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Phencyclidine Disrupts Acquisition and Retention Performance Within a Spatial Continuous Recognition Memory Task

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KESNER, R. P. AND M. DAKIS. *Phencyclidine disrupts acquisition and retention performance within a spatial continuous recognition memory task.* PHARMACOL BIOCHEM BEHAV **44**(2) 419–424, 1993. – Rats with 1 or 2 mg/kg phencyclidine (PCP), 4 mg/kg PCP, or saline injections were tested for acquisition or retention performance of a spatial continuous recognition memory task. Results indicate that relative to controls and rats with injections of 1 and 2 mg/kg PCP rats with 4-mg/kg PCP injections were profoundly impaired in acquisition and somewhat impaired in retention of the task across all lags as measured by increases in latency for repeated items. Phencyclidine, through it presumed blocking action of the NMDA receptor, alters the consolidation of new spatial location information but does not have a major affect on short-term maintenance of previously learned information.

Phencyclidine Acquisition Retention Short-term memory Consolidation
Continuous recognition memory

PHENCYCLIDINE (PCP) is an important pharmacological agent not only because it is a drug of abuse but also because of its CNS action as a competitive antagonist of the NMDA subtype of excitatory glutamate receptor. The NMDA receptor has been proposed to be critically involved in mediating long-term potentiation (LTP), a phenomena hypothetically linked to memory (13). It is known that there is a high density of PCP receptors in the hippocampus, that PCP blocks LTP in the CA1 region of the hippocampus (1,20), and that PCP produces performance deficits on learning and memory tasks sensitive to hippocampal dysfunction (2–4,8,12,14). The exact nature of the PCP-induced learning and memory deficit has not yet been determined. Previous studies have demonstrated that low doses of PCP (2–4 mg/kg) disrupt consolidation of new learning into long-term memory but do not markedly interfere with processes associated with maintaining new or previously learned information within a relatively short time frame (seconds–minutes) (2,4,12,14,18). For example, a low dose of PCP does not alter the rat's ability to acquire a reversal task but disrupts its ability to remember the reversal learning 24 h later (4). Similarly, low doses of PCP do not alter performance within an eight-arm radial maze but affect the ability to remember previous exposure to four of eight arms after a 15-min delay with increases in errors in performing the remaining four arms (2). Also, low doses of PCP do not alter short-term memory for nonspatial cues in a delayed matching-to-sample task (18). Finally, low doses (4 mg/kg) of PCP impair acquisition in a spatial navigation task (dry-land version of water maze) between days (24 h) but not within days (minutes) (8,9).

However, in contrast to the observed PCP effects, large hippocampal lesions produce deficits in both consolidation of new learning and maintenance of new or previously learned information (especially temporal and spatial) within a relatively short time frame (minutes) (7,10,17).

Recently, it has been shown that hippocampal lesions produce a profound deficit in performance of a continuous recognition memory for spatial location task (6). In this task, it is possible to vary list length (lag) and time within a short time frame so that it should be possible to examine the effects of low doses (1–4 mg/kg) of PCP on both the learning of the continuous recognition memory task, which would require both consolidation into long- and short-term memory representation of spatial information, and performance of the previously learned task, which would only require short-term memory representation of spatial information. To the extent that low doses of PCP only affect consolidation processes, deficits should be observed primarily during acquisition compared to retention or performance of the continuous recognition memory task.

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METHOD

Subjects

Eighteen male Hooded Long-Evans rats initially weighing 275–350 g at the start of the experiment were used as subjects. They were housed in standard stainless steel cages in a large, well-lit laboratory room and maintained on a 14 L : 10 D schedule. All animals were placed on food deprivation with ad lib water and maintained at 85% of ad lib weight throughout the experiment.

