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ORIGINAL ARTICLE

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Tolerance to the motor impairment, but not to the reversal of PCP-induced motor activities by oral administration of the mGlu2/3 receptor agonist, LY379268

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Abstract The potent metabotropic glutamate (mGlu) receptor agonist, LY379268, selectively activates mGlu2/3 receptors with EC_{50} values in the low nanomolar range. We have previously shown in rats that LY379268 reverses phencyclidine (PCP)-induced motor activations (increases in ambulations and fine movements, and decreases in the animals time at rest). Here, we have investigated: (1) the dose-response and time course for this action of LY379268 following oral (p.o.) administration and (2) the therapeutic index in this model following acute versus subchronic (4 days) p.o. dosing.

LY379268 (3 mg/kg p.o.) evoked a maximal effect on PCP (5 mg/kg s.c.)-elicited behaviors 4 h post-dosing. At this time point, p.o. LY379268 inhibited the effects on PCP-elicited activities with a similar potency (ED_{50} values ca 1 mg/kg) to that previously obtained following s.c. administration. Doses up to 3 mg/kg p.o. LY379268 were without effect on the rotorod performance of rats when measured at 1, 2, 4, 8, and 24 h post-administration. In agreement with the peak time-effect on PCP-evoked motor behaviors, 10 mg/kg p.o. LY379268 only significantly impaired rotorod performance at the 4-h time point. Interestingly, acute motor impairment produced by higher doses of LY379268 (10, 30, or 100 mg/kg p.o.) was absent following 4-day repeated administration of LY379268. In contrast, the potency of LY379268 for the inhibition of PCP-evoked motor activities was not affected following multiple dosing over a similar period. These results demonstrate that although the reduction of PCP motor activities by LY379268 is maintained after subchronic dosing, tolerance to the motor impairment evoked by the compound occurs, thus greatly widening the therapeutic index of LY379268.

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Introduction

The novel family of metabotropic glutamate (mGlu) receptors mediate their actions in the central nervous system via activation of G-proteins and subsequent induction of second messenger transduction pathways (for review see Conn and Pin 1997). mGlu receptors have been classified into three subgroups on the basis of second messenger coupling and pharmacology. Group I mGlu receptors (mGlu1 and mGlu5) are coupled to phospholipase C and are selectively stimulated by the phenylglycine derivative, (S)-3,5-dihydroxyphenylglycine (S-DHPG) (Schoepp et al. 1994). The other two groups of mGlu receptors (groups II and III) are negatively coupled to adenylyl cyclase and are differentiated on the basis of their agonist pharmacology. Group II mGlu receptors (mGlu2 and mGlu3) are most potently stimulated by LY354740 (Monn et al. 1997; Schoepp et al. 1997) and LY379268 (Monn et al. 1999), and group III mGlu receptors (mGlu4, 6, 7, and 8) are activated by L-amino-4-phosphonobutyric acid (l-AP4; Thomsen 1997).

All three groups of mGlu receptors have been proposed as novel drug targets for psychiatric and neurological disorders (Knopfel and Gasparini 1996; Nicoletti et al. 1996). In particular, the potent, selective mGlu2/3 agonist, LY354740, has been shown to be active in animal models of global ischemia (Bond et al. 1998), Parkinson's disease (Konieczny et al. 1998), drug withdrawal states (Helton et al. 1997; Vandergriff and Rasmussen 1999), and in models of psychiatric disorders such as anxiety (Helton et al. 1998). It is hypothesized that the effects of LY354740 in these disorders might be mediated via the regulation of synaptic transmission by activation of mGlu2 receptors. These presynaptic receptors are located perisynaptically, outside of the normal active zone of the synapse (Ohishi et al. 1994; Shigemoto et al. 1997). Thus, mGlu2 receptors might only be activated under circumstances when

glutamate levels in the synapse are pathologically high, but these receptors would remain inactive under conditions of normal neurotransmission (Scanziani et al. 1997). Indeed, microdialysis studies have shown that LY354740 inhibits glutamate release evoked by veratridine or phencyclidine (PCP) in the striatum and medial prefrontal cortex, respectively, but is without effect on basal glutamate levels (Battaglia et al. 1997; Moghaddam and Adams 1998). The latter report also showed that, in addition to an attenuation of PCP-stimulated glutamate release in the prefrontal cortex, LY354740 also reduced the expression of specific behaviors evoked by PCP in an animal model of psychosis.

