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# The Delayed Effects of Phencyclidine (PCP) Disrupt Latent Inhibition in a Conditioned Taste Aversion Paradigm

SARAH M. TURGEON,*† ELIZA A. AUERBACH* AND MICHAEL A. HELLER*

*Department of Psychology and †Neuroscience Program, Amherst College, Amherst, MA 01002

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TURGEON, S. M., E. A. AUERBACH AND M. A. HELLER. *The delayed effects of phencyclidine (PCP) disrupt latent inhibition in a conditioned taste aversion paradigm.* PHARMACOL BIOCHEM BEHAV **60**(2) 553–558, 1998.—The acute effects of a low dose of phencyclidine (PCP) and the delayed effects of a high dose of PCP on latent inhibition (LI) were assessed in a series of experiments using conditioned taste aversion paradigms. Each paradigm involved a preexposure phase in which water-deprived male rats were allowed access to either water (nonpreexposed; NPE) or 5% sucrose (preexposed; PE), followed by a conditioning phase in which animals were allowed access to sucrose and subsequently injected with the negative reinforcer lithium chloride, and a test phase in which animals were allowed access to both sucrose and water. LI was assessed by comparing the %-sucrose consumed in PE and NPE groups on the test day. The effects of low-dose PCP (2.5 mg/kg) were assessed by comparing LI in animals treated with vehicle or PCP 15 min prior to the onset of the preexposure and conditioning phases. A 4-day paradigm involved 2 days of preexposure followed by a day of conditioning and a test day. This paradigm produced comparable levels of LI in vehicle and PCP-treated animals. A 5-day extinction paradigm involved 2 days of preexposure followed by 2 days of conditioning and a test day. This paradigm abolished LI in vehicle and PCP-treated animals. A 3-day paradigm involved 1 day of preexposure followed by a day of conditioning and a test day. One day of preexposure induced a modified LI effect in both in vehicle and PCP-treated animals. The delayed effects of high dose PCP (8.6 mg/kg) were assessed by comparing LI in animals treated with vehicle or PCP 20 h prior to the onset of the preexposure and conditioning phases in the 4-day paradigm. PCP disrupted latent inhibition in this paradigm. The results are discussed in the context of their relevance to the ability for PCP to model schizophrenic symptomatology. © 1998 Elsevier Science Inc.

Latent inhibition Phencyclidine Schizophrenia

LATENT inhibition is a phenomenon whereby previous exposure to a stimulus impairs the subsequent acquisition of a conditioned response to that stimulus (21). The phenomenon of latent inhibition has been demonstrated in a variety of species (21) including humans (6,22) using a variety of conditioning paradigms. Latent inhibition has been found to be impaired in individuals with acute schizophrenia (6), as well as in humans (16) and rodents (13,31,38–41) treated with the psychotomimetic indirect dopamine agonist amphetamine. Latent inhibition is not impaired in chronic medicated schizophrenics (6,23), and the antipsychotic medications chlorpromazine and haloperidol have been found to reverse amphetamine-induced impairments in latent inhibition in animals (31,42). In addition, a variety of antipsychotic drugs including haloperidol and the atypical antipsychotic drug sulpiride can enhance latent inhibition (10,14). These observations have lead to the hypothesis that amphetamine-induced impairment of latent inhibition in rats is a good animal model for acute schizophrenia (11,14).

Phencyclidine (PCP) is another drug with psychotomimetic properties in humans (5,20,24). Likewise, PCP induces a number of behavioral and cognitive changes in animals thought to model schizophrenia (1,25,27,28,29). Recently, Weiner et al. assessed the ability for PCP to model the disruption of latent inhibition seen in acute schizophrenia. Using a conditioned emotional response paradigm involving tone-shock pairing, they found that low doses of PCP do not disrupt latent inhibition (36). However, the authors note that

Requests for reprints should be addressed to Sarah M. Turgeon, Department of Psychology and Neuroscience Program, Amherst College, Amherst, MA 01002.

