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Effect of repeated administration of phencyclidine on spatial performance in an eight-arm radial maze with delay in rats and mice

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Abstract

Phencyclidine (PCP) is an *N*-methyl-D-aspartate (NMDA) glutamate receptor channel noncompetitive antagonist that produces some of the symptoms of schizophrenia, including delusions, hallucinations, and negative symptoms as well as cognitive impairment. Thus, administration of PCP to rodents and nonhuman primates has been suggested to provide a potential animal model for schizophrenia. There have been some reports that 7–14 days of PCP administration can bring about enduring impairments in working memory in rodents but not all studies have been consistent in this regard. The present study determined whether repeated PCP administration impaired spatial performance in rats or mice trained to make minimal errors in an eight-arm radial maze task with a delay. Male Sprague–Dawley rats and C57BL/6J mice received 14 daily injection of vehicle or PCP (10 mg/kg, sc) followed by a withdrawal period of 1 week. The number of arm reentry errors and the distance traveled to complete the task were not significantly different between PCP-treated and vehicle-treated rats on 2, 8, and 14 days of PCP administration or 8 days following withdrawal of PCP. Mice treated with PCP for up to 2 weeks also had no significant differences in the number of arm reentry errors, travel distances, the numbers of visits to different arms during the first eight choices, or latencies to take all eight pellets compared to the vehicle-treated group. Thus, the present study failed to demonstrate that repeated administration of PCP to rats or mice produces enduring memory impairment. Factors potentially contributing to the discrepancies between various studies are discussed.

Keywords: Phencyclidine (PCP); Schizophrenia; Working memory; Eight-arm radial maze

1. Introduction

Patients with schizophrenia have widespread, multifaceted impairments in many domains of neurocognitive function, including executive function, attention, perceptual/motor processing, vigilance, verbal learning and memory, verbal and spatial working memory, and semantic memory (verbal fluency) (Kenny and Meltzer, 1991). Working memory impairment has been suggested to be the core cognitive deficit in schizophrenia leading to impairment in other domains of cognition (Goldman-Rakic and Selemon, 1997). Therefore, an animal model of working memory impairment, which parallels the deficit found in schizophrenia including response to pharmacological treatment, would be of considerate value to study the pathophysiology and treatment of schizophrenia.

Acute administration of phencyclidine (PCP) or its congener, ketamine, both of which are noncompetitive *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonists, has been reported to induce psychosis in some normal volunteers and to exacerbate psychosis in some patients with schizophrenia (Lahti et al., 1995; Snyder, 1980). PCP and ketamine have also been reported to worsen negative symptoms (e.g., flat affect) in some patients with schizophrenia (Javitt and Zukin, 1991) and to induce or worsen cognitive impairment (Cosgrove and Newell, 1991; Krystal et al., 1994). Thus, PCP administration has been suggested to be a drug-induced model of schizophrenia. There is extensive evidence that acute administration of PCP to rodents impairs performance in working and reference memory (Adams and Moghaddam, 1998; Handelmann et al., 1987; Kesner and Dakis, 1993; Kesner et al., 1993; Stefani and Moghaddam, 2002). There have also been

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several studies of the effect of repeated administration of PCP and ketamine in rodents and monkeys on neurocognitive performance. Jentsch et al. (1997b, 2000) reported that 14 days of PCP treatment produced working memory impairment in rats in a delayed alternation task in a modified T-maze and cognitive impairment in monkeys in an object-retrieval detour task. However, Stefani and Moghaddam (2002) found no deficit in working memory in rats after PCP treatment for 5 days (twice daily) at a dose of 5 mg/kg, which was a lower dose than that used by Jentsch et al. (1997b) who used a discrete paired trials, delayed alternation task in a modified T-maze. In a nondelayed four-arm-baited radial arm maze (RAM) task (Noda et al., 2000), working memory impairment was observed in Male Sprague–Dawley rats after 14 days administration of PCP (10 mg/kg) and a withdrawal period of 1, 2, or 3 weeks. However, two recent studies (Bontempi et al., 2002; Pehrson et al., 2002) found no impairment in memory tasks after 14 days of PCP administration to rats or mice. Fourteen daily injections of PCP (10 mg/kg) to male Sprague–Dawley rats, followed by a withdrawal period of either 1 or 2 weeks, did not produce any cognitive impairment in performance in a Y-maze delayed arm discrimination task, social communication of a food preference, or prepulse inhibition (Bontempi et al., 2002). Moreover, during PCP administration, no significant effect of PCP on total number of errors, number of working memory errors, or response before the first error was observed in mice (Pehrson et al., 2002).