Apparatus

The apparatus consisted of a 12-arm radial maze, constructed of painted white wood, and raised 91.0 cm above the floor. It was kept in a well-lit room with no windows, one door, and eight calendar pictures placed upon the walls around the room. The center platform was 67.0 cm in diameter and the 12 arms radiating from it were accessible through a clear Plexiglas door at the entrance of each arm. The arms were 65.0 cm long × 9.0 cm wide and attached to the central platform with metal braces. Each arm had clear Plexiglas sides, 0.3 cm thick, rising 5.5 cm above the floor of the arm, and extending from the distal end of the arm to 2.5 cm from the central platform. A food well was located at the distal end of each arm and was 2.56 cm in diameter and 1.5 cm deep. The guillotine door at the juncture of each arm and the central platform was 10.0 cm wide, and when in the closed position extended 25.5 cm above the surface of the platform. Clear Plexiglas filled the gaps between the doors on the central platform, effectively forming a cylindrical chamber on the platform into which animals were placed through the open top. The doors could be raised or lowered via a series of pulleys and strings from an adjacent lab room. Each door could be raised an additional 7.5 cm, which exposed to view a round, black dot, 1.5 cm in diameter and 5.0 cm above the floor surface, to serve as an orienting cue.

Acquisition

Pretraining involved one session per day for 9 days in which each rat was placed on the center platform of the 12-arm radial maze with the doors to the arms open. Each food well contained one quarter piece of Froot Loops cereal, and this reinforcement was not replaced within a session. Animals were allowed 10 min to find and eat all the reinforcements. The Plexiglas doors were closed as the rat exited each arm during the last four sessions on this phase of pretraining. After the ninth session, the second phase of pretraining involved shaping the rat to orient to the cue on the Plexiglas doors. The rat was placed on the center platform with all doors in the raised position, and the experimenter controlled which arm was presented at any given time. Presentation of an arm involved raising the door until the black cue dot was visible and quickly lowering it when the rat oriented to the cue. All 12 arms were randomly presented on each session for 9 additional days, following which training began. Animals were then divided into four groups. The first group (n = 3) received 1 mg/kg PCP (IP). The second group (n = 3) received 2 mg/kg PCP (IP), the third group (n = 6) received 4 mg/kg PCP (IP), and the fourth group (n = 6) received saline (IP) injections.

Thirty minutes prior to each daily session, all animals received injections based upon their specific group assignment. Each daily training session consisted of placing a rat on the central platform and then allowing it sequential access to a set of 12 arms of the maze. Each arm was cued by the black dot, and as soon as the animal had oriented to the door it was opened by lowering it. The amount of time that elapsed between opening the door and the rat reaching the end of the arm was measured (the maximum latency was 10 s; if an animal did not start down an arm within 10 s, the door was closed and the next trial began; if the rat took longer than 10 s to completely traverse the arm, the score used for analyses was 10 s). Of the 12 arm presentations, 3 or 4 were arms that had already been presented during that session (repeated arms). Repeated arms were presented with lags ranging from 0–6, where a lag of 0 indicates that the arm was repeated immediately after the first presentation and a lag of 6 indicates that there were six different arm presentations between the first and the repeated presentation. The first time an arm was presented, it contained a quarter piece of Froot Loops cereal for reinforcement; repeated presentations were not reinforced. Which arms were presented, and where they occurred in the random sequence of arm presentations, was counterbalanced across a block of 16 sessions. All rats received a block of 16 sessions that contained 8 instances of each lag.

Retention

One week after the last acquisition trial, the six animals that had received saline injections were given additional, continuous recognition memory sessions using a within-subject design with 2 days of 1 mg/kg (n = 3) or 2 mg/kg (n = 3) PCP injections followed by 2 days of saline injections until animals had received 16 sessions with 8 sessions of saline and 8 sessions of 1 mg/kg PCP or 8 sessions of saline and 8 sessions of 2-mg/kg PCP injections. This was followed by more sessions with 2 days of 4-mg/kg (n = 6) PCP injections followed by 2 days of saline injections until animals had received 16 sessions with 8 sessions of saline and 8 sessions of 4-mg/kg PCP injections.

