption when administered intra-peritoneally (IP) versus subcutaneously, consistent with higher rates of first-pass metabolism of ibogaine to noribogaine when using the IP route (Rezvani et al., 1995b). Finally, in rodents, noribogaine did not produce tremors and ataxia like ibogaine (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 carried out in healthy volunteers indicated that single oral doses of noribogaine from 3–60 mg were safe and well tolerated (Glue et al., 2015).

Nicotine is one of the most addictive drugs; 95% or more of its users with a strong desire to stop using relapse within one year (Albuquerque et al., 2009). Tobacco use remains a major health problem despite widespread knowledge of its damaging consequences. Current smoking cessation therapies including nicotine replacement, bupropion, and varenicline, have had some success (Benowitz, 2009). However, they appear to be inadequate since absolute cessation rates range from only 5–35% for smokers who try these medications, with odds ratios ranging from 2–4 in comparison with placebo treatment (Benowitz, 2009). Consequently, more effective or combination therapies are needed.

Chronic nicotine use leads to physiological changes in nicotinic acetylcholine receptors (nAChRs) function and expression, including up-regulation of high-affinity α4β2 nAChR expression

[1]Behavioral Pharmacology, PsychoGenics Inc., Tarrytown, NY, USA
[2]R&D Laboratory, DemeRx, Inc., Miami, FL, USA
[3]Miller School of Medicine, Miami, FL, USA

Corresponding author:
Emeline L. Maillet, DemeRx Inc., R&D laboratory, Life Science & Technology Park, 1951 NW 7th Ave, Suite 300, Miami, FL 33136, USA.
Email: emaillet@demerx.us

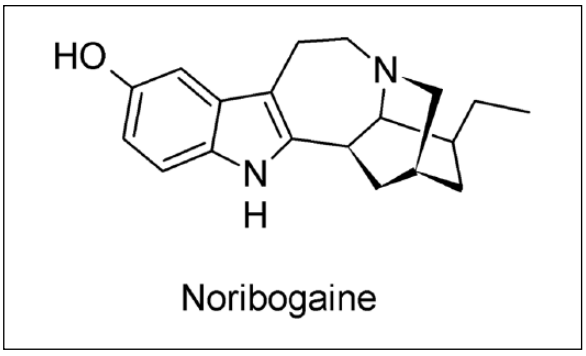

Figure 1. Molecular structure of noribogaine. (15S,17R)-17-ethyl-3,13-diazapentacyclo[13.3.1.02,10.04,9.013,18]nonadeca-2(10),4(9),5,7-tetraen-7-ol (CAS no. 481-88-9).

and reduced receptor function due to desensitization (for review see Changeux, 2010). Studies suggest that β2-containing nAChRs are involved in the reinforcing effects of nicotine (Picciotto et al. 1998). However, β2 null-mice develop symptoms of nicotine withdrawal similar to Wild-Type (WT), suggesting that this subunit may not directly contribute to the physical and emotional/affective aspects of nicotine dependence (Besson et al., 2006) including severe cravings, anxiety, dysphoria, and autonomic dysfunction. Literature indicates that the nAChR subunits responsible for many of the effects of nicotine including sedation, nicotine-induced seizures and most importantly, somatic withdrawal symptoms, are the α2, α3, α5 and β4 subunits which are expressed in a highly restricted pattern in the brain and at high levels in the medial habenula and its main output, the interpeduncular nucleus (IPN), for review see Baldwin et al. (2011). In fact, recent genetic association studies show that single nucleotide polymorphisms (SNPs) in the gene cluster encoding for the α3, α5 and β4 nAChR subunits are associated with increased risk for heavy smoking, inability to quit, and increased sensitivity to nicotine (Improgo et al., 2010). Furthermore, while the development of tolerance is not regulated by α7 nAChR, certain studies indicated that these receptors may control the severity of the withdrawal symptoms (Changeux, 2010; Salas et al., 2007).