PCP's ability to block glutamatergic neurotransmission may lead to a decrease in an animal's ability to switch behaviors (7). Therefore, the enhanced switching of behaviors argued to underlie impaired latent inhibition (35) would not occur. They also note that PCP mimics negative symptoms of schizophrenia, characterized by decreased processing of stimuli, while amphetamine mimics positive symptoms, characterized by increased distractability (8,34). Therefore, they hypothesize that PCP might enhance rather than disrupt latent inhibition (36). In the first set of experiments performed here, we tested the hypothesis that a low dose of PCP enhances latent inhibition in a conditioned taste aversion paradigm and in two modifications of this paradigm in which the expression of latent inhibition in normal animals was reduced.

One problem with testing the effects of acute PCP on latent inhibition is the inability to test the effects of high doses of PCP due to the interference of PCP-induced motor impairment. In humans, the psychotic reaction to PCP tends to be seen as the dose of drug increases (5) and can persist for days or weeks following a single injection (2,20). These observations suggest that the acute effects of a relatively low dose of PCP may not be as capable of modeling schizophrenic symptomatology as the delayed effects of a higher dose of PCP. A previous study by Okuyama, et al. examined the effects of a high dose of PCP on cognitive performance 24 h after injection and found that in such a paradigm, PCP can produce delayed cognitive dysfunction in a water maze task thought to model negative schizophrenic symptomatology (29). Therefore, in the second experiment, we examined the delayed effects of a high dose of PCP on latent inhibition.

## METHOD

### *Subjects*

Ninety-two male Sprague–Dawley rats (Charles River) weighing between 250 and 350 g were individually housed and maintained on a 12 h reverse light–dark cycle for the duration of the experiment. All rats were handled on at least three occasions prior to the onset of the experiment. Twenty-four hours prior to the onset of the experiment, animals were water deprived and only allowed access to water during the course of the experiment. Animals were weighed and their drinking recorded daily during the experiment.

### *Procedure*

*Latent inhibition.* Latent inhibition was assessed using a conditioned taste aversion paradigm adapted from Ellenbroek et al. (12). This paradigm measured the ability of preexposure to sucrose solution to prevent subsequent acquisition of conditioned taste aversion to sucrose. The procedure consisted of a preexposure stage, a conditioning stage, and a test stage. During the preexposure stage, rats were given access to either 50 ml of a 5% sucrose solution (preexposed; PE) or 50 ml of tap water (nonpreexposed; NPE) for 30 min. During conditioning, all animals were given access to 50 ml of a 5% sucrose solution for 30 min immediately followed by an injection of lithium chloride (50 mg/kg in 2 ml/kg, IP). During testing, all animals were given access to both 5% sucrose and water for 30 min. Latent inhibition was assessed by comparing the %-sucrose consumed on the test day (ml sucrose consumed/ml sucrose consumed + ml water consumed) in the PE vs. NPE animals.

*Effects of low-dose PCP on latent inhibition.* The effects of low-dose PCP on latent inhibition were assessed by administering 2.5 mg/kg PCP (2 ml/kg, ip) or saline vehicle (VEH) 15 min prior to the preexposure and conditioning phases of the experiment. This dose was chosen as it was the highest dose found that did not disrupt drinking behavior in pilot studies (data not shown). Four groups of animals were generated: PE-VEH, NPE-VEH, PE-PCP, and NPE-PCP.

The effects of PCP were assessed on three different versions of the latent inhibition paradigm. The first paradigm consisted of 2 days of preexposure, 1 day of conditioning, and 1 day of testing (4-day paradigm); the second consisted of 2 days of preexposure, 2 days of conditioning, and 1 day of testing (5-day paradigm); and the third consisted of 1 day of preexposure, 1 day of conditioning, and 1 day of testing (3-day paradigm). All four treatment groups were assessed in each paradigm ($n = 5$ per group in the 4- and 5-day paradigms, $n = 7$ per group in the 3-day paradigm).

*Effects of high-dose PCP on latent inhibition.* The effects of high-dose PCP on latent inhibition were assessed by administering 8.6 mg/kg PCP (2 ml/kg, IP) or saline vehicle 20 h prior to each day of preexposure and conditioning in a 4-day paradigm. This dose was chosen because it has been shown to produce decreases in cerebral glucose metabolism 24 h following injection (15), and it was the highest dose found that did not produce conditioned taste aversion in a pilot study that mimicked the 4-day protocol except for the replacement of the lithium chloride injection with a vehicle injection (see the Results section). All four treatment groups were assessed in this paradigm ($n = 6$ per group).