RESULTS

Acquisition

Because there were no significant differences between the 1- and 2-mg/kg PCP groups, the two groups were combined for further analysis. The effects of PCP or saline injections on the acquisition of the continuous recognition task [(mean latency (seconds)] are shown as a function of lag in Fig. 1. Also in Fig. 1, mean latency for the first and second presentations of specific arms as a function of PCP or saline injections across lag is shown. The data indicate that rats inhibit responding (remember the first arm) as a function of lag only when they received saline or 1- and 2-mg/kg PCP injections but do not remember the first arm under the influence of 4 mg/kg PCP. A three-way analysis of variance (ANOVA) for groups (drug treatment) as the between factor and lag and first vs. second presentation as the within factors revealed a significant drug effect, $F(2, 15) = 13.5, p < 0.0004$, a significant lag effect, $F(6, 90) = 7.7, p < 0.0001$, a significant first vs. second presentation effect, $F(1, 15) = 96.3, p < 0.0001$, a significant drug × lag interaction, $F(12, 90) = 2.4, p < 0.009$, a significant drug × first vs. second presentation interaction, $F(2,15) = 17.1, p < 0.0001$, a significant lag × first vs. second presentation interaction, $F(6, 90) = 7.7, p < 0.0001$, and finally a significant triple interaction among all three factors, $F(12, 90) = 1.99, p < 0.03$. Thus, the data suggest that the 4-mg/kg PCP group differs from the 1- and