Noribogaine has a distinct binding profile compared to the parent compound, with binding affinities at serotonin (SERT) and dopamine (DAT) transporters and opioid receptors; and marginal affinities to N-Methyl-D-aspartate (NMDA), sigma 2, 5-hydroxytryptamine (serotonin) 2A (5HT2a) receptors in comparison to ibogaine (Baumann et al., 2001a; Mash et al., 1995a, 1995b; Staley et al., 1996). Early work demonstrated an inhibitory action of *iboga* extracts on serum cholinesterase (Vincent and Séro, 1942). Ibogaine was then shown to inhibit nicotinic receptor-mediated catecholamine release from cultured chromaffin cells (Schneider et al., 1996) and noncompetitively block cation influx produced by ganglionic nAChRs (Badio et al., 1997; Fryer and Lukas, 1999). The effects of noribogaine on receptor subunit binding and function of nAChRs has only recently been examined (Maillet et al., 2015a). This study showed that noribogaine is a potent non-competitive inhibitor of the habenula-type α3-(α5, β4, β2) nAChRs and also an inhibitor at α7 nAChRs, supporting future studies to assess its potential usefulness in multiple therapeutic arenas, including smoking cessation, substance abuse related disorders, and anxiety related disorders.

Given noribogaine's pharmacological profile, we hypothesized that noribogaine alone would be an effective treatment for nicotine dependence. The aim of the present study was to evaluate this potential. Several pre-clinical models have been developed to assess the abuse liability of nicotine and used to test potential therapies for smoking cessation. Intravenous self-administration is widely accepted as a valid model to assess the abuse liability of various drugs, including nicotine (Benowitz, 2009). Using this model, pharmacological manipulations can also be tested for their efficacy at inhibiting nicotine self-administration behavior in animals. These studies provide initial evidence for development of a compound as a potential therapy to aid in aiding smoking cessation in humans. We used a rat model of drug self-administration to evaluate the potential of noribogaine for treatment of nicotine dependence. In addition to nicotine self-administration, a separate cohort of food-responding rats was used as non-nicotine control to evaluate generalized suppression of reward function and reinforced behaviors. We report here that noribogaine dose-dependently reduces the reinforcing effects of nicotine in rats.

Materials and methods

Animals

Twenty-two young adult, male Sprague-Dawley rats (300–325 g at arrival) from Harlan Laboratories (Indianapolis, Indiana, USA) were used in this study. Fourteen of them underwent catheter surgery and training of nicotine self-administration. Eight food-maintained responding rats that did not undergo surgery or nicotine training were used to assess the effects of noribogaine on food consumption. Upon arrival, the rats were assigned unique identification numbers (tail marks). Animals were housed 2–3 per cage in suspended polycarbonate rat cages with filter tops, and were acclimated for up to seven days. All rats were examined, handled, and weighed prior to initiation of the study to assure adequate health and suitability. During the course of the study, 12 h/12 h light/dark cycles were maintained. The room temperature was 20–23°C with a relative humidity maintained at 30–70%. Water was provided ad libitum for the duration of the study. Single-housed rats that were implanted with a jugular catheter (14 nicotine training rats), were food-restricted after recovery and maintained at 85% of their free-feeding age-matched control body weight. Food-maintained responding rats (a separate cohort of eight rats) were also single-housed, food-restricted and maintained at 85% of their free-feeding age-matched control body weight. Experiments were approved by the Institutional Animal Care and Use Committee of PsychoGenics Inc. in AAALAC-accredited (Association for Assessment and Accreditation of Laboratory Animal Care) facilities and in accordance with the *Guide to the Care and Use of Laboratory Animals* (NRC, 2011).

Drugs

(−)Nicotine hydrogen tartrate (Sigma-Aldrich, St Louis, Missouri, USA) was dissolved in saline, the pH was adjusted to 7.0 (±0.2), and the solution was filtered through a 0.22 micron syringe filter (Fisher Scientific, Pittsburgh, Pennsylvania, USA) for sterilization purposes. Nicotine tartrate was administered intravenously (IV) (0.03 mg in 0.1 mL over a 0.8 s period). Varenicline was obtained from Acenta Discovery Inc., USA. Buffer constituents were from

