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Effects of the mGlu2/3 receptor agonist LY379268 on motor activity in phencyclidine-sensitized rats

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Abstract

Previous work has shown that mGlu2/3 receptor agonists such as LY379268 inhibit motor responses to acutely administered phencyclidine (PCP) in rats. However, it has not been determined whether mGlu2/3 receptor agonists will reverse the enhanced effects of repeatedly administered PCP (so called PCP sensitization). In these studies, rats were administered daily PCP and monitored for the number of ambulations, fine movements, time at rest and rears using an automated activity system. At Day 10, when compared the first (Day 1) response, PCP-treated animals showed enhanced responses to all measures tested. Augmentations of these PCP-induced behaviors generally peaked between the third and tenth day after PCP administration had begun. Acute administration of LY379268 effectively suppressed PCP-evoked motor behaviors in rats sensitized to PCP. However, daily administrations of LY379268 (for 9 days), along with PCP, did not prevent the expression of the enhanced PCP response on Day 10. Thus, LY379268 administration can suppress PCP responses after either acute or chronic exposure to PCP. However, the underlying plasticity that leads to PCP sensitization was not affected by this treatment.

Keywords: LY379268; Metabotropic glutamate receptor; mGlu receptor; Phencyclidine; Sensitization; Motor activity

1. Introduction

Phencyclidine (PCP) is an open-channel blocker of the *N*-methyl-D-aspartate subclass of ionotropic glutamate receptors (Anis et al., 1983). There are numerous studies detailing the ability of PCP to induce a state in humans that bears a remarkable resemblance to an acute episode of schizophrenia (for reviews, see Javitt and Zukin, 1991; Halberstadt, 1995; Thronberg and Saklad, 1996). In fact, because of the ability of PCP to evoke both positive (delusions, paranoia, hallucinations) and negative (apathy, motor impairment, social withdrawal) symptoms of schizophrenia (Javitt, 1987), it is thought to produce a clinically relevant animal model of schizophrenia. While numerous researchers have used PCP to induce schizophrenic-like symptoms in animals, the parameters for delivery of PCP have varied widely. There are many reports which indicate that acute administration of PCP can evoke multiple behavioral effects, including increased motor behaviors, stereotypy and cognitive disruptions (Murray and Horita, 1979; Steinpreis, 1996; Cartmell et al., 1999). In addition, several studies have shown that repeated administration of PCP also represents an interesting animal model (Xu and Domino, 1994; Castellani and Adams, 1981; Sturgeon et al., 1982). While there are some differences in the behavioral responses to acute versus repeated administration of PCP in animals, both paradigms have been used to investigate the effects of potential antipsychotics.

Although animal models relying on PCP administration have been studied extensively, only recently has the modulation of glutamatergic synaptic transmission by Group II (mGlu2/3) receptor agonists gained more attention as a novel mechanism for the potential treatment of schizophrenia. It is known that mGlu2 and mGlu3 receptors are highly expressed in forebrain regions, such as the prefrontal cortex and hippocampus, where pathologically enhanced glutamate transmission has been implicated in a variety of CNS disorders, including schizophrenia (Ohishi et al., 1993a,b;

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Neki et al., 1996). In vitro studies have shown that mGlu2/3 receptor agonists suppress excitatory glutamatergic transmission in these areas, and that they may function to reduce excitatory synaptic transmission under conditions of excessive glutamatergic transmission (Anwyl, 1999; Marek et al., 2000; Forsythe and Barnes-Davies, 1997). Previous work has also established that mGlu2/3 receptor agonists are able to suppress the enhanced motor responses and specific behaviors subsequent to acutely administered PCP in rats (Moghaddam and Adams, 1998; Cartmell et al., 1999, 2000a,b). These studies have implicated mGlu2/3 receptor agonists as potential novel therapeutic agents in the treatment of schizophrenia because of their ability to block acute PCP-induced behaviors. However, the mGlu2/3 agonists have not been tested in a repeated PCP administration model of schizophrenia to determine whether they are capable of suppression of PCP-evoked behaviors in such a system.

