Evaluation of cognitive and social functions in rats treated with phencyclidine

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Introduction

Cognitive dysfunction is a core deficit of schizophrenia, and social withdrawal is an important part of the negative symptoms of schizophrenia. Exposure to NMDA receptor antagonist phencyclidine (PCP) has been found to cause both cognitive deficits and social isolation in rodents, therefore PCP models may be useful in developing new drugs for schizophrenia. In the present serial studies, we assessed the effects of acute and subchronic PCP administration in rats in several assays relevant to the cognitive impairments associated with schizophrenia and the negative symptoms of schizophrenia. We also evaluated the efficacy of the atypical antipsychotic clozapine in reversing the PCP-induced deficit in some tests.

Methods

Animals

Male adult Long-Evans rats obtained from Harlan Laboratories were used in these studies except in Social Interaction test, which used Sprague-Dawley rats (Harlan). For operant conditioning-based tests (5-choice serial reaction time task, delayed-match-to-position test and cued reversal learning task), rats were singled housed and held at 85% of age-matched free-feeding body-weights. Water was provided *ad libitum*. For novel object recognition (NOR) and Social Interaction tests, rats were housed 3 per cage and provided *ad libitum* access to food and water.

Operant Conditioning-based Tests:

The operant conditioning apparatus (Med Associates, St. Albans, VT) consists of aluminum and Plexiglas chambers with grid floors (32 x 25 x 33 cm), housed in sound-attenuating cabinets.

5-choice serial reaction time (5-CSRTT) task

Naïve rats first underwent acquisition training. One of the 5 apertures was illuminated for 500 ms, and the rat was given 5 second to make choice. Correct response was rewarded with delivery of a single food pellet, signaled by illumination of the magazine light and extinction of the stimulus lights, and followed by initiation of the 10 sec inter-trial interval (ITI). An incorrect response (or failure to make a response) resulted in extinction of the stimulus lights and initiation of the 10 sec ITI. Measures obtained during the test sessions were: (1) percent correct, (2) percent omissions,(3) premature responding, (4) perseverative responding, (5) correct latency, (6) incorrect latency and (7) magazine latency. When rats reached a stable baseline, PCP was administrated 3 mg/kg twice daily for 7 days, followed by 5 day washout before the measurement of the rats' post-dosing performance.

Delayed-match-to-position (DMTP) test

DMPT training began after an autoshaping paradigm. The delays in the DMPT test were 0, 8, 16 or 32 seconds. In the sample phase, one lever was extended; it was retracted after a response was made. After the variable delay, both levers were extended and the rat had 30 sec to make a response. The rats' correct and incorrect choices led to the same consequences as those in 5-CSRTT test, except that the ITI was 5 second in this test. Sessions are completed after 6 sets of 8 trials = 48 trials. Within each set of 8 trials, 4 pairs of specific delays are presented in a pseudorandom order. After the rats were trained, PCP was administrated 3 mg/kg twice daily for 7 days, followed by a 5-day washout before the measurement of the rats' post-dosing performance.

Cued reversal learning task

Using the same apparatus, rats were trained to obtain a food pellet after pressing a lever associated with either an illuminated or non-illuminated cue-light. After reaching 90% correct. PCP treatment (6 mg/kg/day) was applied for 7 days followed by a 5-day washout and a 1 day retention test (same contingency as previously learned). Reversal learning started the day after the retention test and lasted 9 days.

Novel Object Recognition (NOR) Test :

NOR was conducted in an open-field arena (40 x 40 cm) placed in a sound-attenuated room under dimmed lighting. Following two habituation days, a training session (T1) was given in which the rats explored two identical objects for 3 minutes. The test session (T2) was conducted 1 hour after T1. The rat was placed into the test arena in the presence of one familiar and one novel object, and the time spent exploring each object was recorded during 0-3 and 0-5 min. Data are expressed as Recognition Index, which is defined as the ratio of the time spent exploring the novel object over the total time spent exploring both objects (Familiar + Novel) during test session T2.

Subchronic PCP model

In this model, rats were exposed to PCP (2 mg/kg twice daily) for 7 days, followed by a 5-day washout before T1 and T2 sessions. Clozapine (3 mg/kg) was dosed 15 min before T1.

Acute PCP model

Naïve rats were dosed with clozapine (3 mg/kg) immediately followed by PCP (2 mg/kg) 15 min before the T1 of NOR.

Social Interaction Test :

Rats were dosed twice daily with 2 mg/kg PCP for 5 days. On day 6, after acute treatment with either the atypical antipsychotic clozapine (2.5 mg/kg) or the typical antipsychotic haloperidol (0.1 mg/kg), a pair of unfamiliar rats receiving the same treatment (PCP or vehicle) were placed in a Plexiglas open field arena (60 x 42 x 20 cm) and allowed to interact with each other for 6 minutes. The time the rats spent actively interacting with each other was recorded.

Results

Figure 1. In the 7 measures of sustained attention via 5-CSRTT, premature responding was the only one affected by PCP administration. (*: P<0.05)

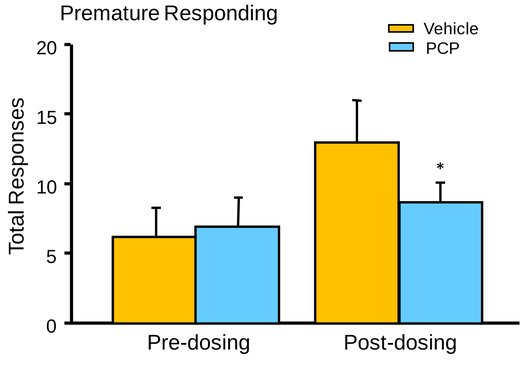


Figure 2. Longer delay was associated with more errors in DMTP, but PCP administration did not affect performance in comparison with vehicle-treated rats.