Sigma-Aldrich Corp. (St. Louis, Missouri, USA). Varenicline tartrate (1.7 mg/kg) was dissolved in saline (0.9% NaCl) and administered IP 30 min prior to test. Dose volume of varenicline was 1 ml/kg. The formulation of varenicline (1.7 mg/kg) was a clear solution. Noribogaine hydrochloride was provided by DemeRx, Inc. The drug was made by Ajinomoto Omnichem, Belgium. Noribogaine HCl (12.5, 25 and 50 mg/kg, converted to free base doses with a correction factor of 1.12) was prepared in 35% of the total required volume of 0.5% Tween 80 in 5% dextrose. The resulting suspension was stirred for at least 30 min. 1.5% methylcellulose was added to make up 65% of the total volume and the suspension was stirred again for at least 30 min. As a result, 12.5 mg/kg and 25 mg/kg doses were clear solutions and 50 mg/kg was a slightly cloudy suspension. The mix of 0.5% Tween 80 in 5% dextrose (35% of total volume) and 1.5% methylcellulose solution (65% of total volume) was used as compound vehicle treatment. Vehicle and noribogaine were administered orally two hours prior to test at a dose volume of 5 mL/kg. All drug doses and concentrations refer to the active drug moiety, expressed as free base.

Apparatus

Intravenous drug self-administration and food-maintained responding training and test took place in operant chambers within sound-attenuating cubicles equipped with an exhaust fan (Med Associates Inc., St. Albans, Vermont, USA). Each chamber contained two levers situated on one wall of the chamber. Only one of the two levers was active (located on the left side). Pressing the active lever caused delivery of reinforcer (nicotine in the case of self-administration study, or food pellets in the food-maintained responding study). The other lever was "inactive", i.e. pressing it did not deliver any reinforcement. A stimulus light was located above each lever, but only the one above the active lever was on during the timeout period (defined below). A house light (providing illumination) was located at the top of opposite wall. For food training, a pellet receptacle was situated between the two levers for delivery of food pellets (Bio-Serv's Dustless Precision Pellets #F0165, 45 mg). An infusion pump mounted above each chamber delivered drug solution via Tygon tubing connected to a single channel fluid swivel, which was mounted on a balance arm above the operant chamber. The output of the liquid swivel was attached to the externalized terminus of the intravenous catheter.

Food training and surgery

Prior to intravenous catheterization, animals were trained to press the active lever to obtain food. Food training started after the rats were food-restricted and reached about 85% of the free-feeding body weight. After acquiring the lever-press response, rats were implanted with intravenous catheters. Catheters were flushed with 0.2 mL of heparin-gentamicin solution every day to avoid clogging and ensure smooth drug infusion. Two days prior to surgery and throughout recovery, rats were on free feeding.

Self-administration procedures

One week after the surgery, single housed rats were food restricted and maintained at 85% of their free-feeding age-matched control body weight throughout the study. During training, rats were allowed to self-administer nicotine solution by pressing the active lever in a fixed-ratio (FR) schedule of reinforcement. In this study we used FR3, i.e. three lever presses for one nicotine delivery (0.03 mg/kg/infusion in 0.1 mL over a 0.8 s period). Delivery of nicotine was followed by a 20 s timeout period, during which no drug was delivered even if the active lever was pressed. During timeout, the stimulus light above the active lever was on. After 26 days of nicotine self-administration training, the rats established stable baseline (less than 20% variation in daily amount of drug infusions over three consecutive days; a minimum of six drug infusions per session). Thereafter, testing with varenicline and noribogaine commenced. Each test session lasted one hour with FR3 nicotine delivery schedule as described above in the training session.

Food maintained rats (used as non-nicotine control for generalized suppression of reward function and reinforced behaviors) were also food-restricted and maintained at 85% of their free-feeding bodyweight. Rats were trained to press the active lever for food reward (Bio-Serv's Dustless Precision Pellets #F0165, 45 mg). The reinforcement schedule was also FR3 with 20 s timeout after each food pellet delivery. These rats did not undergo surgery, but were age-matched to the nicotine self-administration rats.

Study design

A within-subject design in which each rat received all treatments was applied with a Latin square test schedule. All rats demonstrated stable baseline behavior prior to drug testing. Each testing session lasted one hour. The six treatments which were blinded to the experimenter were: saline; varenicline 1.7 mg/kg; vehicle (35% of 0.5% Tween-80 in 5% dextrose and 65% of 1.5% methylcellulose); noribogaine 12.5 mg/kg; noribogaine 25 mg/kg; noribogaine 50 mg/kg.

