Anxiolytic Effects of Noribogaine on Novelty Stress in Rats and Zebrafish

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Abstract

Noribogaine, a novel investigational drug, was evaluated for: a) effects on locomotor activity in rats using a forced swim test; b) effects on exploratory behavior in zebrafish using an open field test; and c) effects on the behavioral profile of ibogaine, a highly anxiogenic drug, in rats using an open field test. Novelty stress, in rats and zebrafish, consistently reduced locomotor activity and exploratory behavior, and augmented the ataxic effects of ibogaine. In contrast, noribogaine attenuated novelty stress-induced decreases in locomotion and exploratory activity in rats and zebrafish. Noribogaine reversed the anxiogenic effects of ibogaine in rats. These results suggest that noribogaine may be a promising anxiolytic candidate for further development.

Introduction

Noribogaine is a novel investigational drug that appears to be closely related to ibogaine but, unlike ibogaine, noribogaine did not produce tremors and ataxia in rodents. A study in healthy volunteers revealed safety and tolerability of single oral doses of 150 to 400 mg noribogaine. A single oral dose of 240 mg noribogaine was rated with large volume of distribution. It is a weak acid, and the majority of the absorbed dose is excreted in urine within 12 hours of dosing. In a recent acute sedative study in rodent models, noribogaine produced sedative effects in mice and rats, and demonstrated a concentration-dependent increase in QI Index. A multiple-doses study conducted in Benchley is ongoing. Molecular characterization indicated that noribogaine is a polypharmacological drug with a broad range of targets, including adenosine receptors, serotonin and dopamine receptors and the opioid receptors. With its potential to target noradrenergic, serotonergic, dopaminergic, and opioidergic systems, noribogaine has the potential to modulate cognitive and motivational, and stress-related components of the extended amygdala.

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Materials and Methods

(1) Functional Observational Battery (FOB) Testing in Female Rats

- Female Sprague-Dawley rats (10 weeks) were anesthetized by subcutaneous injection of a mixture of ketamine, xylazine, and acepromazine (100 mg/kg ketamine, 5 mg/kg xylazine, and 0.5 mg/kg acepromazine) to achieve appropriate levels of sedation.
- Rats were placed in a novel environment, and behavioral observations were recorded using a video camera for a period of 15 minutes.
- The following behaviors were scored: attention, locomotion, grooming, rearing, and loss of posture.

(2) Novel Tank Test (NTT) in Zebrafish

- Zebrafish were acclimated for 24 hours in a novel tank with water adjusted to room temperature (26°C). The apparatus was a 1.5-L rectangular tank (15 cm high x 20 cm wide x 7 cm wide). The water was aerated, and abdominal fin movements and swimming behavior of the zebrafish were recorded using the OpenLab Cytovision software.

Results

(1) Dose-dependent and transient anxiolytic effects of noribogaine in rats during open field assessment

- Noribogaine was found to have anxiolytic effects in a dose-dependent manner, with a low dose of 5 mg/kg showing significant anxiolytic effects.

(2) Effects of noribogaine on anxiogenic behavior in adult zebrafish using NTT test

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Conclusions

- Noribogaine dose-dependently reverses the anxiogenic effects of novelty stress in the open field test and the peak effects were noted 2 hours after administration. Noribogaine is distinguishable from other studies, as noribogaine suppresses the elevated plus maze and the cumulative behavior of zebrafish in the open field test.
- Noribogaine reverses novelty-induced anxiogenic activity in rats and zebrafish which is not associated with sedation, motor impairment, or ataxia.
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