### *Statistics*

The effects of PCP on latent inhibition were assessed by comparing the difference between PE and NPE groups in the PCP and VEH groups in each paradigm using a $2 \times 2$ ANOVA, with the main factors of drug treatment group and exposure. Total consumption was also analyzed with a $2 \times 2$ ANOVA on each experimental day.

## RESULTS

### *Effects of Low-Dose PCP on Latent Inhibition*

*4-Day paradigm.* The conditioned taste aversion paradigm used here produced a clear latent inhibition effect in the 4-day paradigm; however, low-dose PCP did not alter latent inhibition (Fig. 1a). This assertion is supported statistically as a $2 \times 2$ ANOVA found a significant main effect for exposure ($F = 28.91$, $p < 0.001$), but not for drug treatment group ($F = 0.47$).

No differences in drinking were observed on any day of the experiment (Fig. 1b).

*5-Day paradigm.* The addition of a second day of conditioning abolished the latent inhibition effect seen in the 4-day paradigm in both drug treatment groups (Fig. 2a). A $2 \times 2$ ANOVA revealed no significant effects of preexposure ($F = 0.53$) or drug treatment group ($F = 1.68$).

Two-by-two ANOVAs revealed a significant main effect of preexposure the second day, with PE groups drinking slightly more than NPE groups ($F = 5.8$, $p < 0.05$) and a significant main effect of drug treatment group on the second conditioning day with vehicle-treated animals drinking slightly more than PCP treated animals ($F = 8.6$, $p < 0.05$; Fig. 2b).

*3-Day paradigm.* The removal of 1 day of preexposure decreased the magnitude of the latent inhibition effect seen in

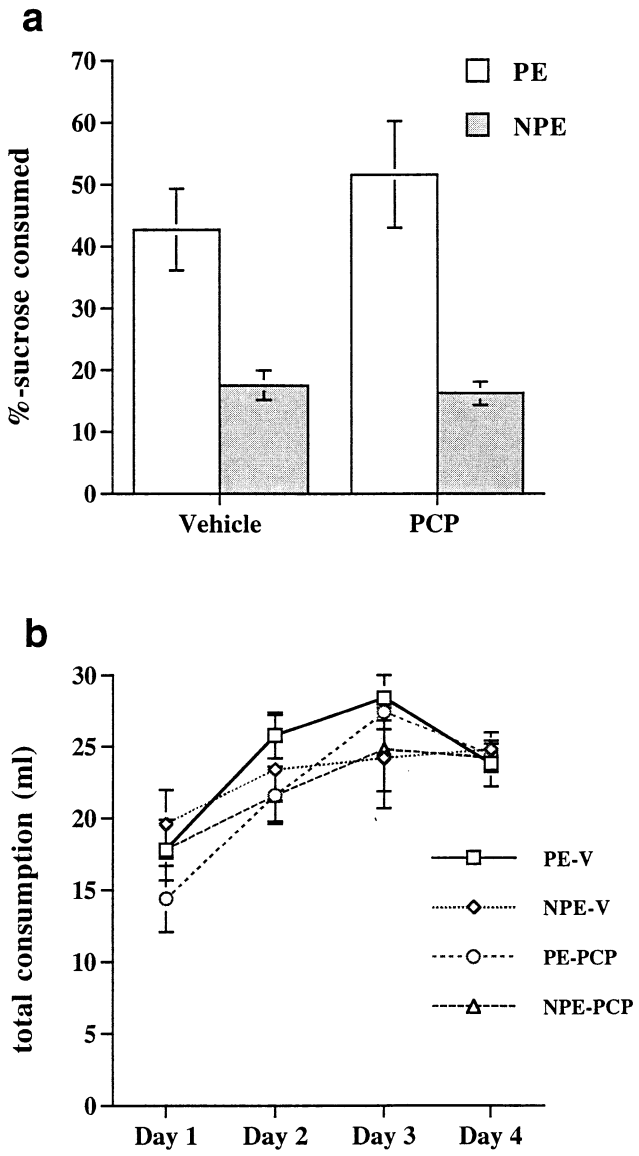


FIG. 1. In the 4-day paradigm, PCP (2.5 mg/kg, 15 min prior to preexposure and conditioning phases) does not alter latent inhibition (a) or total consumption (b). Data presented as mean ± SEM.