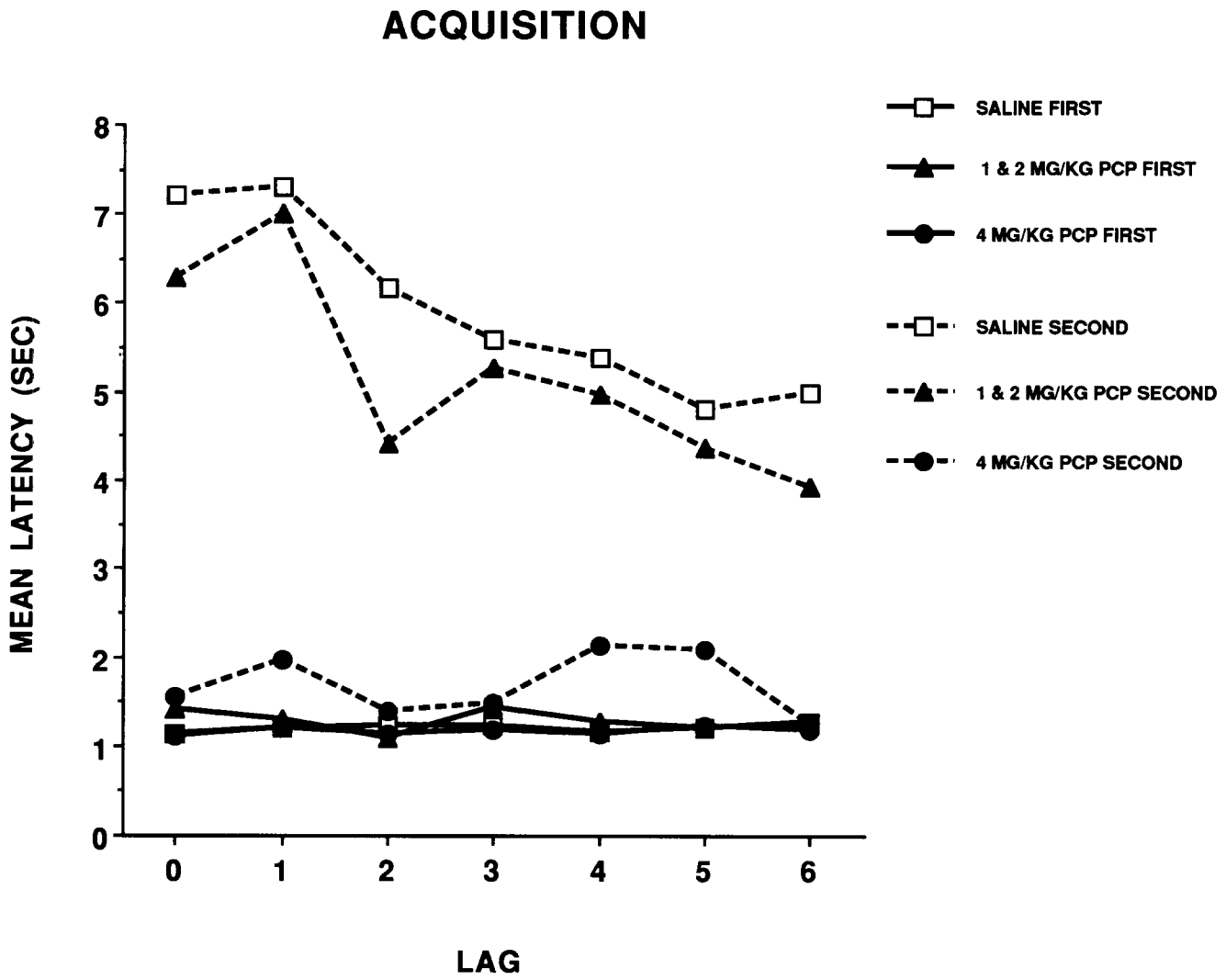

FIG. 1. Mean latency difference (seconds) for the first and second presentation as a function of lag for rats with saline, 1- and 2-mg/kg phencyclidine (PCP), or 4-mg/kg PCP injection during acquisition of the continuous recognition memory task.

2-mg/kg PCP and control groups across lags and only for the second but not the first presentation of a specific arm.

Retention

Because there were no significant differences between the 1- and 2-mg/kg PCP groups, the two groups were combined for further analysis. The effects of 1 and 2 mg/kg PCP or saline injections on performance of the fist and second presentations [mean latency (seconds)] are shown as a function of lag in Fig. 2. The data indicate that there is a small difference between 1 + 2 mg/kg PCP and saline on performance of the continuous recognition memory task. A three-way within-subjects ANOVA revealed a significant drug effect, $F(1, 140) = 8.5$, $p < 0.004$, a significant first vs. second presentation effect, $F(1, 140) = 471.6$, $p < 0.0001$, and a significant treatment × first vs. second presentation interaction effect, $F(1, 140) = 4.8$, $p < 0.03$.

The effects of 4 mg/kg PCP or saline injections on performance of the first and second presentations [(mean latency (seconds)] are shown as a function of lag in Fig. 3. The data indicate that there is a difference between 4 mg/kg PCP and saline on performance of the continuous recognition memory task. A three-way within-subjects ANOVA revealed a significant drug effect, $F(1, 140) = 30.8$, $p < 0.0001$, a significant lag effect, $F(1, 140) = 5.3$, $p < 0.0001$, a significant first vs. second presentation effect, $F(1, 140) = 734.8$, $p < 0.0001$, a significant drug × first vs. second presentation interaction effect, $F(1, 140) = 27.4$, $p < 0.0001$, and a significant lag × first vs. second presentation interaction effect, $F(1, 140) = 4.8$, $p < 0.0001$. Thus, 4-mg/kg PCP, relative to saline, injections produce a significant effect on performance of the continuous recognition memory task.

DISCUSSION

The results indicate that during acquisition 4 mg/kg PCP, but not 1 or 2 mg/kg PCP, produced a performance deficit at all lags. Thus, there is a dose-dependent disruption effect. The finding that 4 mg/kg PCP disrupted acquisition performance