In this article, we first characterized the effects of daily repeated PCP administration in rats using an automated behavioral system, which measures gross ambulatory movement, nonambulatory fine movement, rearing behavior and time spent at rest (Cartmell et al., 1999). This system allowed measurements of behavioral sensitization to repeated PCP administration to be accurately recorded and was the first time, to our knowledge, that this particular automated behavioral system has been employed to evaluate repeated subcutaneous administration of PCP. Subsequently, we investigated the ability of the potent systemically active mGlu2/3 receptor agonist LY379268 (Monn et al., 1999) to suppress PCP responses in rats sensitized to PCP. LY379268 was also preadministered during the sensitization procedure to examine if the underlying plasticity that leads to PCP sensitization was affected by mGlu2/3 receptor activation. Finally, we also examined the possible effects of repeated PCP administrations on mGlu2/3 receptor binding in rat forebrain. Overall, these studies were designed to further explore mGlu2/3 receptor agonists as a novel approach for the treatment of schizophrenia.

2. Methods

All experiments were performed in accordance with Eli Lilly and Company's animal care and use policies. Male Sprague–Dawley rats (250–300 g, Harlan Sprague Dawley, Cumberland, IN, USA) were group-housed (maximum of eight rats per cage) under standard laboratory conditions with ad libitum access to food and water (12 h light/dark cycle, lights off at 6 p.m. and lights on at 6 a.m. each day), for at least 1 day before use.

2.1. Activity assessment

Behaviors were monitored in transparent, plastic shoebox cages of the dimensions 45 × 25 × 20 cm, with 1 cm depth of wood chips as bedding, and a metal grill on top of the cage. Motor monitors (Hamilton Kinder, Poway, CA) consisted of a rectangular rack of 12 photobeams arranged in an 8 × 4 formation. Shoebox cages were placed inside these racks, enabling the activity of the rat to be monitored in an environment similar to the home-cage. The lower rack was positioned at a height of 5 cm, which allowed the detection of PCP-induced head movements in addition to movements of the body of the rat. A second rack placed 10 cm above the first allowed the detection of rearing activity. Software analysis of the beam breaks, under the definitions of Hamilton Kinder, resulted in the measurement of four different parameters: ambulations (pattern of breaking beams, indicating that the animal has relocated its entire body), fine movements (nonambulatory beam breaks), time at rest (total seconds in a 60-min session in which no new beams were broken, measured at 1-s intervals) and rears (breaking of one of the upper-rack photobeams).

In our initial time course experiments, group-housed rats were transferred from the animal holding room in their home cages to a separate activity testing room. Individual rats were placed in an unsoiled testing cage for an acclimation period of 30 min. Rats were then administered injections of varying doses of PCP (2, 5 and 10 mg/kg sc) or vehicle (1 ml/kg normal saline) and were monitored for activity for 1 h as described above. In the first set of experiments, rats were administered PCP or vehicle once daily for 10 consecutive days in this manner, and activity was measured immediately for 1 h. On Days 11–18 (PCP washout period), rats remained group-housed in the animal holding room until Day 18, when they were again transferred and monitored for 1 h following PCP or vehicle injections.

In another set of experiments, rats were again administered PCP (5 mg/kg sc) for 10 consecutive days, however, activity responses to PCP were just measured on Days 1 and 10. Here, rats were only brought to the test room, placed in an unsoiled cage and tested for activity on Days 1 and 10. On Days 2–9, PCP was delivered in their home-cage in the animal holding room environment. In another experiment, the effects of LY379268 on PCP responses was determined in rats sensitized to PCP in this manner. In this case, rats were also administered either saline vehicle or varying doses of the mGlu2/3 agonist LY379268 (1, 3 and 10 mg/kg sc) on Day 10, 30 min prior to injection with PCP (5 mg/kg sc).

To examine if mGlu2/3 receptor activation with LY379268 altered the development of PCP sensitization in rats, animals were weighed, and LY379268 (10 mg/kg sc) or vehicle (1 ml/kg normal saline) was given once daily for 9 days to rats in their home shoe box cage in the animal holding room. Thirty minutes later, rats received a daily administration of PCP (5 mg/kg sc) or PCP vehicle (saline). On Day 10, animals were moved to the activity testing room, weighed, placed in new shoe box cage in the activity frames and acclimated for 30 min prior to administration of PCP (5 mg/kg sc) or PCP vehicle (normal saline). As before, motor activities were monitored for a 1-h period.

2.2. ^{3}H-LY341495 binding in rat brain membranes

To examine if repeated PCP administration in rats was associated with changes in brain mGlu2/3 receptor binding, rats were administered normal saline vehicle (1 ml/kg sc) or PCP (5 mg/kg sc) once daily for 10 days. One hour after the last dose, rats were decapitated, and the forebrains were dissected. Forebrain membranes were prepared from these tissues, frozen and used for binding studies with ^{3}H-LY341495 as described previously (Wright et al., 2001).