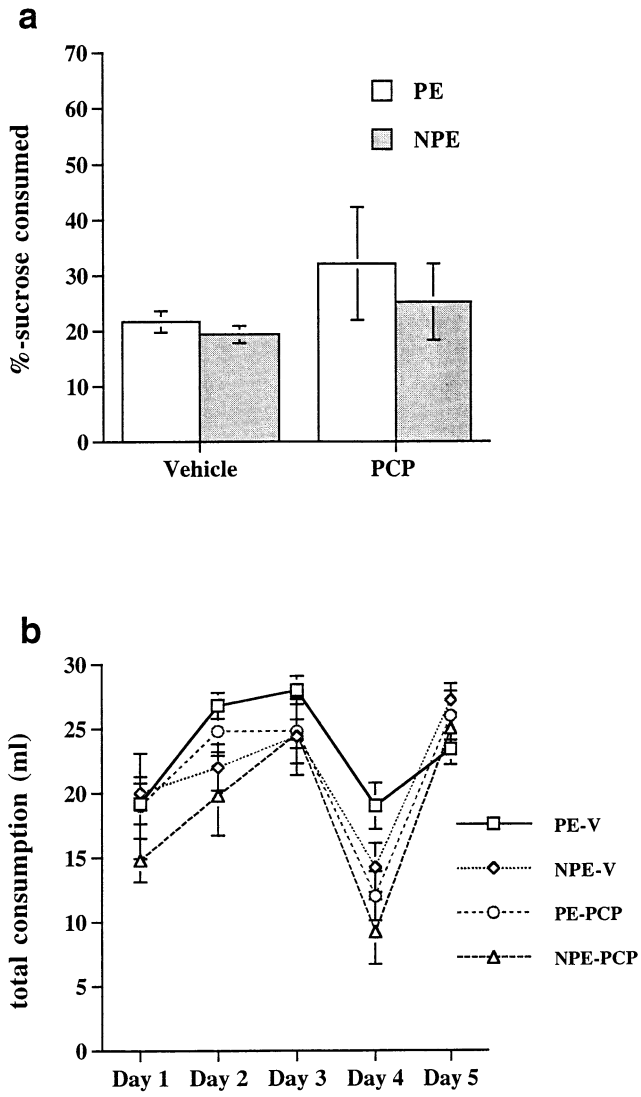


FIG. 2. In the 5-day paradigm, PCP (2.5 mg/kg, 15 min prior to preexposure and conditioning phases) does not enhance latent inhibition (a) but does slightly decrease total consumption on day 4 (b). Data presented as mean ± SEM.

the 4-day paradigm in both drug treatment groups, but did not completely eliminate it (Fig. 3a). A 2 × 2 ANOVA revealed a significant main effect of preexposure ($F = 4.89, p < 0.05$) but not drug treatment group ($F = 2.93$).

A 2 × 2 ANOVA revealed a significant main effect of drug treatment group on the conditioning day with vehicle-treated groups drinking slightly more than PCP treated groups ($F = 5.91, p < 0.05$, Fig. 3b).

*Effects of High-Dose PCP on Latent Inhibition*

*Pilot study.* Pilot data revealed that 8.6 mg/kg PCP given 20 h prior to preexposure and conditioning days did not produce conditioned taste aversion. Animals treated with vehicle injections drank 88.8 ± 4.0% sucrose on the test day while animals treated with PCP drank 85.0 ± 4.2% sucrose on the test day.

*4-Day paradigm.* Animals in the vehicle control groups displayed clear latent inhibition; however, latent inhibition was completely abolished by PCP pretreatment (Fig. 4a). This assertion is supported statistically as a 2 × 2 ANOVA found significant main effects for preexposure ($F = 13.23, p < 0.005$) and drug pretreatment group ($F = 7.08, p < 0.05$) as well as a significant two-way interaction effect ($F = 9.21, p < 0.01$).

Two-by-two ANOVAs revealed a significant main effect of preexposure on the second day with PE groups drinking more than NPE groups ($F = 6.54, p < 0.05$), a significant main effect of drug treatment group on the conditioning day with vehicle-treated groups drinking more than PCP-treated groups ($F = 7.01, p < 0.05$), and a significant main effect of preexposure on the test day with NPE groups drinking more than PE groups ($F = 5.76, p < 0.05$; Fig. 4b).

