Efficacy of antipsychotic treatments in rodent models of social recognition and social interaction

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Introduction

Social interaction and social recognition are fundamental components of the biology of many species. A number of neuropsychiatric disorders , including depression, autism spectrum disorders, obsessive-compulsive disorders, and schizophrenia, are characterized by disruptions in social behavior. Social withdrawal and impaired cognitive function have been associated with the negative symptoms of schizophrenia and the anhedonia in depression. In pharmaceutical industry, social interaction and social recognition tests have been used to evaluate the efficacy of antidepressants and antipsychotics.

The following studies were designed to firstly treat the rats with the NMDA receptor antagonist phencyclidine (PCP) in order to create deficits in social behavioral, and then atypical antipsychotics clozapine, olanzapine, and aripiprazole, as well as typical haloperidol were tested for their efficacy in reversing the deficits.

Methods

Study I: A simple one-trial social interaction protocol was used in this study. Male juvenile SD rats about 200 grams were used (N=14~14 in each group). For five days prior to test, rats were injected twice daily with either PCP (2 mg/kg) or vehicle (control group).

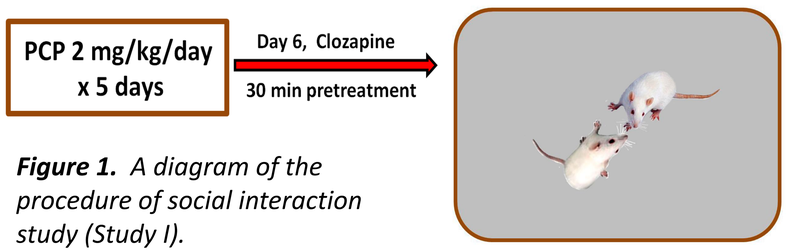

Figure 1. *A diagram of the procedure of social interaction study (Study I).*

On day 6, vehicle, clozapine 1.25 or clozapine 2.5 mg/kg were administered in different groups, a pair of unfamiliar rats receiving the same treatment were placed in an arena (60 x 45 x 20 cm) and allowed to interact with each other for 6 minutes. Social interaction is regarded when a rat showed active exploration to another one.

Following the first experiment, clozapine 2.5 mg/kg was compared with atypical antipsychotic aripiprazole and with typical antipsychotic haloperidol in two separate experiments with the same protocol.

Study II: We used a paradigm with 5-trials (simple called T1-T5, respectively) of social recognition in this study. Male LE rats about 300 grams (N=15~19 in each group) were used in the study. The training box had a 50 x 50 x 50 cm dimension. A round-shaped (20 cm in diameter) mesh cage to house stimulus rats (the drug-naïve rats only used to initiate social behavior of the test rats) was located at center of the training box. Social interaction was defined as active and direct exploration (touching and sniffing) to the mesh cage in which a stimulant rat was housed. The procedure is shown in figure 2.

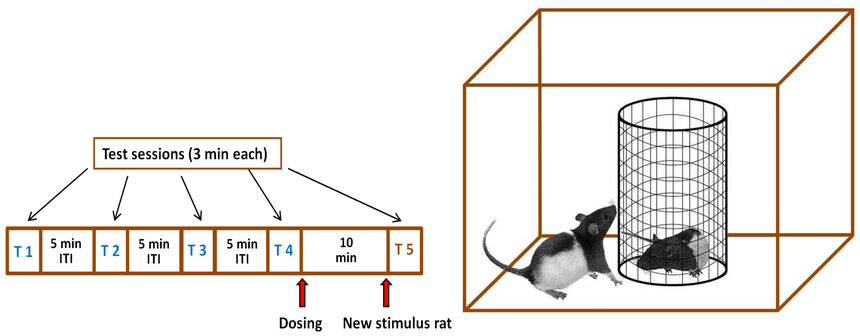

Figure 2. *A diagram of the procedure of social recognition study (Study II).*

In the test the stimulus rat was kept in the mesh cage across T1-T4. As soon as the completion of T4, the rats in different groups were dosed with vehicle, PCP 2 mg/kg, PCP + clozapine 3 mg/kg, or PCP + olanzapine 1 mg/kg. Also before T5 started, the old stimulus rat was replaced by a new one. Social recognition memory was indicated by the progressive decline of social interaction in T1-T4 and especially by the recovery of the interaction time in T5 after a new stimulus rat is introduced.