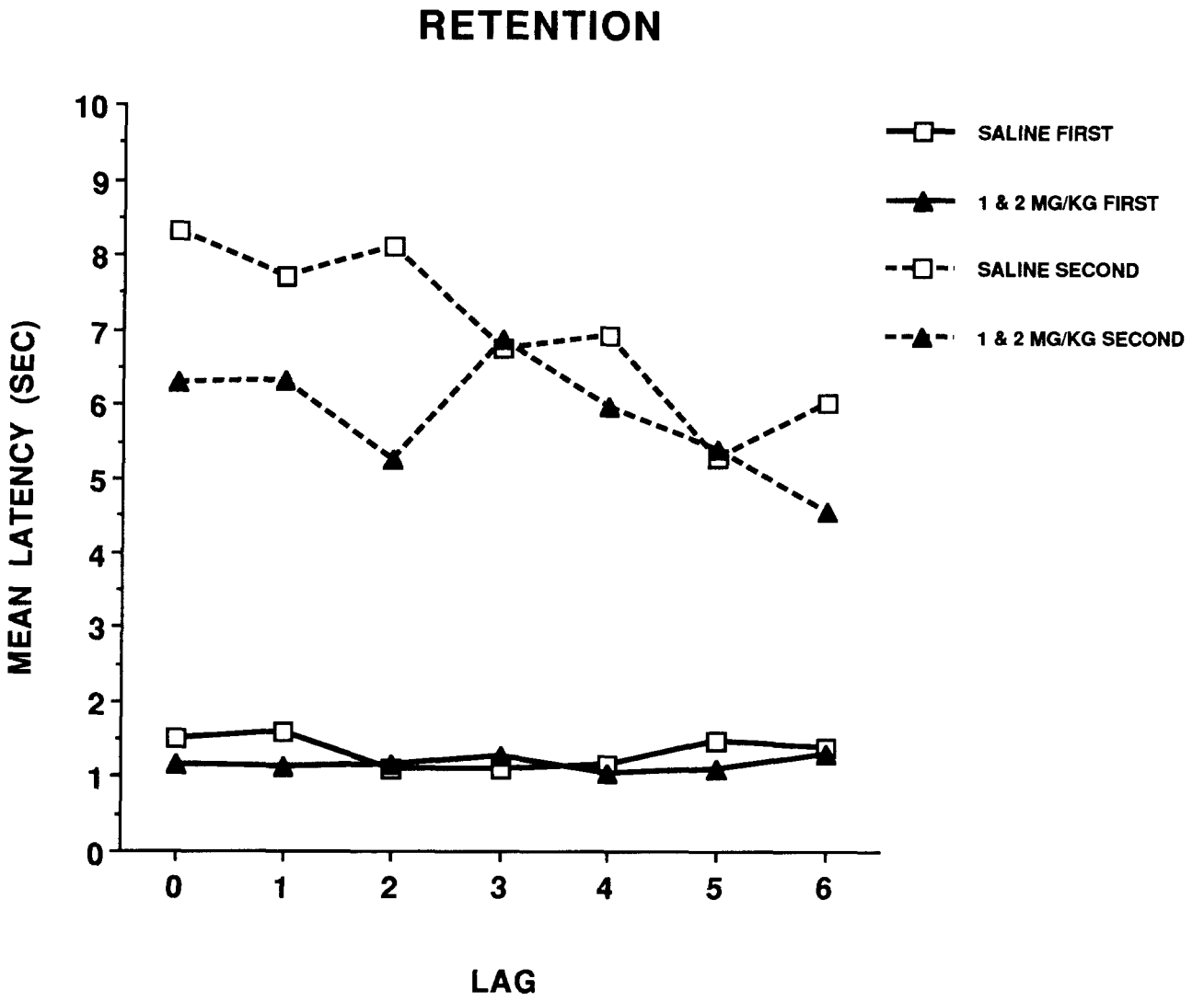

FIG. 2. Mean latency difference (seconds) for the first and second presentation as a function of lag for rats with saline or 1- and 2-mg/kg phencyclidine (PCP) injections during performance of the continuous recognition memory task.