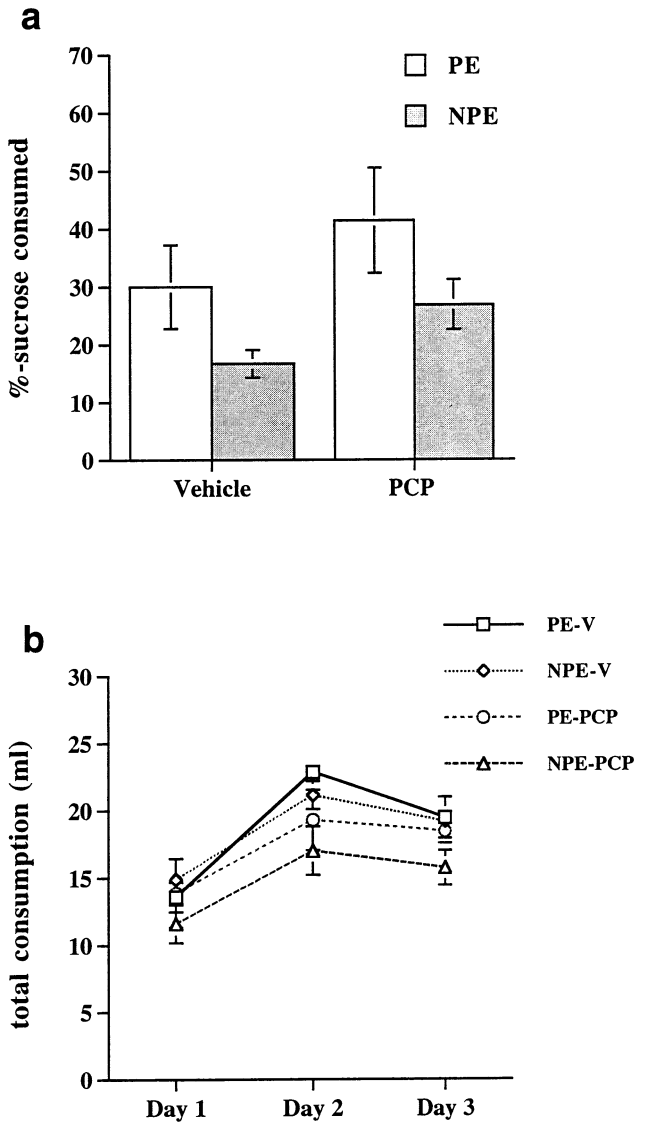


FIG. 3. In the 3-day paradigm, PCP (2.5 mg/kg, 15 min prior to preexposure and conditioning phases) does not enhance latent inhibition (a) but does slightly decrease total consumption on day 2 (b). Data presented as mean ± SEM.