Data analysis

The data of nicotine infusions or food pellets obtained during test sessions were analyzed via repeated measure analysis of variance (ANOVA) followed by Fisher LSD post-hoc comparisons where appropriate. Percentage of inactive lever presses of nicotine maintained rats were also analyzed with repeated measure ANOVA for non-specific behavioral effects. An effect is considered significant if $p<0.05$. Data are represented as the mean and standard error of the mean (SEM). Statistical outliers fell beyond mean ± (2×standard deviation) are removed from the analysis. With this criterion, 0–2 outliers were eliminated in different measures (see results section). For measures of inactive lever press of food maintained rats, due to their very low frequency and skewed distribution, the repeated measure ANOVA followed by Fisher LSD post-hoc comparisons were run on pre-ranked percentage data, and all data were included without elimination of extreme data points.

Results

Nicotine self-administration

The effects of noribogaine and varenicline on nicotine infusion are shown in Figure 2. A repeated measure ANOVA testing found

a significant main effect of treatment ($F(5,58)=29.708$, $p<0.001$). Post-hoc comparisons indicated that compared to vehicle treatment noribogaine at 25 and 50 mg/kg significantly decreased nicotine infusion by 27% and 61%, respectively ($p<0.001$). Similarly, varenicline at 1.7 mg/kg treatment significantly decreased nicotine infusion by 65% compared to saline. The lowest dose of noribogaine tested at 12.5 mg/kg showed a trend ($p<0.10$) in decreasing nicotine self-administration by 13% compared to vehicle.

The measures of lever response during nicotine self-administration are summarized in Table 1. The ratios of inactive vs active lever responses (the percentage of inactive lever press compared to overall lever response) were similar in all treatments (~16–20%) ($F(5,54)=0.356$, $p>0.05$). This suggests that there were no Central Nervous System (CNS) or motor side effects (reinforcement-independent rate-altering effects) at any dose of noribogaine.

Food-maintained responding

The effects of noribogaine and varenicline on food responding in food maintained responding rats are shown in Figure 3. A repeated measure ANOVA testing found a significant main effect of treatment ($F(5,33)=16.905$, $p<0.001$). Post-hoc comparisons indicated that compared to vehicle treatment, noribogaine at 25 and 50 mg/kg decreased food responding by 10% ($p<0.05$) and 23% ($p<0.001$), respectively. Noribogaine at 12.5 mg/kg and varenicline at 1.7 mg/kg had no effect on this measure with a trend for varenicline to increase food responding by ~8%.

The lever response measures of food maintained animals in different treatments are shown in Table 2. Statistics (repeated measure ANOVA on pre-ranked percentage of inactive lever responses) showed a significant main effect of treatment ($F(5,35)= 3.300$, $p<0.05$). This main effect is almost solely contributed by high dose noribogaine at 50 mg/kg, as shown in post-hoc comparisons (**$p<0.01$ compared to vehicle treatment). Although noribogaine at 50 mg/kg showed significantly higher percentage of inactive lever response comparing to vehicle treatment, the inactive responding was extremely low (median of 1.6% in >350 overall lever presses during the one-hour testing session). In view of this low frequency response and lack of evident reinforcement-independent rate-altering effects, the potential meaning of the slightly enhanced inactive lever response in food maintained rats at the highest dose of noribogaine appears non-significant under the conditions of the present study.

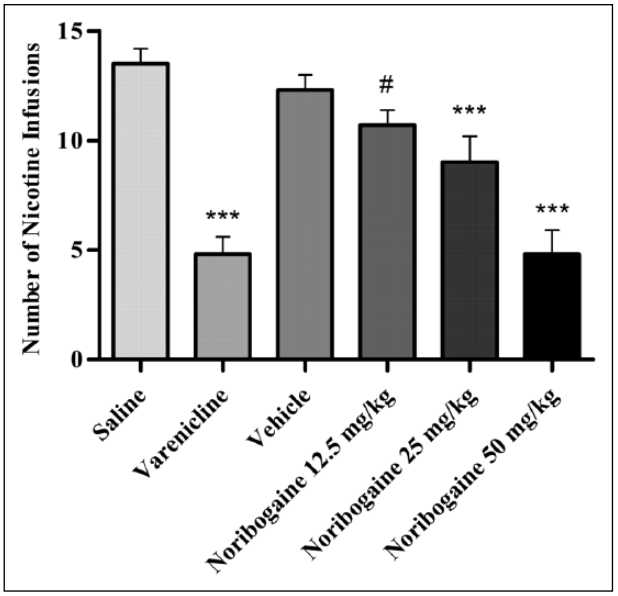

Figure 2. Effects of noribogaine and varenicline on nicotine self-administration in rats. Data represent mean±standard error of the mean (SEM) of $n=13$ animals. #$p<0.10$; ***$p<0.001$ compared to vehicle or saline treatment. The y-axis shows the total number of animal-initiated nicotine infusions during the one-hour test session.