2.3. Statistical analysis

Statistical analyses of behaviors were carried out using the GraphPad PRISM statistical program (GraphPad, San Diego, CA). Data were analyzed by a one-way ANOVA, and then post hoc comparisons for each dose group versus the same dose group on Day 1, or versus control groups, were made using Newman–Keuls Multiple Comparison Test. $P < .05$ was considered significant.

2.4. Materials

PCP was obtained from Sigma (St. Louis, MO). LY379268 was synthesized as described previously (Monn et al., 1999). ^{3}H-LY341495 was synthesized as described previously (Ornstein et al., 1998).

3. Results

3.1. Effect of daily repeated PCP on motor activities in rats

As shown in Fig. 1, similar to what we have shown previously (Cartmell et al., 1999), acute PCP dosing (on Day 1) produced dose-related increases in ambulations (Panel A), fine movements (Panel B) and decreased rest time (Panel C). However, a single dose of PCP did not produce appreciable changes in rearing behavior (Fig. 1, Panel D).

With repeated daily dosing, PCP-induced ambulations progressively increased, peaking on Day 3, and in the case of 5 mg/kg sc, but not the other doses, remained significantly increased at Day 10 when compared to the Day 1 response (Fig. 1, Panel A). On Day 18 (after 8 days of no PCP administration), this response to PCP was no longer significantly different from Day 1 responses. The higher PCP dose (10 mg/kg sc) showed a similar pattern of changes but produced a less robust enhanced response on all days. At 2 mg/kg PCP, no significant changes in ambulations with

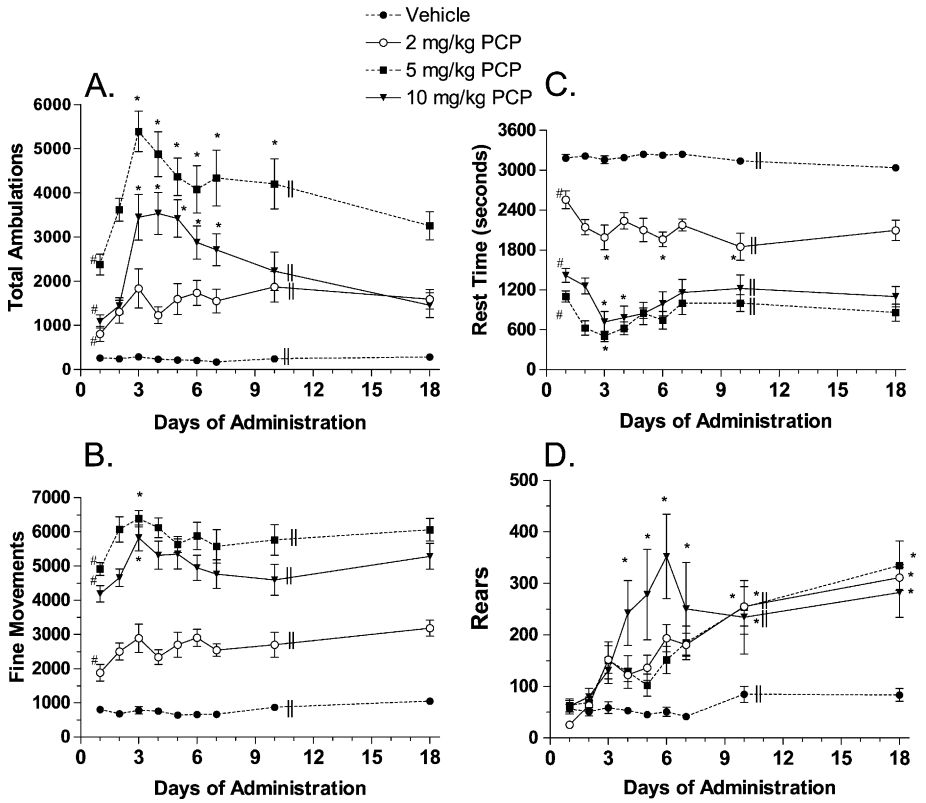

Fig. 1. Effects of varying doses of repeated administration of PCP (milligrams per kilogram) on behaviors as measured in an automated locomotor behavior monitor. Behaviors were monitored over a 60-min period following subcutaneous injection of varying doses of PCP or saline. Rats were administered saline or PCP on Days 1 through 10, and following 8 days of no treatment, the rats were rechallenged with PCP or saline. Data (means ± S.E.) are presented as the total number of behaviors expressed during the 60 min period; $n = 12$ rats. * $P < .05$ when compared with values recorded on Day 1. $^{\#}P < .05$ when compared to vehicle treatment on Day 1.

repeated administration were noted on any day when compared to the Day 1 response.