Results

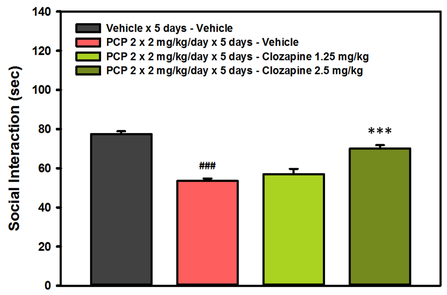

Figure 3 (Study I). *PCP treatment for 5 days significantly decreased social interaction. Clozapine 2.5 mg/kg reversed the deficits (###: P<0.001 compared to vehicle-treated group; ***: P<0.001 relative to PCP group.)*

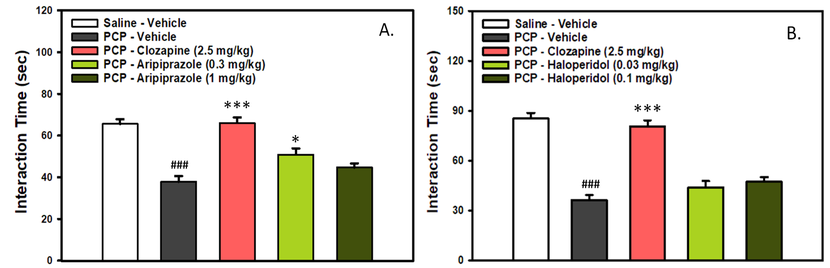

Figure 4 (Study I) . *PCP treatment significantly decreased social interaction. Clozapine 2.5 mg/kg, aripiprazole 0.3 mg/kg but not haloperidol showed efficacy in reversing the deficit of social interaction. (###: Ps<0.001 compared to vehicle-treated group; *** and * : Ps<0.001 and P<0.05 relative to PCP group.)*

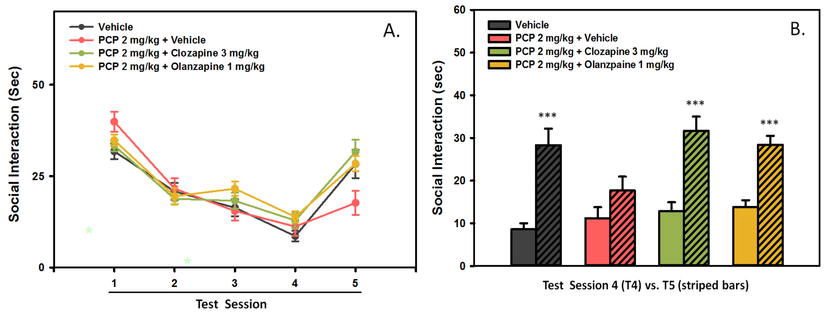

Figure 5 (Study II). ***(****A) The four groups are homogeneous and they all showed progressively decreased exploration after repeated exposure to the same stimulant rat during T1-T4 (P<0.001). In T5 when a new stimulus rat was introduced, vehicle group but not the PCP group significantly rebounded. Clozapine and olanzapine reversed PCP-induced deficits. (B) A further analysis on the same data of T4 and T5. Both clozapine and olanzapine showed efficacies to reverse the deficits of social recognition.*

Summary

- Rats with 2x2 mg/kg/day x 5 days PCP treatment showed significant decrease of social interaction in the test in day 6; the deficit was reversed by atypical antipsychotics clozapine 2.5 mg/kg and patricianly reversed by aripiprazole 0.3 mg/kg.
- In the 5-trial social recognition test, rats showed progressively decreased exploration to the same stimulus rat but restore the exploration to a new stimulus rat in T5. Acute PCP treatment at 2 mg/kg largely block the rebound. Co-administration of clozapine 3 mg/kg or olanzapine 1 mg/kg reversed the deficits.
- This study may provide a validated PCP model of social interaction / recognition for evaluation of efficacy of atypical antipsychotics in treating negative symptoms and cognitive disruption in schizophrenia.