The RAM has been used to study learning and memory in rodents. In particular, spatial memory function can be measured with the radial maze task with reward for correct behavior provided at the end of each arm (Olton, 1979). The present study was designed to test whether chronic administration of PCP to the rats or mice produces spatial memory impairment in an eight-arm-baited maze task with a delay and to clarify the discrepant results reported by various laboratories including a preliminary study from this laboratory (Noda et al., 2000).

2. Materials and methods

2.1. Animals

Male Sprague–Dawley albino rats (175–225 g on arrival) and C57BL/6J mice (16.5–18.5 g on arrival) were used in this study. The animals were housed on a 12/12-h light–dark cycle with the light phase being 7:00 a.m. to 7:00 p.m. and had continuous access to drinking water. One week before training, food deprivation was initiated and continued until the body weight of the rats or mice was 80–85% of initial levels. Animals used in this study were cared for in accordance with the guidelines of the Institutional Animal Care and Use Committee of Vanderbilt University. "Principles of laboratory animal care" (NIH Publication No. 85-23, revised 1985) were followed.

2.2. RAM task

2.2.1. Apparatus

The apparatus (Neuroscience, Tokyo, Japan; see Fig. 1) in which the rats were tested consisted of a 40-cm elevated eight-arm RAM made of black Plexiglas and was located in a sound-attenuated and dimly lit room. The eight arms ($12 \times 5 \times 50$ cm) extended from an octagonal central starting platform (32 cm in diameter), had a food cup (3 cm in diameter and 1 cm in depth) placed at their floor extremity, and had a single food pellet (50 mg) as bait. The central platform was enclosed with a removable guillotine door (22 cm high) in order to confine and block the ability of the rat to enter an arm. The RAM was surrounded by various extra maze cues such as tables. Their orientation relative to the maze was kept constant throughout the experiment.

The mice were tested in an automated eight-arm RAM also made of black Plexiglas (Miyakawa et al., 2001), which is similar to that used with the rats. Each arm ($9 \times 15 \times 50$ cm) radiated from an octagonal central starting platform (perimeter 12×8 cm). Identical food wells, 1.4 cm deep and 1.4 cm in diameter, were placed at the distal end of each arm. The pellet sensors were able to automatically record pellet intake by the mice.

2.2.2. Eight-arm-baited RAM task with a delay

Rats were shaped for 5 days. Each of the rats were placed in the center starting platform and allowed to explore the arm for 5 min with pellets of food scattered throughout the maze. They were gradually restricted to the area closer to food cups. After shaping, rats were individually trained in the eight-arm-baited RAM. All eight arms were baited with food pellets. Each rat was placed individually in the starting platform and allowed to acquire all eight pellets within a maximum of 8 min. A trial was terminated immediately after all eight pellets were consumed or 8 min had elapsed. The rat was confined in the center platform for 10 s after each arm choice. Each rat received one trial per day.

