INTRODUCTION

Schizophrenia is a severe mental disorder characterized by the presence of symptoms usually grouped into three categories: positive, negative, and cognitive signs. Many acute and sub-chronic animal models have been established and used in preclinical studies related to schizophrenia. In particular, phencyclidine (PCP) is used to induce schizophrenia-like deficits in rodents. The construct validity of some models has been criticized because they do not take into consideration the neurodevelopmental origin of schizophrenia. In this study, we focused on the neonatal PCP exposure and post-weaning social isolation model, aiming to induce schizophrenia-like symptoms in the rat. This dual-hit model, which combines an adverse early-life challenge followed by stress during adolescence, aims to induce at adulthood enduring behavioral deficits related to some signs of schizophrenia.

MATERIAL AND METHODS

- **Model induction:** Male Wistar rat pups were treated with PCP (10 mg/kg i.p.) on postnatal days (PND) 7, 9 and 11. Control rats were injected with physiological saline. On PND 24 all pups were weaned, neonatal PCP-treated rat pups were placed in individual cages for social isolation for the rest of the study while control rats were group housed (4 rats per cage).
- **Activity Meter test:** Rats were placed in cages equipped with photocell assemblies in order to measure the number of movements in the horizontal and vertical planes. The number of crossings and rears was recorded by computer in 20-minute intervals for 40 minutes.
- **Social Recognition test:** An unfamiliar juvenile was introduced into the home cage of an experimental rat for 5 minutes. Following this first contact (C1), the juvenile was returned to its isolation cage for 30 minutes until a second contact (C2) with the same experimental rat. The time the experimental rat spent investigating (sniffing, grooming, licking, closely following) the juvenile was recorded. The recognition indexes (C2/C1) was calculated.

RESULTS

- **Activity Meter test:** PCP-treated and post-weaning social isolated [PCP-PWSI] rats displayed a significant increase in the number of crossings, as compared with vehicle-treated and group-housed [V-GH] rats at 2, 3 and 6-month old (+69%, p < 0.01, +100%, p < 0.001 and +163%, p < 0.001). Similar effects were observed on the number of rears (+108%, +157% and +229%, respectively, p < 0.001). These data indicate the presence of an enduring locomotor hyperactivity in PCP-PWSI rats.
- **Social Recognition test:** PCP-PWSI rats displayed a significant decrease in the investigation time during the first contact with the juvenile rat, as compared with V-GH rats at 2 and 3-month-old (+23%, +21%, respectively, p < 0.01). A similar trend was also observed at 6-months old. The recognition ratio significantly increased in PCP-PWSI rats, as compared to V-GH rats at 2, 3 and 6-month old (+0.23, p < 0.01, +0.36, p < 0.001 and +0.23, p < 0.05). These data indicate the presence of an enduring social behavior impairment in PCP-PWSI rats.

Data were obtained from three batches of rats (a batch per age, n = 15-23 per group) and analyzed by comparing PCP-PWSI rats with V-GH rats for each test using unpaired Student’s t tests. NS = Not Significant; * = p < 0.05; ** = p < 0.01.

EFFECTS OF CHRONIC TREATMENT WITH CLOzapINE AND ARipipRAZOLE AT 2-MONTH OLD

The Activity Meter Test was performed on day 13 of the treatment with Clozapine or Aripiprazole. The Social Recognition Test was performed 24 hours after the Activity Meter Test. On testing days, Clozapine or Aripiprazole were administered 30 minutes before the test.
- **Activity Meter test:** PCP-PWSI rats treated daily over two weeks with Clozapine (3mg/kg, i.p.) or Aripiprazole (3mg/kg, i.p.) displayed a significant decrease in the number of crossings, as compared with vehicle-treated PCP-PWSI rats (-50%, p < 0.001 and -71%, p < 0.001). Similar effects were observed on the number of rears (+40%, p < 0.05 and -68%, p < 0.001). These data indicate that Clozapine and Aripiprazole inhibit locomotor hyperactivity of PCP-PWSI rats.
- **Social Recognition test:** A trend towards an increase in the investigation time during the first contact with the juvenile rat was observed in the Aripiprazole-treated PCP-PWSI rats. Clozapine significantly decreased the social recognition index in PCP-PWSI rats compared vehicle-treated PCP-PWSI rats (0.28, p < 0.05). These data indicate that Clozapine attenuates social recognition deficits observed in PCP-PWSI rats.

Data were obtained from one batch of rats aged 2-month old (n = 12 per group) and analyzed by comparing drug-treated PCP-PWSI rats with Vehicle-treated PCP-PWSI rats at each test using unpaired Student’s t tests. NS = Not Significant; # = p < 0.05; ## = p < 0.01, ### = p < 0.001. Vehicle-treated PCP-PWSI rats was compared to vehicle-treated VGH rats using also unpaired Student’s t tests. NS = Not Significant; * = p < 0.05; ** = p < 0.01.

CONCLUSION

Our findings reveal that the dual-hit neonatal PCP and post-weaning social isolation model is associated with the presence of enduring hyperactivity and social recognition deficits that are relevant to symptoms affecting schizophrenic patients. Chronic treatment with Clozapine normalizes the behavior of animals. These results confirm the construct and predictive validity of this model. Dual interventions at two crucial early-life neurodevelopmental stages (corresponding to the third trimester of pregnancy and adolescence in humans) lead to the presence of chronic behavioral deficits that can be reversed with antipsychotic drugs used to treat schizophrenia in humans.