Inhibitors of the N-methyl-D-aspartate (NMDA) receptor induce psychosis-like behavior in various animal species, including humans. However, both epidemiological and preclinical data also suggest that schizophrenia may result from abnormal neurodevelopment. An animal model of schizophrenia-related deficits induced by early interference with NMDA receptor functions may therefore have translational value. We evaluated the long-term consequences of neonatal treatment with phencyclidine (PCP) in the rat as well as their reversal by antipsychotics.

**INTRODUCTION**

Hyperactivity in adulthood seems to be a robust characteristic of the PCP model, although its expression is age-dependent. Exaggeration of hyperactivity in response to an acute challenge with PCP is less robust than spontaneous hyperactivity. Progressive development of hyper-reactivity to PCP, as reflected by stereotypic behavior, may be a key characteristic of the model. The neonatal PCP model of psychosis-related behavior in the rat can therefore be used in the evaluation and development process of new chemical entities for antipsychotic-like activity and assist with translation to the clinic.

**MATERIAL & METHODS**

- **Animals:** Female Wistar rats, together with their litters, were obtained 1 day after delivery and were housed under standard housing conditions (1 cage per male and litter). On day 21 male pups were weaned and housed in separate housing cages (N= 4 per cage).
- **Treatments:**
  - First experiment: dose response of PCP. Male pups received 3 subcutaneous injections of PCP at 0, 5, 10 or 20 mg/kg on postnatal days 7, 9 and 11.
  - Second experiment: reversal by antipsychotics. Male pups received 3 subcutaneous injections of PCP at 0 or 20 mg/kg on postnatal days 7, 9 and 11. The rats were then administered once daily with haloperidol (0.25 mg/kg i.p.), clozapine (1 mg/kg i.p.) or vehicle (0.2% HPMC in physiological saline i.p.) from week 7 to Week 11.
- **Experimental procedures:**
  - Activity Meter Test: The activity meter consists of Plexiglas cages contained within a darkened cabinet. Each cage is equipped with photocell assemblies in order to measure the number of movements by each animal (one per cage) in the horizontal plane. The number of horizontal crossings by each animal is recorded by computer in 10-minute intervals and cumulated over the 40-minute period.
  - PCP-induced Hyperactivity Test: Immediately after the Activity Meter Test, rats are injected with PCP (3 mg/kg s.c.) and are immediately replaced in the activity meter. The scores for activity (horizontal crossings) are recorded by computer over 10-minute intervals and cumulated over a 30-minute period.
  - PCP-induced Stereotypy Test: Immediately after the PCP-hyperactivity test, rats are placed in individual Plexiglas enclosures and scored for the intensity of stereotypies on a 4 point scale. Observations are performed at 10 minute intervals for 3 hours. A total stereotype score per animal is obtained by accumulating the stereotype scores obtained at each interval.
  - Statistics: The data are represented as mean ± SEM. Statistical analysis of drug effects were performed by comparing treated groups with appropriate control group using unpaired Student’s t test.

**RESULTS**

- **Activity Meter Test**
  - Increased locomotion behavior in the mature rats previously treated at 5, 10 and 20 mg/kg (Week 12) confirmed at 20 mg/kg (Week 11) in the reversal experiment.
  - Haloperidol (0.25 mg/kg) and to a lower extent clozapine (1 mg/kg) reversed neonatal PCP-induced hyperactivity (Week 11).

- **PCP-Hyperactivity Test**
  - Significant increase in PCP-hyperactivity in mature rats previously treated with PCP at 5 and 10 mg/kg (Week 9) and at 20 mg/kg (Week 12) confirmed at 20 mg/kg (Week 11) in the reversal experiment.
  - Haloperidol weakly and significantly inhibits PCP challenge induced/hyperactivity but clozapine is not clearly active.

- **PCP-Stereotypy Test**
  - Increased PCP-induced stereotypies in rats previously treated with PCP at 5 and 20 mg/kg (Week 6), 20 mg/kg (Week 9) and 5, 10 and 20 mg/kg (Week 12) confirmed at 20 mg/kg (Week 11) in the reversal experiment.
  - Haloperidol and clozapine significantly reversed the effects of neonatal PCP.

| N= 9 or 10 per group. | Unpaired Student’s t test * = p < 0.05, ** = p < 0.01, *** = p < 0.001, as compared with vehicle control group. # compared with Neonatal PCP control.

**CONCLUSION**

A copy of this poster can be downloaded from our website www.porsolt.com