When measuring fine (nonambulatory) movements, on Day 1, a dose-related stimulatory effect of PCP (a maximal effect of ~6-fold over saline at 5 mg/kg sc) was noted. Repeated PCP produced enhancements over the Day 1 response at 5 and 10 mg/kg sc, but this was only statistically significant following the third PCP dose (Fig. 1, Panel B). Likewise, PCP induced dose-related decreases in rest time at Day 1, again with 5 mg/kg sc producing a maximal response (Fig. 1, Panel C). Repeated PCP produced further enhancements of this effect, which were statistically significant at 3–4 days of administration when compared to Day 1. However, with the exception of the 2 mg/kg sc dose, which remained enhanced at Day 10, the responses to 5 and 10 mg/kg PCP at the later days returned to values not significantly different from Day 1.

Fig. 1 (Panel D) shows the results obtained on rearing behavior. Here, acute (Day 1) PCP did not appreciably elicit this behavior. However, the repeated administration of PCP at all doses tested produced a progressive emergence of this behavior. For example, on Day 3, the 2, 5 and 10 mg/kg sc doses of PCP all increased rearing ~3-fold when compared to saline-treated animals. On Day 10, each of these doses produced ~5-fold increases in rearing when compared to saline, and these values were significantly enhanced when compared to the corresponding Day 1 values. In particular, the most robust rearing responses were noted at 6 days following 10 mg/kg sc PCP. However, on Day 10, these values adapted somewhat to the responses noted for the lower doses. On Day 18, when animals had not received PCP after Day 10, the PCP rearing response to all doses remained at significantly enhanced levels when compared to Day 1, and similar in magnitude to the enhanced responses noted on Day 10.

We next examined the possibility that drug–environment conditioning may have been responsible for the observed sensitization caused by repeated PCP administration. In a second set of experiments, rats were only tested on Days 1 and 10 and had PCP (5 mg/kg sc) delivered in their home-cage environment on the intervening days (Fig. 2). When the rats that received repeated administration of PCP (Days 1–10) were compared with rats only receiving a single dose of PCP (Day 1), an even more pronounced behavioral sensitization to repeated PCP administration was observed. When compared to Day 1, the 10th dose of PCP produced highly significant increases in PCP ambulations (~3-fold, Fig. 2, Panel A), increases in PCP fine movements (~1.6-fold, Fig. 2, Panel B), decreases in rest time (~40% of Day 1, Fig. 2, Panel C) and increased rearing (~30 fold, Fig. 2, Panel D).

3.2. Effect of LY379268 on behaviors evoked by repeated PCP administration

The effects of the mGlu2/3 agonist LY379268 were examined on rats that had undergone 10 days of treatment with PCP (Fig. 3). These rats received PCP (5 mg/kg sc) for