Discussion

The present study demonstrated the efficacy of noribogaine in reducing nicotine drug self-administration up to 64% in rats two hours after oral administration of the drug as compared to saline. Noribogaine significantly decreased nicotine self-administration in rats in a dose-dependent manner while food responding remained stable at the lower dose of noribogaine, and a moderate depression (up to 23%) of food pellet responding in food-maintained control rats was observed at the highest dose. A dose of 50 mg/kg noribogaine, when given orally, was equi-effective to 1.7 mg/kg intraperitoneal varenicline. The findings indicate that noribogaine attenuates the reinforcing effects of nicotine, which helped ascertain its potential as a treatment for nicotine dependence. Further studies to assess noribogaine efficacy in paradigms of nicotine withdrawal symptomatology and drug reinstatement, as well as evaluation of noribogaine's tolerance, i.e. decrease of its efficacy upon repetitive use, are warranted.

Table 1. Lever response measures during the one-hour test session on nicotine self-administration in rats.

		Varenicline (mg/kg)		Noribogaine (mg/kg)			
		0 (saline)	1.7	0 (vehicle)	12.5	25	50
Active lever responses	**Mean**	40.75	15.00	37.15	32.31	27.54	15.23
	SEM	2.23	2.42	2.24	2.00	3.50	3.41
Inactive lever responses	**Mean**	8.08	2.92	9.42	8.23	6.00	3.83
	SEM	1.92	0.75	0.95	1.93	1.45	1.35
Percentage of inactive lever responses	**Mean**	16.05	16.50	20.47	18.67	18.32	19.52
	SEM	3.52	3.53	1.62	3.52	3.77	4.79

SEM: standard error of the mean. There was no statistical difference in percentages of inactive lever response in different treatments.

Noribogaine has previously demonstrated efficacy at attenuating self-administration to other drugs of abuse such as ethanol and cocaine (see introduction) (Glick et al., 1996; Mash and Schenk, 1996; Rezvani et al., 1995a). This suggests its potential to attenuate drug self-administration to a combination of nicotine with these drugs. In fact, poly-drug use is most commonly seen in human addictive behaviors and adequate drug-based therapies for poly-substance dependence remains a major challenge (for review see Kenna et al., 2007). For example, modafinil failed to demonstrate a clear amelioration to cocaine addiction in the clinic (Dackis et al., 2012) despite encouraging pre-clinical results. Interestingly, in another study carried out on 125 cocaine-dependent subjects, the major finding was that modafinil decreased craving and cocaine use, but only in subjects without co-morbid alcohol dependence (Anderson et al., 2009). Thus, it is clear that effective treatments for primary drug dependence must encompass a certain level of robustness toward co-morbidity to other commonly abused substances, such as ethanol and nicotine (Kenna et al., 2007). If noribogaine proves as efficacious as the combinations of nicotine-ethanol, nicotine-cocaine, ethanol-cocaine, or ethanol-nicotine-cocaine, it would largely increase the likelihood of successful translation to clinical paradigms with participants afflicted by poly-substance dependence.

