Ibogaine-like effects of noribogaine in rats

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Abstract

Ibogaine is a naturally occurring alkaloid that has been claimed to be effective in treating addiction to opioids and stimulants; a single dose is claimed to be effective for 6 months. Analogously, studies in rats have demonstrated prolonged (one or more days) effects of ibogaine on morphine and cocaine self-administration even though ibogaine is mostly eliminated from the body in several hours. These observations have suggested that a metabolite may mediate some of the effects of ibogaine. Recently, noribogaine was identified as a metabolite of ibogaine. Accordingly, the present study sought to determine, in rats, whether noribogaine had pharmacological effects mimicking those of ibogaine. Noribogaine (40 mg/kg) was found to decrease morphine and cocaine self-administration, reduce the locomotor stimulant effect of morphine, and decrease extracellular levels of dopamine in the nucleus accumbens and striatum. All of these effects were similar to effects previously observed with ibogaine (40 mg/kg); however, noribogaine did not induce any ibogaine-like tremors. The results suggest that noribogaine may be a mediator of ibogaine's putative anti-addictive effects.

Keywords: Ibogaine; Noribogaine; Morphine; Cocaine; Drug self-administration; Microdialysis; Dopamine

Ibogaine, an alkaloid found in the root bark of the African shrub Tabernanthe iboga, has been claimed to be effective in treating addiction to opioids and stimulants; a single dose is claimed to be effective for 6 months. Analogously, studies in rats have demonstrated prolonged (one or more days) effects of ibogaine on morphine and cocaine self-administration even though ibogaine is mostly eliminated from the body in several hours. These observations have suggested that a metabolite may mediate some of the effects of ibogaine. Recently, noribogaine was identified as a metabolite of ibogaine. Accordingly, the present study sought to determine, in rats, whether noribogaine had pharmacological effects mimicking those of ibogaine. Noribogaine (40 mg/kg) was found to decrease morphine and cocaine self-administration, reduce the locomotor stimulant effect of morphine, and decrease extracellular levels of dopamine in the nucleus accumbens and striatum. All of these effects were similar to effects previously observed with ibogaine (40 mg/kg); however, noribogaine did not induce any ibogaine-like tremors. The results suggest that noribogaine may be a mediator of ibogaine's putative anti-addictive effects.
interface. The intravenous self-administration system con-

sisted of polyethylene-silicone cannulas constructed ac-
cording to the design of Weeks [11], BRS/LVE harnesses

and commutators, and Harvard Apparatus infusion pumps
(#55-2222). Shaping of the bar-press response was ini-
tially accomplished by training rats to bar-press for water.

Cannulas were then implanted in the external jugular vein

according to procedures described by Weeks [11]. Self-ad-

ministration testing began with a single 24-h session fol-

lowed by daily 1-h sessions, 5 days (Monday–Friday) a

week. Depending upon the group, a lever-press response

produced either a 20 μl (morphine) or 50 μl (cocaine)

infusion of drug solution (0.01 mg of morphine sulfate or

0.1 mg of cocaine hydrochloride) in about 0.4 (morphine)

or 1.0 (cocaine) second. Since all rats generally weighed

250 ± 20 g, each response delivered approximately 0.04

mg/kg of morphine or 0.4 mg/kg of cocaine. Experiments
to assess the effects of noribogaine were begun when

baseline self-administration rates stabilized (< 10% varia-

tion from 1 day to the next across 5 days), usually

after 2 weeks of testing. Noribogaine or saline was ad-

ministered to different groups of rats responding for morphine

or saline; injections were made on Wednesdays, fifteen

minutes before a self-administration session. In order to

provide an indication of the specificity of noribogaine’s

effects on bar-pressing for morphine and cocaine, noribo-

gaine was also administered to other rats bar-pressing for

water on a comparable schedule (continuous reinforce-

ment; 1-h sessions).

The effect of noribogaine on morphine-induced locomo-

tor stimulation was studied using the same procedures

employed with ibogaine [10]. Locomotor activity was as-

sessed using cylindrical photocell activity cages (60 cm,

three crossing beams) interfaced to an IBM compatible

386 computer. Different groups of rats were pretreated

with noribogaine or saline, and 19 h later, treated with

morphine sulfate (5 mg/kg, i.p.) immediately before being

placed into the activity cages. Locomotor activity was

monitored for 3 h thereafter.

The microdialysis procedures used to assess the effects

of noribogaine on extracellular levels of dopamine and its

metabolites in the nucleus accumbens and striatum have

been used extensively in this laboratory (e.g. [2,5]). Briefly,

under pentobarbital anesthesia, rats were implanted stereo-

taxically with guide cannulas over the nucleus accumbens

(rostral, + 0.5 mm; lateral, −2.9 mm; ventral, −7.0 mm) [8].

The two cannulas were fixed firmly in the skull with dental cement. One cannula was implanted in the left side of the brain, and the other in the right side of the brain; the side (left or right) assigned to each region (nucleus accumbens or striatum) was alternated from animal to animal.

At least 4 days after surgery, a rat was placed in a
dialysis chamber, a cylindrical (30 cm diameter) Plexiglas

cage providing free access to food and water. Probes (2 or

3 mm, respectively, for nucleus accumbens or striatum;

CMA 8309562 or CMA8309563) were then lowered into

the guide cannulas. The dialysis probes were continuously

perfused with a solution containing 146 mM NaCl, 2.7

mM KCl, 1.2 mM CaCl₂ and 1.0 mM MgCl₂ at a flow

rate of 1 μl/min. On the next morning (15 20 h later),

the dialysis experiment was carried out on a freely moving

animal. Twenty-min fractions were collected in vials con-
taining 2 μl of 1.1 N perchloric acid solution (containing

5 mg/l EDTA and 5 mg/l sodium metabisulfite). Upon

completion of an experiment, rats were killed and histolog-

ical analysis of each brain was performed to verify the

locations of the probes.

