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

B.J. Caldarone, M. Nilges, M.L. Manzano, S.A. Malekiani, A.C. Fedolak, P. McGonigle, and T. Hanania*

PsychoGenics Inc., Tarrytown, NY 10591, USA

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 senstive 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 23ºC 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 (4mg/kg) and placed in the chambers for a 60 min test session.

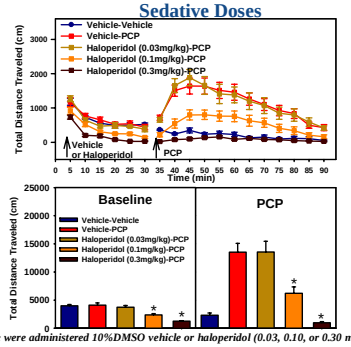
Table 1.

Antipsychotics Tested	
Typicals	Atypicals
PCP	
Haloperidol (0.03, 0.1, 0.3mg/kg)	Clozapine (1mgkg)
Chlorpromazine (0.3, 1.0mg/kg)	Olanzapine (0.01, 0.03, 0.10mg/kg)
Pimozide (10, 30mg/kg)	
Amphetamine	
Haloperidol (0.3mg/kg)	Clozapine (3mgkg)

Statistical Analysis

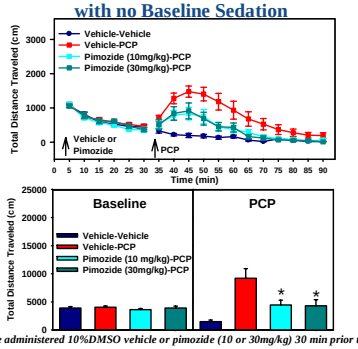
- Locomotor activity data were analyzed using analysis of variance (ANOVA) followed by Fisher's PLSD post hoc test when appropriate. An effect was considered significant if $p<0.05$.

Figure 1: The Typical Antipsychotic Haloperidol Inhibits PCP-Induced Hyperactivity only at Sedative Doses



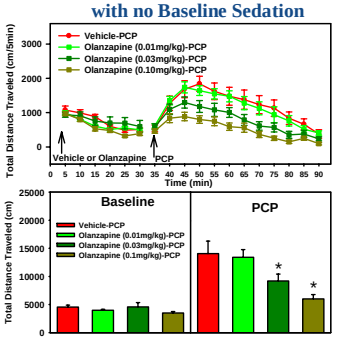
Mice were administered 10%DMSO vehicle or haloperidol (0.03, 0.10, or 0.30 mg/kg) and baseline activity was measured for 30 min. Mice were then administered PCP (5mg/kg) and activity was measured for 60min.
*Data are mean ±SEM. *p<0.05 vs. Vehicle-Vehicle (baseline) or Vehicle-PCP (PCP)*

Figure 3: The Typical Antipsychotic Pimozide Inhibits PCP-Induced Hyperactivity with no Baseline Sedation



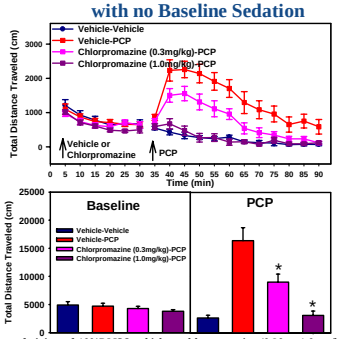
Mice were administered 10%DMSO vehicle or pimozide (10 or 30mg/kg) 30 min prior to a 30 min baseline activity measurement. Mice were then administered PCP (5mg/kg) and activity was measured for 60min.
*Data are mean ±SEM. *p<0.05 vs. Vehicle-PCP*

Figure 5: The Atypical Antipsychotic Olanzapine Inhibits PCP-Induced Hyperactivity with no Baseline Sedation



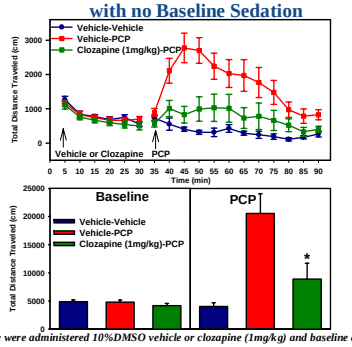
Mice were administered water vehicle or olanzapine (0.01, 0.03, or 0.10 mg/kg) and baseline activity was measured for 30 min. Mice were then administered PCP (5mg/kg) and activity was measured for 60min.
*Data are mean ±SEM. *p<0.05 vs. Vehicle-PCP*

Figure 2: The Typical Antipsychotic Chlorpromazine Inhibits PCP-Induced Hyperactivity with no Baseline Sedation



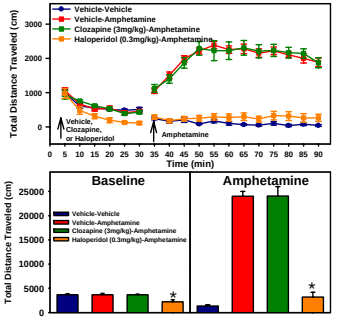
Mice were administered 10%DMSO vehicle or chlorpromazine (0.30 or 1.0 mg/kg) and baseline activity was measured for 30 min. Mice were then administered PCP (5mg/kg) and activity was measured for 60min.
*Data are mean ±SEM. *p<0.05 vs. Vehicle-PCP*

Figure 4: The Atypical Antipsychotic Clozapine Inhibits PCP-Induced Hyperactivity with no Baseline Sedation



Mice were administered 10%DMSO vehicle or clozapine (1mg/kg) and baseline activity was measured for 30 min. Mice were then administered PCP (5mg/kg) and activity was measured for 60min.
*Data are mean ±SEM. *p<0.05 vs. Vehicle-PCP*

Figure 6: Haloperidol, but not Clozapine, Inhibits Amphetamine-Induced Hyperactivity



Mice were administered 10%DMSO vehicle, haloperidol (0.30 mg/kg) or clozapine (3mg/kg) and baseline activity was measured for 30 min measurement. Mice were then administered amphetamine (4mg/kg) and activity was measured for 60min.
*Data are mean ±SEM. *p<0.05 vs. Vehicle-Vehicle (baseline) or Vehicle-Amphetamine (amphetamine)*

References

- *Freed WJ, Bing LA & Wyatt RJ (1984). Effects of neuroleptics on phencyclidine (PCP)-induced locomotor stimulation in mice Neuropharmacology. 23(2A):175-81.*
- *Freed WJ, Weinberger DR, Bing LA, Wyatt RJ (1980). Neuropharmacological studies of phencyclidine (PCP)-induced behavioral stimulation in mice. Psychopharmacology 71(3):291-7*
- *Jentsch JD & Roth RH (1999). The neuropsychopharmacology of phencyclidine: From NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 20(3):201-25.*
- *O'Neill MF & Shaw G. (1999). Comparison of dopamine receptor antagonists on hyperlocomotion induced by cocaine, amphetamine, MK-801 and the dopamine D1 agonist C-APB in mice. Psychopharmacology 145(3):237-50.*
- *Ujike H & Sato M (2004). Clinical features of sensitization to methamphetamine observed in patients with methamphetamine dependence and psychosis. Annals of the New York Academy of Sciences 1025:279-87.*

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.