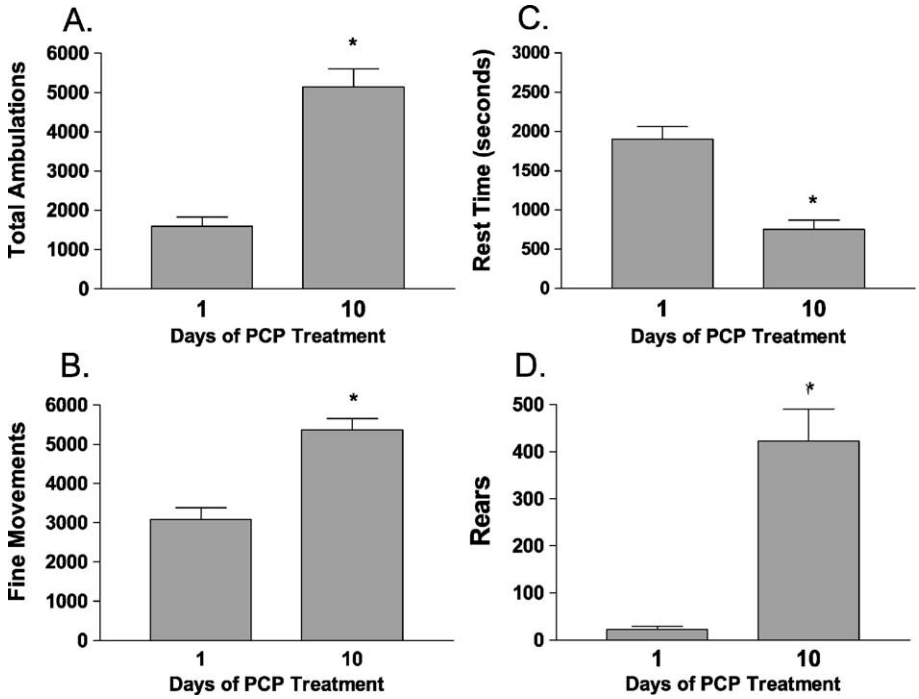

Fig. 2. Effects of a single dose verses repeated doses of PCP (milligrams per kilogram) on behaviors as measured in an automated locomotor behavior monitor. Behaviors were monitored over a 60-min period following subcutaneous injection of PCP. Behavioral measures were taken on Days 1 and 10, while the rats received PCP injections in their home-cage environments on the intervening days. Data (means ± S.E.) are presented as the total number of behaviors expressed during the 60 min period; $n = 12$ rats. * $P < .05$ when compared with values recorded on Day 1.

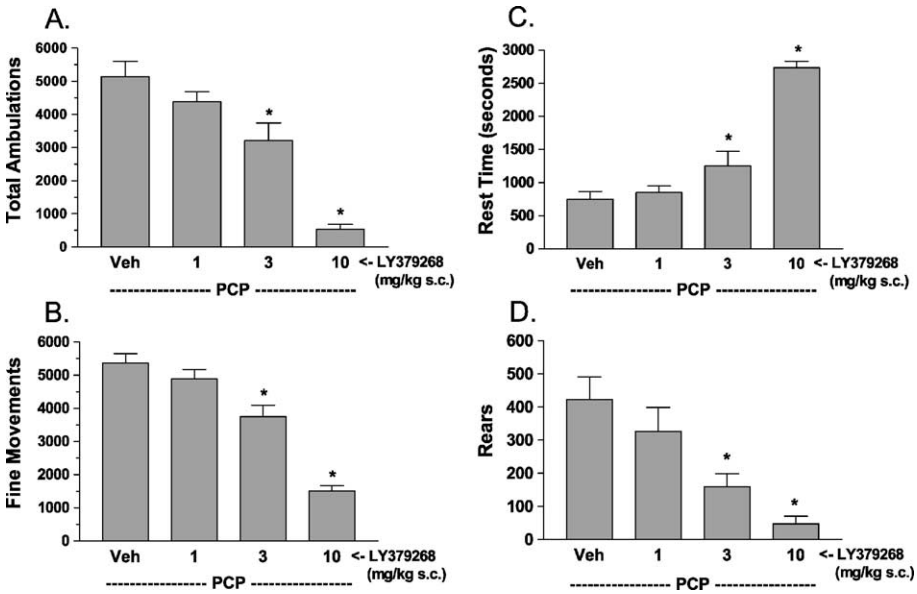

Fig. 3. Effect of varying doses (milligram per kilogram) of the selective mGlu2/3 receptor agonist LY379268 on the reversal of PCP (5 mg/kg) sensitized behaviors. Rats received PCP injections (5 mg/kg sc) once daily for 9 days. On Day 10, behavioral measures were taken for 1 h after 5 mg/kg sc PCP. LY379268 or saline vehicle were administered 30 min prior to PCP injections on Day 10. Data (means ± S.E.) are presented as the total number of behaviors expressed during the 60 min period; $n = 12$ rats. * $P < .05$ when compared with saline injected controls.