Perfusate samples were analyzed by HPLC with electro-

chemical detection. The HPLC consisted of a Waters pump

(model 510), a WISP autosampler (model 712), a Phase

Separation Spherisorb C-18 column (S3 ODS2; 10 cm ×

4.6 mm) and a Waters detector (model 464). The mobile

phase consisted of 6.9 g/l sodium monobasic phosphate,

450 mg/l heptane sulfonic acid, 80 mg/l disodium EDTA,

and 110 ml/l methanol; the solution was adjusted with

HCl to pH 3.7 and was pumped at a rate of 1.2 ml/min.

Chromatograms were processed using Hewlett-Packard

HPLC 2D Chem Station software.

Fig. 1 shows the effects of noribogaine on morphine

and cocaine self-administration and on bar-pressing for

water. Acutely (Day 1), noribogaine decreased morphine

and cocaine intake as well as responding for water

(ANOVA, P < 0.01, in each case). However, while re-

sponding for water returned to baseline a day later, noribo-

gaine continued to depress morphine and cocaine intake

for at least a day afterwards. In both of the latter cases, a

group × days interaction was significant (P < 0.05 in a

two-way ANOVA for days 2–7), and paired t-tests with-

baseline values were significant (P < 0.05) for day 2 in

both of the noribogaine treatment groups. The extent of

these aftereffects (one or more days later) on drug self-ad-

ministration varied from rat to rat; responses beyond a day

later (Day 2) ranged from no further effect to a prolonged

depression of morphine or cocaine intake for up to 2

weeks.

The Med Associates interface and software provided

cumulative and event records of responding for each self-

administration test session. For both morphine and co-

caine, normal patterns of responding were characterized by

an initial burst of drug intake at the beginning of each

session followed by regularly spaced responding thereafter.

Two kinds of noribogaine-induced effects, very similar to

those produced by ibogaine and other iboga alkaloids [2],

were clearly apparent. Acutely, on the day of administra-

tion, noribogaine suppressed responding almost entirely in

most animals. In contrast, the prolonged aftereffects of

noribogaine on morphine and cocaine intake were charac-
The effects of noribogaine bear a striking resemblance to the effects previously observed with ibogaine [2,4,5,9]. Both ibogaine and noribogaine depressed morphine and cocaine self-administration for prolonged and variable periods of time, both antagonized the locomotor stimulant effect of morphine, and both decreased extracellular levels of DA in NAC and striatum; even the noribogaine-induced increases in DA metabolites were similar to previous results with ibogaine [5].

The similarity of ibogaine's and noribogaine's effects raises the issue of the extent to which ibogaine's effects are mediated by conversion to noribogaine. If noribogaine were totally responsible for ibogaine's effects, it might be expected that noribogaine would be much more potent than ibogaine, i.e., in order to account for ibogaine's effects when noribogaine is to be greater than ibogaine ever, it is more likely that noribogaine is the active compound in ibogaine (fourfold).

Fig. 2 shows the effect of noribogaine on morphine-induced locomotor stimulation. Noribogaine reduced the effect of morphine during the first hour of testing (ANOVA, significant treatment × time interaction, P < 0.009; Newman–Keuls, first hour, P < 0.05).

Fig. 3 shows the acute effects of noribogaine on extracellular levels of dopamine in the nucleus accumbens (NAC) and striatum. Noribogaine significantly (ANOVA) decreased DA levels in both regions (P < 0.02 and 0.05 in NAC and striatum, respectively). There were also transient but significant (ANOVA and Newman–Keuls) increases (20–40%; data not shown) in striatal DOPAC (20–40 min) and in both NAC and striatal HVA (40–80 min; P < 0.04–0.001).
effects at a time (e.g., more than 24 h after administration) when ibogaine itself is no longer detectable in brain and noribogaine is present at modest concentrations [6]. Systemically, based on the present results, this does not appear to be the case (i.e., the effects of noribogaine were no greater than those of the same dose of ibogaine); and, in fact, preliminary data with lower doses suggest that noribogaine may be slightly less potent than ibogaine. However, ibogaine is much more lipid soluble than noribogaine [12], the former entering the brain more readily than the latter, so it is possible that noribogaine is considerably more potent than ibogaine at critical sites of action; indeed, noribogaine’s affinities for kappa opioid receptors [9] and serotonin transporter sites [7] are considerably greater (fourfold and tenfold, respectively) than those of ibogaine. It should also be noted that, at 40 mg/kg, ibogaine elicits very obvious whole body tremors (e.g., [2]) whereas, in the present study, noribogaine, at the same dosage, elicited no apparent tremors, consistent with previous observations of others in mice [12]. It appears then that noribogaine does not mediate all of ibogaine’s effects but may rather selectively mediate those putative anti-addictive effects that persist for prolonged periods of time. We have previously observed that ibogaine is sequestered in fat, and have suggested that ibogaine’s long-term effects are mediated by slow release from fat tissue and subsequent conversion to noribogaine [3]. The present data are certainly consistent with this hypothesis.

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References