Treatments with non-competitive NMDA receptor antagonists, such as PCP, are commonly used as models for schizophrenia due to their ability to produce schizophrenia-type symptoms in humans (for reviews see Javitt and Zukin 1991; Halberstadt 1995). Behaviors exhibited by rats following an acute dose of 5 mg/kg PCP include stereotypies such as head weaving and sniffing, backward walking as well as increased locomotion and falling (Murray and Horita 1979; Castellani and Adams 1981). Moghaddam and Adams (1998) showed that LY354740, at a dose of 10 mg/kg reversed head weaving and the increase in locomotion elicited by 5 mg/kg PCP. This study indicated that mGlu2/3 receptors might play a significant role in schizophrenia. We have recently extended the work by Moghaddam and Adams, showing that both mGlu2/3 receptor agonists LY354740 and LY379268 reversed specific motor behaviors evoked by PCP. Parenteral (s.c.) doses of 3 and 10 mg/kg LY379268 and LY354740, respectively, almost completely abolished the increased locomotor activity and expression of fine motor movements evoked by PCP (5 mg/kg; Cartmell et al. 1999). The effects of 3 mg/kg LY379268 on PCP-evoked motor activities were completely reversed by the selective mGlu2/3 antagonist, LY341495 (1 mg/kg; Kingston et al. 1998; Ornstein et al. 1998). However, despite these marked effects on PCP-elicited behaviors, both LY354740 and LY379268 produced only minimal effects on similar behaviors stimulated by d-amphetamine (d-AMP, 3 mg/kg; Cartmell et al. 1999). It has been suggested that the occurrence of extra-pyramidal side effects of neuroleptics in the clinic might be predicted by their ability to inhibit specific d-AMP-evoked behaviors. Therefore, it is feasible that potential antipsychotic actions of LY354740 and LY379268 (unlike the classic neuroleptic haloperidol) might be devoid of extra-pyramidal side effects due to their limited actions on d-AMP-evoked motor activities. Furthermore, in contrast to haloperidol, complete inhibitions of PCP-evoked motor behaviors were observed at doses of LY354740 and LY379268 that did not produce motor impairment.

These effects of LY354740 and LY379268 on PCP-evoked behaviors indicate that activation of mGlu2/3 receptors provides a novel mechanism by which to further investigate psychosis. In this paper, we examined the dose-response and time course for this action of LY379268, the most potent mGlu2/3 compound in this model, following oral (p.o.) administration. Furthermore, to examine the influence of subchronic exposure on the therapeutic index of LY379268, the effects of LY379268 p.o. in the PCP motor activity model and in the rotorod test for motor impairment were also investigated following acute versus 4-day multiple dosing.

Materials and methods

Male Sprague Dawley rats (250–300 g) were group-housed (maximum of seven rats per cage) under standard laboratory conditions with ad libitum access to food and water (12 h light/dark cycle). However, rats were fasted during the night prior to oral LY379268 administration. Multiple dosing experiments consisted of single daily p.o. administrations of LY379268 or sterile water (1 ml/kg) for 4 consecutive days. During these subchronic dosing studies, rats were fasted only during the nights before test days 1 and 4.