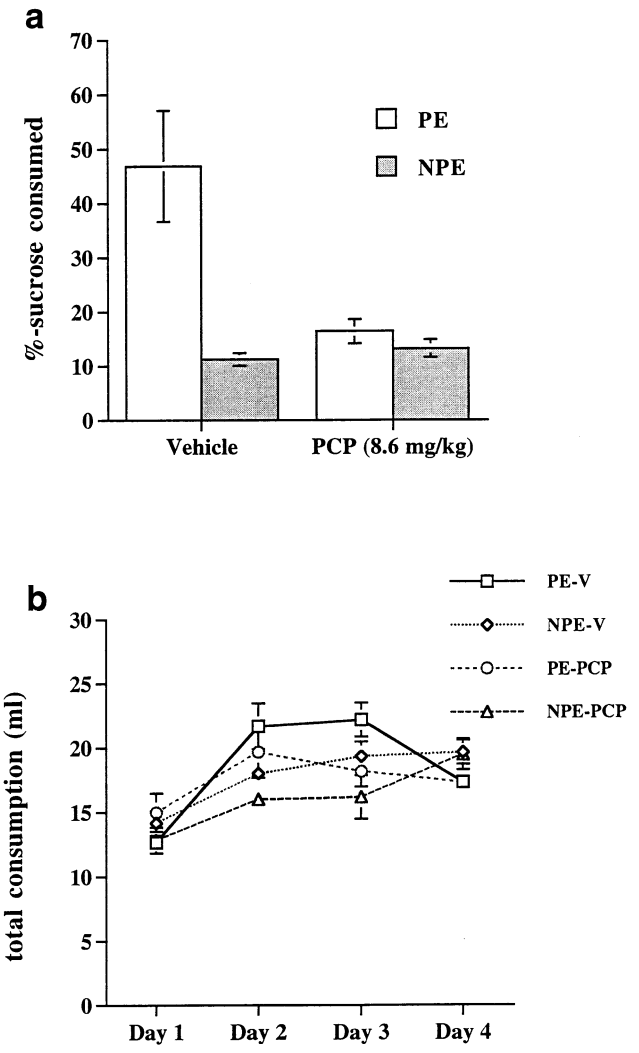


FIG. 4. In the 4-day paradigm, PCP (8.6 mg/kg, 20 h prior to preexposure and conditioning phases) disrupts latent inhibition (a) and slightly decreases total consumption on day 3 (b). Data presented as mean ± SEM.

## DISCUSSION

The results of the first set of experiments suggest that the acute effects of a low dose of PCP neither disrupt nor enhance latent inhibition in a conditioned taste aversion paradigm. Clear inhibition was demonstrated in the 4-day paradigm, as animals that had been preexposed (PE) to sucrose drank significantly more sucrose on the test day than those who were not preexposed (NPE). This behavioral response indicates that the PE animals failed to acquire the conditioned response between the sucrose and the negative reinforcer lithium as strongly as the NPE animals. The relationship between the PE and NPE animals was not altered by PCP. These results are in agreement with those of Weiner et al. in a conditioned emotional response paradigm (36), suggesting that their finding of no disruption by PCP generalizes to the conditioned taste aversion paradigm.

The 5- and 3-day paradigms were designed to test the hypothesis that low-dose PCP enhances latent inhibition. In the 5-day paradigm, the conditioning phase was prolonged by 1 day in an attempt to overcome the effects of preexposure in the vehicle-treated rats such that an enhancement of latent inhibition might be observable in the PCP-treated rats. Although the attempt to overcome the effects of preexposure was successful in the vehicle-treated rats, PCP did not enhance latent inhibition. However, it is possible that 2 days of conditioning produced a sufficiently strong conditioned taste aversion that an enhancement of latent inhibition by PCP could not overcome the effects of two pairings of sucrose and lithium. The drop in overall liquid consumption on day 4 is likely due to the fact that the animals received a sucrose lithium pairing on day 3 and were averse to sucrose, but unlike on day 4 of the 4-day paradigm, they did not have access to water.

In the 3-day paradigm, the preexposure phase was reduced to a single day in an attempt to create a situation in which preexposure was insufficient to induce latent inhibition in the vehicle rats. A previous study has successfully used reduction of the preexposure phase in a conditioned emotional response paradigm to demonstrate the latent inhibition-enhancing effects of the antipsychotic drugs haloperidol and sulpiride (14). One day of preexposure did not completely prevent latent inhibition, but the effect was less robust than in the 4-day paradigm. However, PCP was also unable to enhance latent inhibition in this paradigm.

The inability for the acute effects of low dose PCP to enhance latent inhibition argues against the hypothesis that the failure of PCP to disrupt latent inhibition in a conditioned taste aversion paradigm is due to PCP-induced decreases in switching behavior (36). However, because only low doses can be assessed in such an acute paradigm, this finding does not eliminate the possibility that the delayed effects of higher doses of PCP might alter latent inhibition. Thus, the final experiment was performed to test the hypothesis that a high dose of PCP would alter latent inhibition when administered 20 h prior to the preexposure and conditioning phases in a 4-day paradigm. A clear disruption of latent inhibition by PCP was observed under these conditions.

One potential source of confound in a conditioned taste aversion latent inhibition study is drug-induced conditioned taste aversion. PCP has been shown (although at higher doses than the one used here) to induce conditioned taste aversion to sucrose when administered immediately after sucrose exposure (30). Such an effect might produce the appearance of disruption of latent inhibition by reducing sucrose consumption on the test day in the PE–PCP group. However, conditioned taste aversion does not appear to be a factor here, as pilot data reveal that in the absence of the lithium injection, PE–V and PE–PCP animals drank comparable amounts of sucrose on the test day.

