Introduction

- Repeated exposure to psychostimulants, such as cocaine, produces behavioral sensitization which is characterized by augmented locomotor response to repeated stimulant challenge.
- Sensitization has been proposed to play a critical role in the development and maintenance of drug addiction (Robinson and Berridge, 1993).
- The present study determined whether locomotor sensitization in the mouse was a good predictor of abuse liability in humans.

Hypothesis

- Drugs that are abused in humans will show locomotor sensitization in the mouse model.

Sensitization Definition

- Increase in locomotor activity following successive injections of the drug and/or increased sensitivity to a challenge dose following a washout period.

General Methods

Animals

- Male C57BL/6J or Balb/cJ mice from Jackson Laboratory (Bar Harbor, ME) were housed in groups of four and maintained on a 12hr/12hr light/dark cycle. Room temperature was maintained between 20 and 23°C with a relative humidity between 30% and 70%. Chow and water were provided ad libitum for the duration of the study. All procedures were approved by PsychoGenics' Institutional Animal Care and Use Committee.

Locomotor Activity

- Locomotor activity was measured in Plexiglas square chambers (27.3 x 27.3 x 20.3 cm; Med Associates Inc., St. Albans, VT) surrounded by infrared photobeam sources. Distance traveled (cm) was measured as the index for activity. Mice were injected with vehicle or the appropriate test compound and placed in the chambers for a 30 min session.

Forced Swim Test

- Balb/cJ male mice were individually placed into clear glass cylinders (15 cm tall x 10 cm wide, 1 L beakers) containing 23±1°C water 12 cm deep (approximately 800 mL). The time the animal spent immobile was recorded over a 6 min trial. Immobility was defined as the absence of all movement except those required by the mouse to keep its head above the water.

Statistical Analysis

- Locomotor activity data were analyzed using analysis of variance (ANOVA) followed by Fisher’s LSD post hoc test when appropriate. An effect was considered significant if p<0.05.

Table 1. Compounds Tested

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<thead>
<tr>
<th>Compound Strain</th>
<th>Dose (mg/kg)</th>
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<tr>
<td>C57BL/6J</td>
<td>10</td>
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Table 2. Locomotor Sensitization Design

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<td></td>
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Figure 1: Cocaine produced sensitization in C57BL/6J but not Balb/cJ mice

Figure 2: Bupropion, an antidepressant DAT/NET inhibitor, produced sensitization in the challenge test

Figure 3: Modafinil, a wake-promoting DAT inhibitor, produced sensitization in the challenge test

Figure 4: DOV 216,303, the antidepressant DAT/NET/SERT inhibitor, produced sensitization in the challenge test

Figure 5: JZAD-IV-22, a DAT/NET/SERT inhibitor, did not produce sensitization in the challenge test

Figure 6: JZAD-IV-22 produced antidepressant-like effects in the forced swim test

Summary

- C57BL/6J, but not Balb/cJ mice, showed locomotor sensitization to cocaine (15mg/kg).
- Bupropion, an antidepressant DAT/NET inhibitor, produced locomotor hyperactivity, but not locomotor sensitization in mice. Bupropion shows no evidence of abuse liability in humans.
- Modafinil, a wake-promoting weak DAT inhibitor, showed locomotor sensitization in the challenge test.
- Although modafinil is a schedule IV medication under the Controlled Substances Act, post-marketing evidence suggests that modafinil has limited potential for large-scale abuse. Modafinil's limited abuse liability, however, may be related to its poor chemical properties (e.g. poor solubility and degradation when heated).
- DOV 216,303, a DAT/NET/SERT inhibitor that showed efficacy in a Phase II clinical trial for depression, did not produce acute locomotor activation or locomotor sensitization.
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Conclusions and Future Directions

The locomotor sensitization assay:

- shows some predictive validity in assessing abuse liability in humans.
- can be utilized to screen therapeutic compounds with a dopaminergic component for abuse liability.
- suggests that PsychoGenics’ ‘triple’ reuptake inhibitors such as JZAD-IV-22 may have less potential for abuse in humans than DOV 216,303.
- Additional compounds, both with and without abuse liability in humans, will be screened to further validate the mouse locomotor sensitization assay.

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