Activity assessment. Following a 30-min acclimation period, rats were orally administered LY379268 (1 ml/kg) or sterile water (1 ml/kg), and then returned to transparent, plastic shoe-box cages of dimensions 45×25×20 cm, with 1 cm depth of wood chips as bedding and a metal grill on top of the cage (or returned to their original cages for 24-h time points). After the designated time, the rats were given a s.c. injection of PCP (Sigma Chemicals, St. Louis, Mo., USA) or sterile water (1 ml/kg) and once again returned to the shoe-box cages for immediate locomotor activity monitoring. Motor monitors (Hamilton Kinder, San Diego, Calif., USA) consisted of a rectangular rack of 12 photobeams arranged in a 8×4 formation. Shoe-box cages were placed inside this rack, enabling the activity of the rat to be monitored. The 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. Software analysis of beam breaks, under the definitions of Hamilton Kinder, resulted in the classification of three measures of behavior (see Cartmell et al. 1999); ambulations, non-ambulatory or fine motor movements, and time at rest (number of 1-s intervals where there were no beam breaks in a 1-h session).

Rotorod performance. An automated rotorod apparatus (San Diego Instruments, San Diego, Calif., USA) was used as a test for sedation/ataxia. Ninety minutes prior to drug administration, rats were trained to stay on the rotorod, rotating at 4 rpm, over four successive trials. Those rats which remained on the rod for a consecutive 60-s period were re-tested 30 min prior to drug administration. Rats successful in the re-testing session were then administered LY379268 (p.o.) or sterile water (1 ml/kg), and returned to shoe-box cages (or original cages for 24-h time points). After the designated time, rats were again tested on the rotorod for a period of up to 60 s.

Statistical analysis. Statistical analyses of behaviors were carried out using the GraphPad PRISM statistical program. Data were analyzed by a one way analysis of variance (ANOVA), and then post hoc comparisons for each dose group versus control or PCP alone were made using Newman-Keuls multiple comparison test. A value of $P<0.05$ was considered significant. ED_{50} values were calculated from mean data using the median-effect plot of Chou and Talalay (1983).

Results

Oral administration of LY379268 evoked a time-dependent reversal of PCP (5 mg/kg s.c.)-evoked motor activities. A significant reversal of PCP activity by 3 mg/kg LY379268 was observed 1 h after dosing, however, the