The criterion for arm entry was placement of all four limbs inside an arm. After 7 days training, a 60-s delay

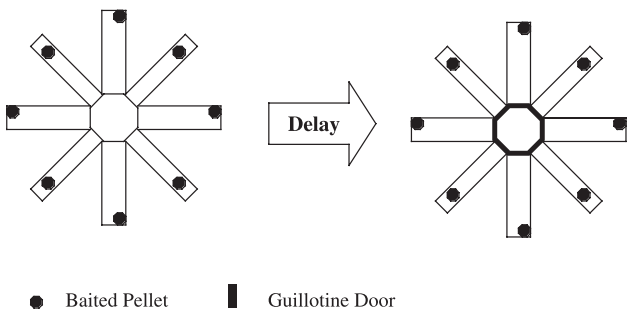

Fig. 1. Diagram of the delayed eight-arm-baited radial maze. The delayed time (60 s) was initiated after 7 days training. The delay period was extended to 120 s in the following training session. The animals were test in the RAM with a 120-s delay.

between entries was initiated. Rats received three to five training sessions based upon the performance (consumption of all pellets within 8 min). For the 16th to the 18th trial, the delay period was extended to 120 s. After each group of trials, the arms and central platform of the maze were cleaned to ensure that the rats could not follow their own odor or that of other rats. The training for the mice was similar with that for the rats. In the case of mice, each trial was terminated immediately after all eight pellets were consumed or 10 min had elapsed. Data acquisition, control of guillotine doors, and data analysis were performed by Image RM software (see Image analysis).

Rats and mice, which fulfilled the criterion of less than one reentry error in a training trial and less than a total of two errors for three consecutive training sessions, were included in the RAM test. Trained rats or mice were then randomized to two groups: saline treatment and PCP (10 mg/kg sc) treatment. PCP or saline was administrated once a day for 14 consecutive days. On the 4th, 6th, and 14th days of PCP treatment, the rats were tested 24 h after the last PCP injection and prior to the next injection. Mice were tested in the maze on the 2nd, 8th, and 14th days after the last PCP treatment.

2.3. Image analysis

All applications used for the behavior studies (Image RM, Image SI, and Image FZ) were run on a Macintosh computer. Application was based on the public domain NIH Image program (developed by Wayne Rasband at the U.S. National Institute of Mental Health) and was modified for each test (O'Hara, Tokyo, Japan).

2.4. Statistical analysis

The data for both the rat and mouse experiments were analyzed by separate one-way ANOVAs for each of the days the animals were tested in the maze (StatView 4.5 for the Macintosh). A probability of $P < .05$ was considered significant in this study. All results are given as means ± S.E.M.

3. Results

Fig. 2 showed the effect of PCP treatment on spatial performance in eight-arm-baited radial maze in rats. During three consecutive training sessions, the mean number of reentry error of the rats was 0.4 ± 0.15 (baseline). Reentry errors were assessed on the 4th, 6th, and 14th days of PCP treatment and as well as the 8th day after PCP withdrawal. On the 4th day, the PCP-treated rats showed a trend towards increased number of arm reentry errors. However, the difference between the two groups was not significant [$F(1,21) = 3.9$, $P = .09$]. On the 6th and 14th days of PCP treatment, or the 8th day of withdrawal, no significant difference in the number of reentry errors was observed between the saline-treated and PCP-treated groups [$F(1,22) = 0.45$, $P = .60$; $F(1,22) = 0.014$, $P = .91$; and $F(1,22) = 0.41$, $P = .65$, respectively] (Fig. 1A). Moreover, the difference in travel distance between the two groups was not significant on the 4th, 6th, and 14th days of PCP treatment [$F(1,22) = 1.5$, $P = .10$; $F(1,22) = 1.05$, $P = .32$; and $F(1,22) = 0.44$, $P = .62$, respectively] (Fig. 1B).