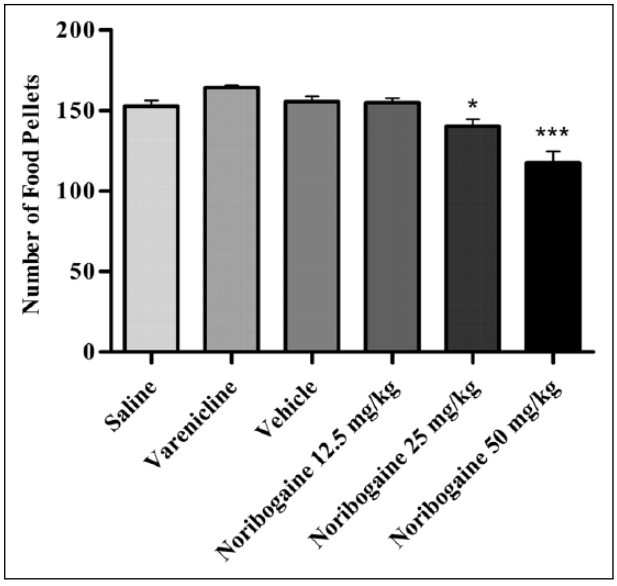

Figure 3. Effects of noribogaine and varenicline in food maintained responding rats. Data represent mean±standard error of the mean (SEM) of n=8 animals. *p<0.05; ***p<0.001 compared to vehicle or saline treatment. The y-axis shows the total number of food pellets obtained by the animals during the one-hour test session.

In our study, we used varenicline as a positive control and showed that noribogaine can attenuate the reinforcing effects of nicotine to the same degree of efficacy of varenicline at the dose tested. Varenicline is a partial agonist at α4β2 and a full agonist at α7 neuronal nicotinic receptors, with a selectivity ratio of 8 for α4β2 to α7 (Mihalak et al., 2006). Varenicline has lower potency but higher efficacy at α3β4 receptors, with a selectivity ratio of 24 for α4β2 vs α3β4. The mechanism of action of varenicline in attenuating the reinforcing effects of nicotine in animal models, and decreasing nicotine smoking in human, was initially postulated to principally implicate its activity at the α4β2 nAChRs and thus partially substituting to nicotine (Coe et al., 2005). Noribogaine does not display particular activity at the α4β2 nAChRs but has inhibitory power at habenula-type α3(α5, β2 β4) containing nAChRs and at the homomeric α7 nAChRs. AT-1001, a high affinity α3β4 nAChRs inhibitor with >90 fold selectivity over α4β2 and α7 nAChRs dose-dependently blocked nicotine self-administration in rats (Toll et al., 2012). Thus, pharmacological manipulations implicating different mechanism of action can lead to similar behavioral outcomes.

A recently published study proposed that the effect of varenicline on ethanol consumption is likely due to its activity on α3β4 receptors instead of α4β2 (Chatterjee et al., 2011), which is in line with contemporaneous reports emphasizing neuronal nAChRs as a common substrate for nicotine and ethanol dependence (e.g. Hendrickson et al., 2013). A mechanism implicating the inhibition of α3β4 nAChRs was suggested to mediate the effects of the polypharmacological drug 18-methoxycoronaridine (18-MC) at decreasing self-administration of drug of abuse including nicotine and ethanol in rats (Glick et al., 2000; Rezvani et al., 1997). Interestingly both ibogaine and noribogaine, which are structurally related to 18-MC, also inhibit pure α3β4 nAChRs, ibogaine being more potent than 18-MC in that regard. Finally, recent results from our group showed that ibogaine and noribogaine were more potent inhibitors at endogenous receptors composed of

Table 2. Lever response measures during the one-hour test session in food maintained responding rats.

		Varenicline (mg/kg)		Noribogaine (mg/kg)			
		0 (saline)	1.7	0 (vehicle)	12.5	25	50
Active lever responses	**Median**	462	487.5	472.5	468	411	349.5
	Range	405–498	426–507	405–501	429–492	144–480	249–462
Inactive lever responses	**Median**	0.5	0	0	0	0	5
	Range	0–20	0–1	0–2	0–23	0–47	0–30
Percentage of inactive lever responses	**Median**	0.11	0	0	0	0	1.59
	Range	0–4.10	0–0.21	0–0.44	0–4.48	0–24.61	0–8.40
Rank of percentage of inactive lever responses	**Median**	20.5	23	23	23	23	7.5[a]
	Range	4–23	19–23	15–23	3–23	1–23	2–23

Analysis of variance (ANOVA) on pre-ranked percentage data showed that noribogaine at 50 mg/kg had a significant higher inactive lever response relative to vehicle treatment. [a]p<0.01.

α3, α5, β4, and β2 nAChRs subunits, a population notably found in the medial habenula and the interpeduncular nucleus (see introduction), raising further considerations for mechanisms involving the nicotinic cholinergic system and a central calmative activity.

