Comparison of Typical and Atypical Antipsychotics on PCP-Induced Hyperactivity in Mice


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Introduction

Schizophrenia is a disorder characterized by delusions, hallucinations, disordered thought, and social withdrawal. In humans, NMDA receptor antagonists such as phencyclidine (PCP) can produce symptoms that resemble some aspects of schizophrenia (Jentsch and Roth, 1999). Drugs that facilitate dopamine release, such as amphetamine, can also mimic schizophrenic symptoms (Ujike & Sato, 2004).

In animal models, both PCP and amphetamine produce a profound locomotor hyperactivity, which in some cases, can be antagonized by antipsychotic drugs (Freed et al., 1980; 1984; O’Neill & Shaw, 1999). The PCP and amphetamine-induced hyperactivity models were used in the present study to investigate whether they could distinguish between typical and atypical antipsychotics.

Hypothesis

PCP-induced hyperactivity will be sensitive to atypical, but not typical antipsychotics.

Amphetamine-induced hyperactivity will be sensitive to typical, but not atypical antipsychotics.

Methods

Animals

Male C57BL/6J mice from Jackson Laboratory (Bar Harbor, Maine) were housed in groups of four and maintained on a 12 hr/12 hr 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. Prior to testing, all mice were examined on a regular basis, handled, and weighed to assure adequate health and suitability. In each test, animals were randomly assigned across treatment groups. 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 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 baseline session. Mice were then injected with PCP (5mg/kg) or d-amphetamine (1mg/kg) and placed in the chambers for a 60 min test session.

Table 1.

Antipsychotics Tested

<table>
<thead>
<tr>
<th>Typical</th>
<th>Atypical</th>
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</thead>
<tbody>
<tr>
<td>Haloperidol (0.01, 0.1, or 0.3mg/kg)</td>
<td>Clozapine (1mg/kg)</td>
</tr>
<tr>
<td>Chlorpromazine (0.1, or 0.05mg/kg)</td>
<td>Olanzapine (0.01, 0.03, or 0.1mg/kg)</td>
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<tr>
<td>Pimozide (0.05mg/kg)</td>
<td>Amphetamine (1mg/kg)</td>
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</tbody>
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References


Summary

- In C57BL/6J mice, both phencyclidine (PCP) (5mg/kg) and amphetamine (4mg/kg) produced the expected increases in locomotor activity.
- PCP-induced hyperlocomotion was inhibited by both typical (chlorpromazine and pimozide) and atypical (clozapine and olanzapine) antipsychotics with no accompanying baseline sedation. The typical antipsychotic haloperidol, however, only reduced PCP-induced hyperactivity at doses that also caused baseline sedation.
- Amphetamine-induced hyperlocomotion was inhibited by a typical antipsychotic (haloperidol) but not by the atypical antipsychotic clozapine.
- Future studies will test whether inhibition of amphetamine-induced hyperactivity is sensitive only to typical antipsychotics.
- Screening compounds in parallel in the PCP and amphetamine assays may help to identify drugs for the treatment of schizophrenia that are free of the extrapyramidal side effects associated with typical antipsychotics.