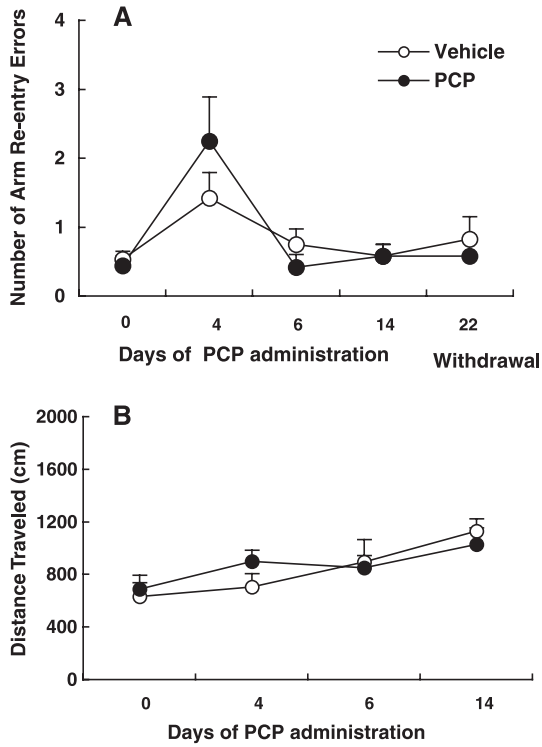

Fig. 2. Effect of repeated administration of PCP on spatial performance in rats on the eight-arm-baited RAM test. Rats were confined for 10 s in the center platform after each arm choice. After 7 days training, a 60-s delay was initiated. The delay period was extended to 120 s in the 16th, 18th trial, and the test. Data were given as means ± S.E.M. ($N = 11$ or 12). There is no significant difference between PCP-treated and vehicle-treated groups in the number of arm reentry errors and travel distance.

During three consecutive training sessions, the mean reentry errors of the mice were 1.5 ± 0.4 (baseline). There was no significant difference in the number of arm reentry errors between saline-treated and PCP-treated mice on the 2nd, 8th, and 14th day of PCP administration [$F(1,20) = 2.95$, $P = .10$; $F(1,20) = 3.01$, $P = .09$; and $F(1,20) = 2.01$, $P = .19$, respectively] (Fig. 3A). In addition, the number of visits to different arms during the first eight choices [$F(1,20) = 0.66$, $P = .42$; $F(1,20) = 1.85$, $P = .39$; and $F(1,20) = 0.57$, $P = .40$, respectively] (Fig. 3B), latencies to take all eight pellets [$F(1,20) = 0.78$, $P = .38$; $F(1,20) = 0.55$, $P = .39$; and $F(1,20) = 0.60$, $P = .41$, respectively] (Fig. 3C), or travel distance [$F(1,29) = 3.96$, $P = .09$; $F(1,20) = 2.87$, $P = .15$; and $F(1,20) = 2.66$, $P = .16$, respectively] (Fig. 3D) was not significantly different between the two groups on the 2nd, 8th, and 14th day of PCP administration. These data indicate that repeated administration of PCP did not produce any perform-