Baldwin et al. (2011) proposed that the continuous use of drugs of abuse, notably nicotine, would result in habenular hyperactivity representing a compensatory mechanism for drug-triggered dopamine release. In that frame, drug cessation could be seen as a non-compensatory habenular hyperactivity that results in a state of continuous disappointment (negative emotional state), driving repeated drug use. Drugs that alter habenular activity, a categorization that noribogaine might be grouped with, were proposed as potential therapies against tobacco smoking and drug addiction in general.

In addition, it has been shown that if β2-containing nicotinic receptors were governing consumption during the initial phase of nicotine access, the α7 receptors may be more important for continuing nicotine self-administration over a period of months (Levin et al., 2009). Long-term cigarette smoking, often of several years, is a reality and this study brought interesting receptor-targeting considerations for smoking cessation drug candidates. Future investigations utilizing cholinergic receptor knock-out mouse models may prove useful to investigate the specific roles of noribogaine modulation at the nicotinic receptor populations found in the habenula and α7 receptors in the frame of addiction, impulse control, motivation, mood and emotion.

Even though increased dopamine in the brain reward system is generally viewed as the final common pathway for the reinforcing properties of drugs, other neurotransmitters such as serotonin, endogenous opiates, gamma-aminobutyric acid (GABA), and acetylcholine non-exhaustively are involved in the modulation of both drug self-administration and dopamine levels (Lowinson et al., 1997). Noribogaine is a poly-pharmacological drug and has known activities at the SERT reuptake inhibitor (Baumann et al., 2001a), and the mu and kappa opioid receptor (Maillet et al., 2015b). Increasing serotonergic component, for example, may be important in down-modulating motivational factors to obtain a drug (Lowinson et al., 1997). Noribogaine or ibogaine themselves did not directly altered the levels of dopamine in the nucleus accumbens of rats (Baumann et al., 2001b) but ibogaine for instance was shown to block nicotine-induced but not cocaine-induced dopamine rise in this brain region (Glick et al., 2000). The most commonly used pharmacotherapeutic intervention aimed to cease and/or mitigate addiction to a drug of abuse is drug-replacement therapy, which noribogaine does not appear to belong to. However, other valid approaches may be reduction of the rewarding components of the drug; reduction of the excessive attribution of incentive salience to drugs and drug-related stimuli (Robinson and Berridge, 1993), and reduction of the negative states associated to withdrawals and abstinence (Koob and Le Moal, 2001). Future studies may help to better define the actual attributes of noribogaine toward these pathways.

The findings of this study also show that noribogaine can decrease behavioral self-administration toward a nondrug reinforcer, food reward, in rats. The magnitude of this effect was a decrease of 10% and 23% at 25 mg/kg and 50 mg/kg noribogaine whereas drugs known to strongly affect this endpoint such as lorcaserin, and fenfluramine were reported to decrease food-responding up to ~60–63% (Higgins et al., 2012; Pickens et al., 2012). A 14-day toxicological study conducted in free-fed rats indicated that noribogaine up to 100 mg/kg displayed equivalent levels of food intake and body weight compared to control rats (Supplementary Material). Thus noribogaine's effects on food-responding did not appear correlated to potential appetite suppressant properties and may be mostly limited to rewarding situations – a domain of drug abuse. This pattern suggests interesting properties at modulating the circuits processing the encoding of natural rewards which are commonly thought to be "hijacked" by drugs of abuse.

A caveat in drug-based therapies for substance dependence is seen with reallocation to another forms of non-adaptive behaviors, and the pursuit of alternative drug but also nondrug reinforcers (Banks and Negus, 2012). In fact, studies have shown that stimuli and activities that are known to have a potential for behavioral and nondrug addictions such as gambling, shopping, orgasm, video game playing, appetizing food activated many of the same brain regions than drugs of abuse, for review (Olsen, 2011). Natural reinforcers are indeed capable of leading to behavioral and neurotransmission adaptations reminiscent of those seen after exposure to drugs of abuse (Olsen, 2011). Future studies utilizing choice procedures would be interesting designs to assess noribogaine's effects on reallocation of behaviors in comparison to available drug therapies for substance dependence.

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Declaration of Conflicting Interests

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