Another potential source of confound would be an effect of PCP on overall liquid consumption. The only drug-related difference in total consumption in the delayed paradigm was observed on the conditioning day when vehicle-treated groups drank slightly more sucrose than PCP-treated groups. However, the predicted effect of a difference in this direction would be a stronger association between sucrose and lithium in the vehicle-treated animals, which is opposite to the effect observed. Therefore, PCP-induced effects on total consumption cannot explain the observed effects of PCP on drinking patterns on the test day.

Finally, lithium has been reported to have antipsychotic effects in humans and might confound the results of the current study. Should lithium be acting as an antipsychotic in this paradigm, we would expect lithium to block the disruption of latent inhibition by PCP. Therefore, an antipsychotic effect of lithium might explain the absence of a disruption in latent inhibition seen following acute low doses of PCP. However, this explanation seems unlikely, as the same inability of PCP to block latent inhibition has been demonstrated in a conditioned emotional response paradigm that does not use lithium (36). In addition, an acute low dose of amphetamine has recently been shown to successfully block latent inhibition in a conditioned taste aversion paradigm quite similar to the one used here (13).

The underlying pharmacological mechanism by which the delayed effects of PCP disrupt latent inhibition in a conditioned taste aversion paradigm is unclear. PCP acts as a noncompetitive *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist (4,20), has affinity for sigma receptors (32), and also possesses dopamine agonist properties (9,17,19,26). The dose of PCP used in this study has been found to produce delayed decreases in glucose metabolism in cortical and limbic structures at 24 h (15). Although the delayed effects of PCP on glucose metabolism are thought to be mediated through the action of PCP at the NMDA receptor complex (15), the delayed effects of PCP on water maze performance are reversed by the sigma ligand NE-100 (29). In addition, intrastriatal but not intraaccumbens amphetamine disrupts latent inhibition in a conditioned taste aversion paradigm, implicating the nigrostriatal dopamine system in latent inhibition as assessed by conditioned taste aversion (13).

The ability for PCP to disrupt latent inhibition in this paradigm may have important implications for the development of animal models of schizophrenia. Amphetamine-induced disruption of latent inhibition is argued to be an animal model of schizophrenia with good construct, face, and predictive validity (11). However, PCP-induced psychosis differs from amphetamine-induced psychosis in a number of respects. Although amphetamine-induced psychosis is characterized by behaviors that mimic the acute or positive symptoms of schizophrenia (3,18), the responses to PCP include behaviors that mimic both the positive and the chronic or negative symptoms of schizophrenia (19,20). In addition, although neuroleptic medications can alleviate the symptoms of amphetamine-induced psychosis, they are generally ineffective in the treatment of PCP-induced psychosis (2). The inability for PCP to disrupt latent inhibition in the previous study was not thought to call into question the validity of amphetamine-induced disruption of latent inhibition as an animal model for schizophrenia, but rather to point out the specificity of impaired latent inhibition as a model of positive schizophrenic symptomatology and the predominant ability for PCP to induce negative schizophrenic symptomatology (36). The authors suggest that amphetamine and PCP may selectively model positive and negative schizophrenic symptomatology, respectively (36). The present observation that PCP can disrupt latent inhibition argues for the ability of the delayed effects of high-dose PCP to model positive schizophrenic symptomotology in animals.

However, the validity of latent inhibition as a model for schizophrenia may need to be reexamined. Although disrupted latent inhibition has been observed in a subpopulation of schizophrenic patients (6), not all studies have replicated these findings (33). In addition, while antipsychotic drugs have been found to alleviate amphetamine-induced disruption of latent inhibition (31,39), the effect of antipsychotics on PCP-induced disruption has not yet been assessed. It should also be noted that latent inhibition in different learning paradigms may be mediated by different neural substrates. Although the dorsal striatum has been implicated in latent inhibition as assessed by a conditioned taste aversion paradigm (13), the nucleus accumbens plays a clear role in latent inhibition as assessed by a conditioned emotional response paradigm (35,37). Therefore, comparisons between studies of latent inhibition as assessed by different paradigms must be made with caution.

In summary, inasmuch as latent inhibition can be considered to be an animal model for schizophrenia, the present findings suggest that PCP may indeed be the drug of choice for modeling both the negative and the positive symptoms of schizophrenia. However, further investigation of the pharmacology of this response is necessary to clarify the validity of PCP-induced disruption of latent inhibition as a model for schizophrenic symptomotology.

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