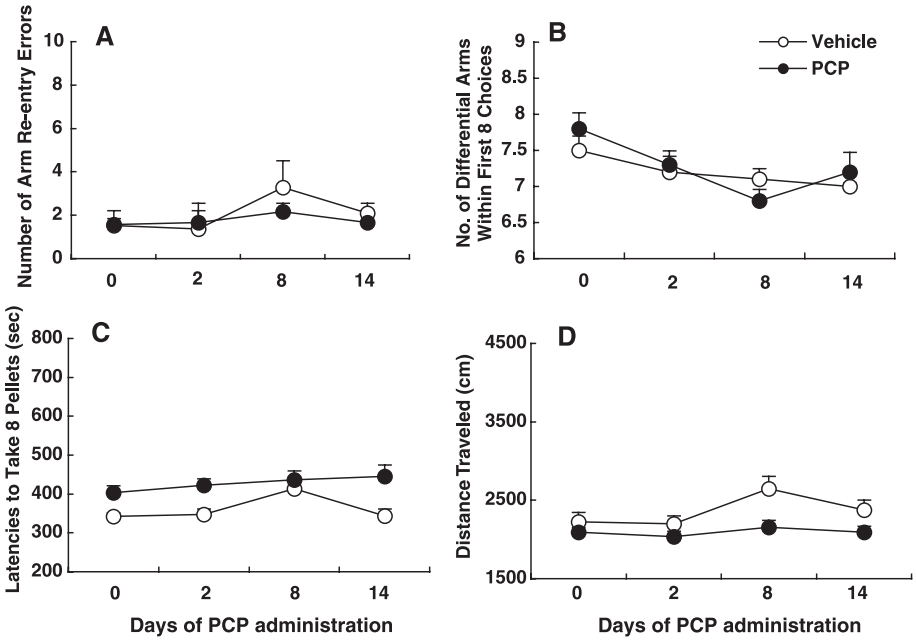

Fig. 3. Effect of repeated administration of PCP on spatial performance in mice in the eight-arm-baited RAM test. Mice were confined for 5 s in the center platform after each arm choice. After 7 days training, a 60-s delay was initiated. The delay period was extended to 120 s in the 16th, 18th trial, and the test. Data were given as means ± S.E.M. ($N = 10$ or 11). (A) Number of arm reentry errors. (B) Number of visits to different arms during the first eight choices. (C) Latencies to take all eight pellets. (D) Travel distance.

ance impairment during or after PCP treatment in this delayed eight-arm-baited RAM either in rats or mice.

4. Discussion

The main findings in this study were that arm reentry errors and travel distance were not significantly different between PCP- and vehicle-treated group in rats on 2, 8, and 14 days of PCP (10 mg/kg) administration or 8 days following withdrawal of PCP. PCP-treated mice also showed no significant difference in arm reentry error, travel distance, the number of visits to different arms during the first eight choices, and latencies to take all eight pellets compared to the vehicle-treated group. Thus, the present data with a delayed eight-arm-baited RAM demonstrated that repeated PCP administration caused no impairment in either rats, in a manually controlled RAM, or mice, in an automatically controlled RAM, which suggests that failure to observe impairment induced by PCP in this paradigm in the rats is unlikely to result from cues obtained from the experimenter.

The RAM has been suggested to be superior to other methods for testing working memory in rodents as the requisite task more closely resemble the natural food-seeking behavior of species such as rats than previous methods (Olton and Samuelson, 1976). When all arms of a RAM are baited, the solution to the task requires working memory because the correct response to the arm (to enter it once and obtain the reward) changes within a trial (Honig, 1978). Thus, this method permits assessment of the effect of subchronic PCP administration on spatial working memory. The results reported here are consistent with the recent conclusions that repeated administration of PCP causes no persistent deleterious effect on cognitive and social behaviors in rats and mice (Bontempi et al., 2002; Pehrson et al., 2002) and do not confirm the earlier studies, which reported that repeated daily administration of PCP produced working memory impairment in T-maze alternation in rats (Jentsch et al., 1997b), cognitive impairment in monkeys (Jentsch et al., 1997a, 2000), and working memory impairment in four arm-baited RAM without a delay in rats (Noda et al., 2000). In the T-maze, a variable-delayed alternation paradigm was utilized in order to introduce a delay function that requires working memory (Jentsch et al., 1997b). The working memory impairment produced by 14 days PCP treatment observed in the T-maze was related significantly to the delay time (Jentsch et al., 1997b). The delay-dependent impairment suggests that the performance impairments were related to cognitive rather than nonspecific dysfunction. The results in the RAM without delay possibly reflect a deficit in learning ability or reference memory rather than working memory. The delay-dependent impairment previously observed by Jentsch et al. (1997b) in the T-maze suggests that this could also occur in the RAM. In the present study, only a single delayed time was started during the test. It is possible that longer delay intervals would produce different results.

Acute PCP administration is known to increase locomotor activity at lower doses or cause motor ataxia at higher doses (Sturgeon et al., 1979). Increased locomotor activity or ataxia could alter performance without affecting memory