implies an effect on either processes associated with short-term memory representation or consolidation of new learning into long-term memory. The results are thus only partially consistent with the Handelmann et al. (4) and Kesner et al. (8) data, in which PCP disrupted consolidation of new learning but did not alter performance based upon the operation of short-term memory processes. One possible explanation might be that the continuous recognition task is more difficult than the T-maze and spatial navigation tasks used by (4,8) because of added interference on short-term memory processes and consolidation of new information induced by different numbers of intervening arms between repetitions. It is not likely that 4 mg/kg PCP affected performance in this task because upon the first presentation of the arms rats ran as quickly as saline-injected rats. Further, during retention rats with 4 mg/kg PCP were able to inhibit responding on the second presentation of the arms. Also, in this task no changes in locomotor ability or consumption of reinforcement were observed in rats with 4-mg/kg PCP injections.

Similar results have been found with a different antagonist, MK-801, in that a dose of 0.07 mg/kg impaired both short-term memory processes and consolidation of new information of a water maze spatial navigation task (5). However, 0.01 mg/kg MK-801 did not disrupt the ability of rats to learn to reverse a position habit (short-term memory representation), even though they had no memory for the experience the following day (consolidation into long-term memory) (22).

The results also indicate that there is a disruption of performance during retention, with a greater disruptive effect observed primarily for the 4-mg/kg PCP dose. It should be noted that the disruptive effect is much smaller than that observed during acquisition. Clearly, these animals do remember the task, even though they respond somewhat more quickly on the second presentation, suggesting a memory impairment associated with maintenance of short-term memory information. Because no consolidation of information into long-term memory is required during retention performance, it is likely that the devastating effect of PCP on acquisition of the con-