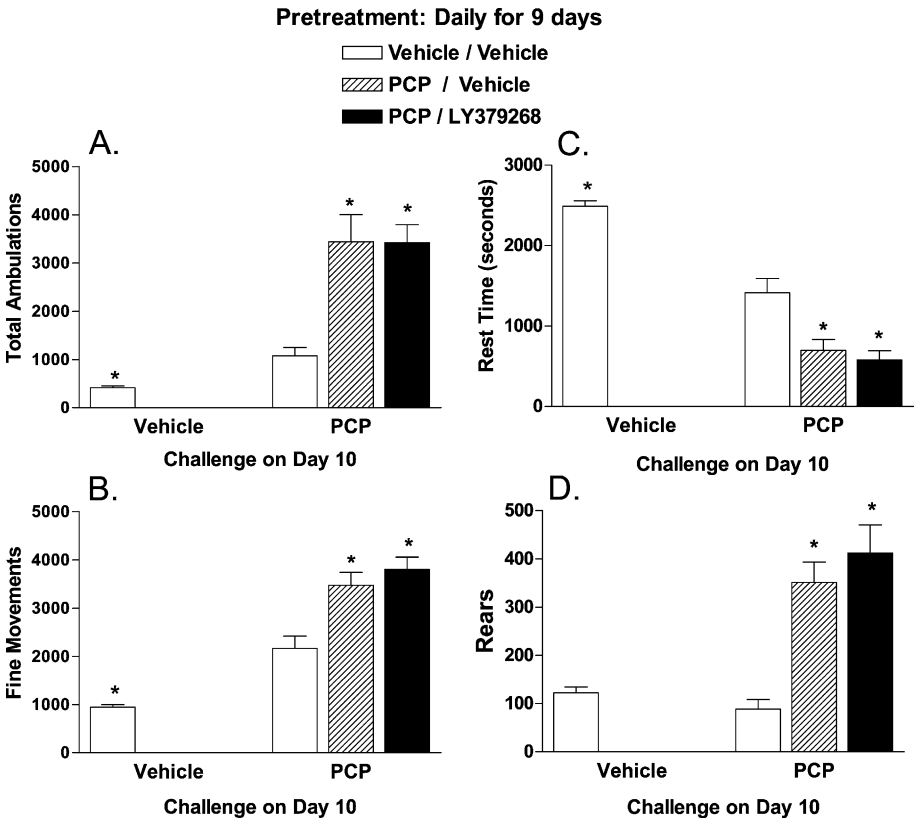

Fig. 4. Effect of daily LY379268 pretreatment on the development of PCP sensitization in rats. LY379268 (10 mg/kg sc) or saline vehicle were administered 30 min prior to PCP (5 mg/kg sc) or its vehicle on Days 1–9. On Day 10, rats from each group were challenged with saline vehicle or PCP (5 mg/kg sc), and behaviors were monitored over a 60-min period. Data (means ± S.E.) are presented as the total number of behaviors expressed during the 60 min period; $n = 10$ rats. * $P < .05$ when compared with vehicle/vehicle pretreated controls receiving PCP on Day 10.

10 consecutive days and were only tested on Day 10 (PCP was delivered in the home-cage environment on the intervening days). On Day 10, the rats were pretreated with either saline or varying doses of LY379268 (1, 3 and 10 mg/kg sc) 30 min prior to the administration of PCP. In these experiments, the effects of LY379268 were highly significant against all four parameters induced by PCP at the 3 and 10 mg/kg sc doses.

To examine if LY379268 would alter the development of PCP sensitization, rats were pretreated with LY379268 (10 mg/kg sc) or its vehicle for 9 days prior to each daily dose of PCP (5 mg/kg sc). On Day 10, pretreated rats were again challenged with vehicle or PCP. As shown in Fig. 4, rats treated with PCP for 9 days had significantly enhanced responses to Day 10 PCP when compared to rats receiving only vehicle for the 9-day pretreatment period (compare the vehicle/vehicle group to the PCP/vehicle group in each panel of the figure showing responses to PCP challenge on Day 10). When compared to rats that received vehicle instead of LY379268, the Day 10 PCP response was also significantly higher when compared to animals receiving PCP only on Day 10 (compare the PCP/LY379268 and PCP/vehicle groups in each panel of the figure showing responses to PCP challenge on Day 10) (Fig. 4A–D). In animals that received PCP for 10 days (sensitized rats), treatment with LY379268 (first 9 days) has no significant effect when compared to vehicle controls (no LY379268). In other words, LY379268 treatment during the sensitization period had no significant effects on the Day 10 PCP response in these animals.

3.3. ^{3}H-LY341495 binding in rats administered repeated PCP

The binding of ^{3}H-LY341495 to forebrain membranes of rats receiving 10 days of repeated PCP were compared to rats receiving saline vehicle for 10 days or saline vehicle for 9 days/acute PCP on Day 10. Here, no significant differences in ^{3}H-LY341495 receptor affinities (K_d) or number (B_{max}) were noted (see Table 1). Likewise, pretreatment of rats with LY379268 for 9 days, along with PCP for 10 days, also produced no significant differences in ^{3}H-LY341495 binding (see Table 1) when compared to these other treatments.