or learning. In the delayed eight-arm-baited RAM employed here, repeated PCP for 14 days produced no impairment in spatial performance in rats or mice. This is consistent with the report that repeated administration of PCP produces no decrease in acetylcholine release in the prefrontal cortex (Jentsch et al., 1998), which is important to learning and memory. However, the same PCP administration schedule caused significant working memory impairment in a T-maze in rats (Jentsch et al., 1997b). Therefore, it appears that the conventional RAM task as employed here lacks sensitivity to detect the effect of subchronic PCP on working memory. It is noteworthy that exposure to noncompetitive NMDA receptor antagonists transiently injures neurons within the retrosplenial cortex of the rat (Olney et al., 1989), and that chronic administration of PCP (15 mg/kg) induces a pattern of neurotoxicity in limbic brain regions similar to the damage produced by acute PCP administration (Olney et al., 1989; Corso et al., 1997). The present data suggest that PCP administration produces no enduring changes in brain structure or function, which impact on spatial memory, although persistent neurotoxicity with associated spatial learning deficits has been shown in MK-801-treated mice (Wozniak et al., 1996). Therefore, it would be of interest to examine whether the RAM is able to demonstrate an adverse effect of PCP on learning ability and reference memory.

The fact that acute (Adams and Moghaddam, 1998; Handelmann et al., 1987; Kesner and Dakis, 1993; Kesner et al., 1993; Stefani and Moghaddam, 2002) but not chronic PCP, with a period of adequate withdrawal to permit removal of any remaining PCP, produces impairment in memory-dependent performance in rodents suggests that at the doses employed in the chronic studies, there are no enduring changes in brain structure or function that impact on memory. Many studies have indicated that the dose of PCP has a great influence on the performance in different tasks. The effects of ketamine in humans on cognition are highly dose dependent (Moretti et al., 1984; Krystal et al., 1994). Low doses of PCP (1 mg/kg), which do not cause stereotypy or motor deficits in rodent, have been reported to interfere with reference (long-term) but not working (short term) memory in a T-maze in rats (Handelmann et al., 1987). In contrast, higher doses of PCP (6–8 mg/kg) disrupt both working (short-term) and reference (long-term) memory, as evidenced by disruptive effects on performance in a RAM and within a non-spatial-delayed matching-to-sample task and active avoidance learning (Kesner et al., 1983; McCann and Winter, 1986; Pontecorvo et al., 1991). It should be noted that higher doses of PCP produce changes in locomotor activity, which may bias the measurement of both working and reference memory.

The level of training may be another critical variable underlying the discrepancy in investigations of the effect of PCP on working memory in a RAM apparatus. Working and reference memory are highly dependent upon each other in this task. With repeated training, at least some working memories are consolidated into reference memory. The extent to which this occurs will depend upon the amount of training. Substantial differences in baseline error rates for working memory and reference memory have been reported with scopolamine after various durations of training (Lydon and Nakajima, 1992). With insufficient training, scopolamine selectively impaired working memory in the eight-arm RAM in rats (Lydon and Nakajima, 1992). On the other hand, they found that well-trained animals were more likely to show an increase in reference memory errors when treated with scopolamine. In a nondelayed RAM paradigm (Noda et al., 2000), only rats that fulfilled the criterion of less than two working memory errors in a training trial and less than a total of three errors for three consecutive training session were used for the RAM test. However, the rats used in the delayed RAM paradigm in the present study made less than one arm reentry error in a training trial and less than a total of two errors for three consecutive training session. It is possible that repeated PCP treatment might be more likely to produce impairment in reference memory in these quite well-trained animals, which had very low error rates at the end of training. Moreover, it has been reported that peripheral injections of PCP appear to have specific effects on long-term memory consolidation processes but appear to have only small effects on working memory during acquisition of a new task or performance of a previously learned task (Kesner and Dakis, 1995). In addition, the importance of the level of training is supported by previous studies showing that better trained habits are less susceptible to the disruptive effects of scopolamine (Deutsch and Rogers, 1979). Well-trained animals were more likely to show an increase in reference memory error following scopolamine treatment.

In conclusion, the present study demonstrated that repeated PCP treatment produces no spatial performance impairment in an eight-arm-baited RAM paradigm in either rats or mice even with a delay. Therefore, administration of PCP to rats or mice for up to 14 days at a dose of 10 mg/kg followed by testing on a previously learned spatial working memory task does not provide an adequate model of working memory impairment in schizophrenia. However, it cannot be excluded that a different behavioral paradigm or schedule of PCP treatment could provide a model for some aspects of the cognitive deficit present in schizophrenia.

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