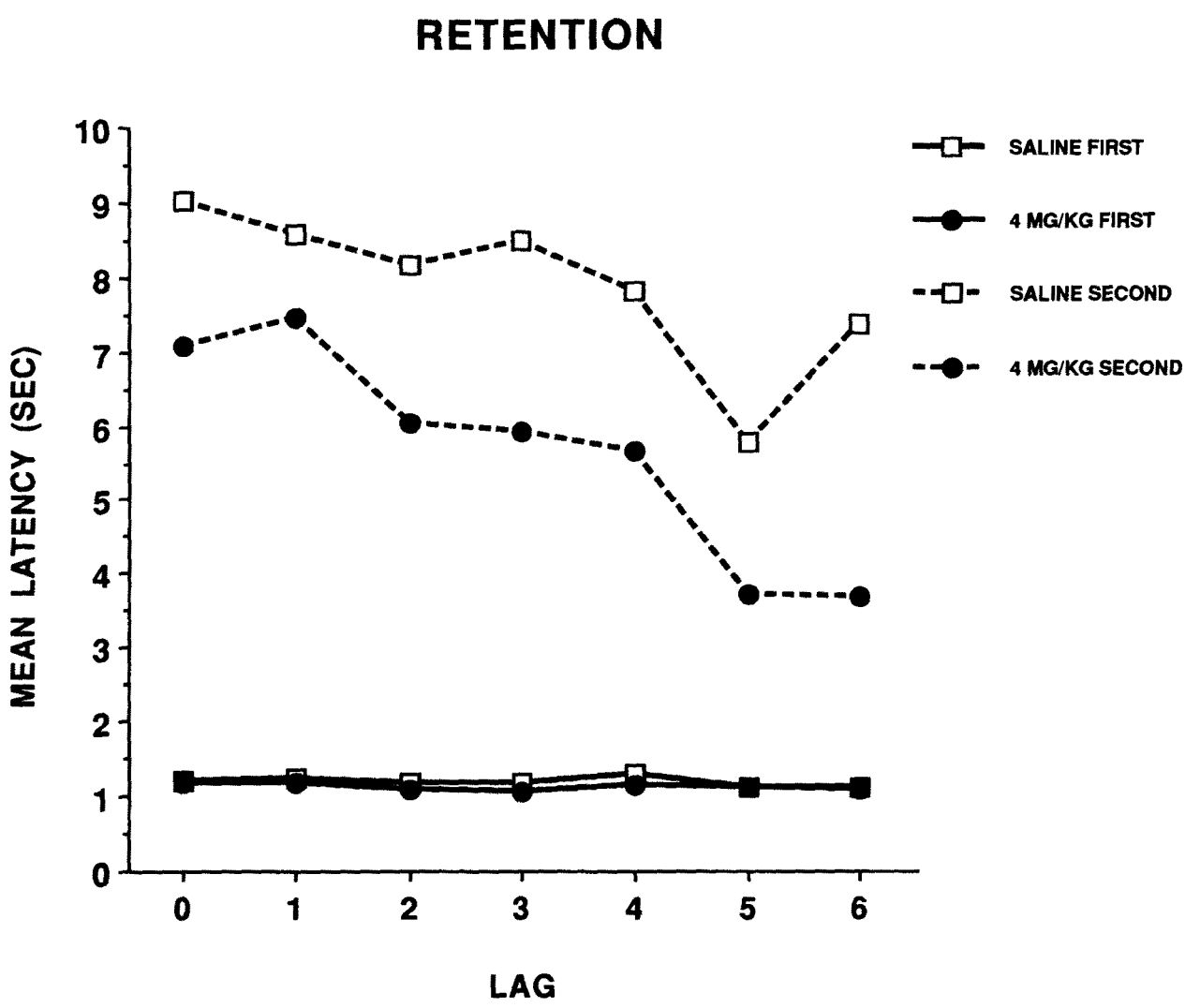

FIG. 3. Mean latency difference (seconds) for the first and second presentation as a function of lag for rats with saline or 4-mg/kg phencyclidine (PCP) injections during performance of the continuous recognition memory task.

tinuous recognition memory task is primarily on the consolidation of new information rather than an effect on short-term memory representation of spatial information.

A similar but more diminished effect on short-term memory processes has been reported with low doses (0.625–0.1 mg/kg) of a different noncompetitive NMDA receptor antagonist, MK-801, in that no deficits were observed in performance within delayed nonmatching-to-sample tasks using spatial or nonspatial cues (13,19,21,22). These tasks presumably measure the operation of short-term memory.

To what extent could these effects have been due to PCP's supposed blockade of NMDA receptors in the hippocampus? It is known that a 4-mg/kg dose of PCP can block LTP recorded in the CA1 region of the hippocampus (20). Thus, it not too surprising to find that 4 mg/kg PCP can produce effects somewhat similar but not identical to what has been observed with hippocampal dysfunction.

If one assumes that the hippocampus mediates both the short-term maintenance of new or previously learned information (working or data-based memory) as well as consolidation of new learning, especially learning that involves the encoding of temporal and spatial attributes, then it appears that PCP has its major effect primarily in altering the consolidation of the new information component of hippocampal function. Thus, in situations in which long-term retention is measured for newly acquired information one would expect similar effects of PCP and hippocampal dysfunction and in situations that do not require consolidation and prominently involve the maintenance of information in short-term memory one would expect a dissociation between the effects of PCP and hippocampal dysfunction. Support for these predictions is provided by the present study, as well as other studies reported previously. For example, in the acquisition of a spatial navigation task long-term memory as measured across days is clearly disrupted by both hippocampal lesions (11,16) and PCP and MK-801, as well as AP-5 (all three drugs act as antagonists of the NMDA receptor) (5,7,15). In retention performance of the continuous recognition memory task, large hippocampal lesions produce a total retention performance deficit for all lags, whereas 4 mg/kg PCP produces only a mild retention

performance deficit (6). In delayed spatial matching-to-sample tasks measuring short-term memory performance, hippocampal lesions produce a severe deficit (7), whereas 4 mg/kg PCP does not (9). Thus, it appears that PCP, perhaps through its blocking effect on NMDA receptors, can produce effects similar to the hippocampus in terms of affecting the consolidation of new information but differs from the hippocampus in terms of not having a major effect on the short-term maintenance of previously learned information.

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