Table 1
Effect of single- versus multiple-dose PCP administration on ^{3}H-LY341495 binding to rat forebrain membranes[a]

Treatment group	K_d (nM)[b]	B_{max} (pmol/mg)[b]
Vehicle × 10 days	1.08 ± 0.19	2.26 ± 0.05
Vehicle × 9 days/PCP on Day 10	0.83 ± 0.04	2.28 ± 0.08
PCP × 10 days	0.78 ± 0.03	2.04 ± 0.12
LY379289/PCP × 9 days/PCP on Day 10	0.65 ± 0.01	2.08 ± 0.08

[a] Rats were decapitated and brains were removed at 1 h after the last dose on Day 10.

[b] Data represent means ± S.E., $n = 3$.

4. Discussion

These studies examined the effect of repeated administration of PCP on rats using an automated motor behavior assessment system. Our results indicate that the repeated administration of PCP results in sensitization to ambulations, fine movements, rearing and time spent at rest. Sensitization to PCP-evoked behaviors was generally found to be maximal at doses of 5 mg/kg PCP, although there were some variations depending on the variable measured. Rearing behavior, for example, was maximally sensitized when a dose of 10 mg/kg was used, while the decrease in time spent at rest showed the greatest sensitization when a dose of 2 mg/kg PCP was used. Despite these variations, all doses of PCP tested tended to induce behavioral sensitization when PCP was administered repeatedly. It should be noted that only enhanced rearing behavior remained statistically elevated following an 8-day washout period, in which animals were left untreated with PCP. The reasons for this phenomenon are not known, perhaps rearing behavior stems from a neural pathway that shows different plasticity than other pathways, in that once it has been altered by repeated PCP administration, it may be more difficult for this pathway to return to a basal state. Others have reported a very marked sensitization to PCP-induced general activity responses that remained for a number of days following PCP withdrawal. For example, Hanania et al. (1999) showed that 5 days of repeated PCP (20 mg/kg) produced behavioral sensitization (total activity counts), which lasted for up to 8 days following PCP withdrawal. The reasons for differences in studies such as these may relate to these differences in PCP dose, PCP dosing regimens and/or the activity parameters that were measured.

It was also found that the behavioral sensitization caused by repeated PCP administration was not due to the environment in which the drug was administered per se. In fact, rats that were only tested on Days 1 and 10 and administered PCP in their home cage environments on the intervening days showed more statistically reproducible sensitization than rats that were tested consecutively on all ten days of PCP administration. Also, when monitoring rats for 30 min prior to PCP dosing on the fifth consecutive day of PCP administration, it was found that PCP-treated rats did not show any changes in basal ambulations or fine movements (data not shown). These results indicate that rats do indeed show a marked behavioral sensitization to repeated administration of PCP, which can be readily measured using our automated behavioral monitoring system.

The acute effects of LY379268 on basal activity measurements and motor function on the rotarod apparatus have been detailed previously. Acutely administered LY379268 at ≥ 3 mg/kg will decrease basal motor activities in animals and higher acute doses, 10–100 mg/kg, will impair rats on the rotarod (Cartmell et al., 1999, 2000a). However, repeated doses of LY379268 lead to a rapid and complete tolerance to rotarod motor impairment, but does not affect

the activity response to PCP (Cartmell et al., 2000b). Thus, it is unlikely that LY379268 changes in spontaneous motor activity or neuromuscular motor impairments per se can account for the actions of LY379268 against PCP behaviors.

In addition to showing a measurable behavioral sensitization to repeated PCP administration, these studies revealed that the specific mGlu2/3 agonist LY379268 is able to effectively suppress PCP-induced behaviors in sensitized rats. However, LY379268 pretreatment at a dose (10 mg/kg sc) that we have shown to fully suppress acute PCP had no effects on sensitization to PCP per se. It should be noted that the acute actions of PCP in animals, although suggested as a useful model for studying mechanisms of antipsychotic drug actions, have not yet been validated as a model of human schizophrenia (Halberstadt, 1995; Thronberg and Saklad, 1996). Likewise, there is active debate on the subject of repeated versus chronic PCP as a useful or even better animal model than acute PCP (Jentsch and Roth, 1999). Clearly, the investigation of novel agents in these tests, along with clinical studies to determine efficacy in schizophrenia will be the ultimate validation of these paradigms. Our data here show that an mGlu2/3 receptor agonist agent with its profile might be quite useful to investigate this issue in the clinic. It is clear that mGlu2/3 receptor agonists suppress or possibly normalize glutamate transmission and can block certain acute actions of PCP in rats. Furthermore, these agents have been shown to mimic atypical antipsychotics in certain other ways, including the functional antagonism of the excitatory actions of $5HT_{2A}$ agonists in the rat prefrontal cortex (Marek et al., 2000) and increases in monoamine release and turnover, similar in profile to other agents such as clozapine and risperidol (Cartmell et al., 2000c,d). The observation here that LY379268 is still effective in blocking PCP behaviors in sensitized rats adds further data suggesting that mGlu2/3 agonists interesting potential novel antipsychotic agents.