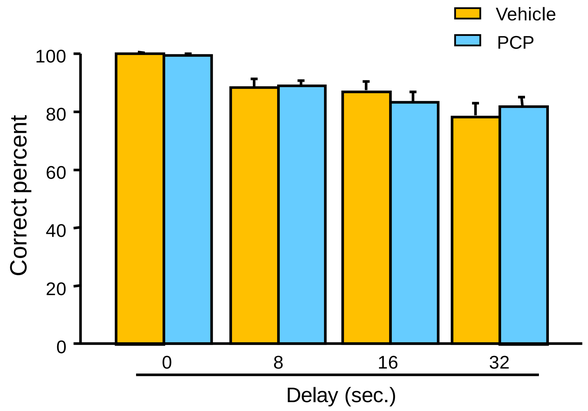


Figure 3. Subchronic PCP treatment resulted in a small but significant decrement in accuracy during reversal learning [PCP treatment effect: F (1, 26)=5.616, P<0.05)].

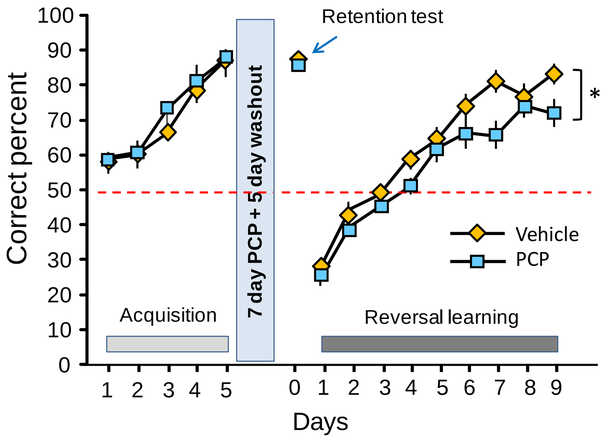


Figure 4. Subchronic PCP administration impaired NOR performance, and clozapine reversed the deficit (*P<0.05; **P<0.01, compared with PCP/Vehicle group).

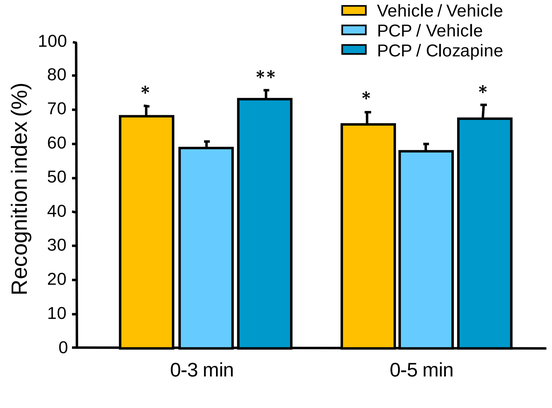


Figure 5. Acute PCP administration impaired NOR performance and co-administration of clozapine reversed the deficit. (*P<0.05; **P<0.01, compared with PCP group)

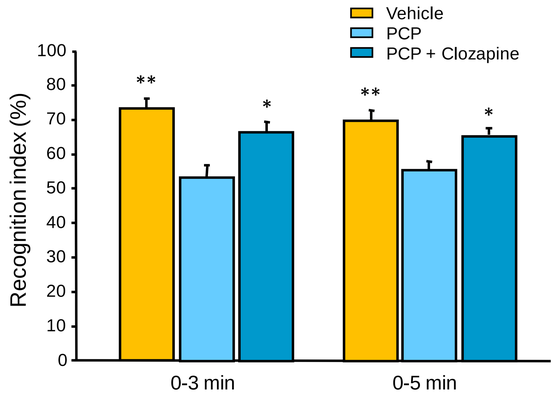
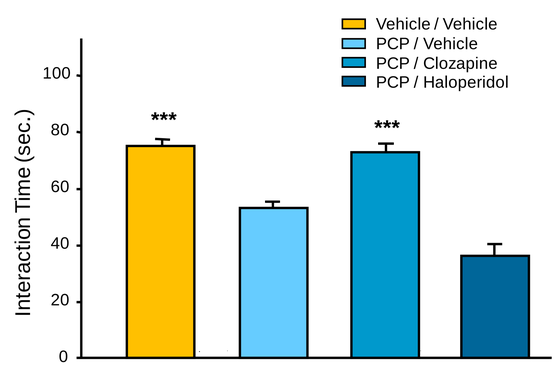


Figure 6. Administration of the atypical antipsychotic clozapine, but not the typical antipsychotic haloperidol, reversed PCP-induced social interaction deficit (*P<0.001 compared with PCP/Vehicle group).**



Discussion

Although there were some positive data, the 5-CSRTT and DMTP tasks were insensitive to PCP treatment. It is noteworthy that in both tasks, rats were trained to a high degree of performance, and this may be a factor for the ineffectiveness of PCP treatment. Survey of the literature suggests that the 5-CSRTT is not well suited to capture translational measures of CIAS. Interestingly, the high levels of performance in both tasks may make these assays suitable for detecting cognitive deficits induced by potential antipsychotic medications.

PCP caused deficits in NOR and Social Interaction, and reversal learning, tests. Alternative reversal learning tasks may prove more sensitive to PCP-induced deficits. Importantly, administration of the atypical antipsychotic clozapine attenuated PCP-induced deficits in both NOR and Social Interaction tests, suggesting they may be useful models of cognitive impairments and negative symptoms of schizophrenia for future drug discovery efforts.