The significance of the observation that mGlu2/3 receptor agonists did not block the development of PCP sensitization to the potential clinical utility of these agents depends on the how useful this procedure models schizophrenia pathology. Nevertheless, we can conclude from our studies here that LY379268 does not alter the underlying changes or plasticity that leads to PCP sensitization. Furthermore, our studies indicate that the expression of PCP induced behaviors per se during sensitization does not affect the underlying processes leading to this phenomenon. The dose of LY379268 (10 mg/kg sc) used during the sensitization period to block PCP has been show to be fully effective against either acute (Cartmell et al., 1999, 2000b) or sensitized PCP responses (studies here). Moreover, our previous work (Cartmell et al., 2000a) has shown that there is no tolerance to the repeated injections of LY379268 when measuring its ability to block PCP-induced motor activations (Cartmell et al., 2000b). Likewise, we show here that mGlu2/3 receptors per se showed no adaptive changes to repeated PCP or PCP + LY379268. This may explain why the mGlu2/3 receptor agonist retained efficacy in PCP-sensitized rats. That said, compared to our previous work (Cartmell et al., 1999), LY379268 was about three times less potent in blocking PCP behaviors in sensitized rats when compared to acute PCP. However, this might be explained by the dramatic increase in the PCP response that needs to be overcome after sensitization. Previous work has also concluded that the expression of acute locomotor responses to PCP is not a requirement for development of PCP sensitization. For example, Phillips et al. (2001) reported that the D1 antagonist SCH23390, which blocks the acute response to PCP, had little effects on the development of PCP sensitization.

It has been shown that repeated doses of PCP similar to those used here in rats also leads to other phenomenon including neurotoxicity characterized by neuronal vacuolization (Olney et al., 1991) Repeated dosing with PCP also produces up-regulation of NR1 subunit expression, increases in NMDA receptor functions in brain slices and apoptotic cell death (Wang et al., 1999, 2000; Hanania et al., 1999; Johnson et al., 1998). mGlu2/3 receptor agonists, including LY379268, have been shown to be neuroprotective in certain models of brain ischemia where apototic cell injury is prominent (Bond et al., 2000). Thus, it would be interesting to further explore if the development of these other phenomenon might be prevented by this agent. Notably, Phillips et al. (2001) also reported that the AMPA/kainite antagonist DNQX, which has been shown by others (Olney et al., 1991; Sharp et al., 1995) to prevent NMDA antagonist-induced neurotoxicity, did not block the development of PCP sensitization. Their data suggested overlap, but nonidentity, between the mechanisms underlying these two phenomenon. Notably, they also observed that the AMPA/kainate antagonist 6,7-dinitroquinoxaline-2,3-dione (DNQX) did not block the development of PCP sensitization. mGlu2/3 receptor agonists also act in certain circuits (e.g., prefrontal cortex) (Marek et al., 2000) by suppressing postsynaptic activation of excitatory AMPA/kainate receptors, but in this case, via decreasing presynaptic release of glutamate. Thus, this mechanism may be responsible for why LY379268 also did not block PCP sensitization. Possibly, the utility of mGlu2/3 agonists in treating psychosis might be from simply correcting or normalizing abnormal brain circuitry in relevant limbic brain regions. In any case, the advantage or disadvantage of an agent such as LY379268, which does not alter development of PCP sensitization, remains to be established.

In summary, we found that repeated dosing of PCP to rats leads to sensitization that manifests as prominent and long-lasting increases in PCP-induced rearing, as well as other behavioral parameters (ambulations and fine movements). Furthermore, in rats sensitized to PCP, we observed that LY379268 potently blocked the greatly enhanced PCP behaviors, including rearing, ambulations and fine movements. Interestingly, LY379268 treatment did not alter the development of PCP sensitization. These data clearly dis-

sociate the mechanisms involved in the expression versus development of sensitization to PCP. Furthermore, as the acute and chronic effects of PCP in animals and humans has been used as a conceptual model of schizophrenia pathology in humans, mGlu2/3 receptor agonists may be useful to clarify the clinical relevance of these animal models to the glutamate hypothesis of schizophrenia.

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