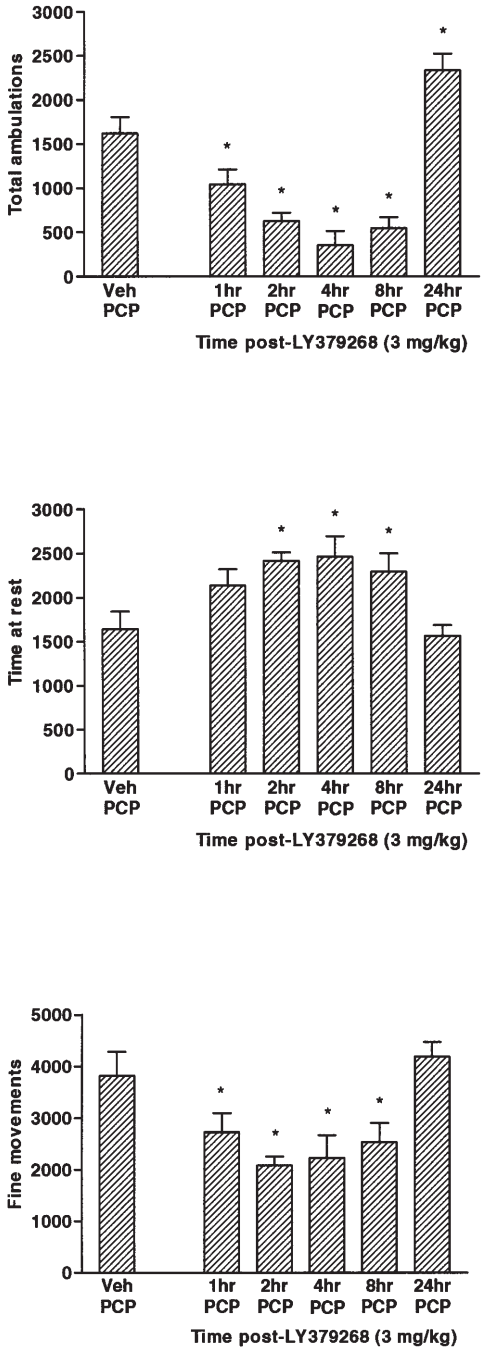

Fig. 1 Time course of the effects of LY379268 (3 mg/kg p.o.) on phencyclidine (PCP) (5 mg/kg s.c.)-evoked motor activities measured in an automated activity monitor. Rats were administered vehicle or LY379268 (1 ml/kg) and then challenged with PCP (1 ml/kg) after 1, 2, 4, 8, or 24 h. Motor activities were then monitored for the subsequent 60 min. Data (mean ± SEM) are presented as total number of behaviors expressed during 60 min; n=7 rats. *P<0.05 when compared to the corresponding vehicle/PCP control

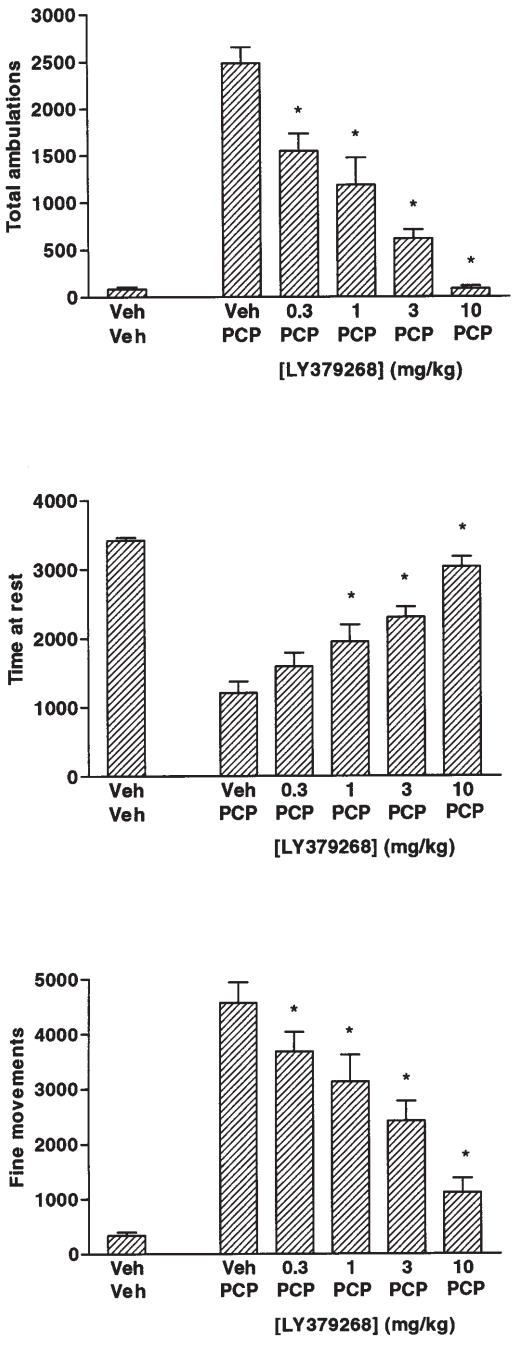

Fig. 2 Effect of various doses of LY379268 (p.o.) on PCP (5 mg/kg s.c.)-evoked motor activities measured in an automated activity monitor. Rats were administered vehicle or LY379268 (1 ml/kg) p.o. and then challenged with PCP (1 ml/kg) s.c. 4 h later. Motor activities were then monitored for the subsequent 60 min. Data (mean ± SEM) are presented as total number of behaviors expressed during 60 min; n=7 rats. *P<0.05 when compared to the corresponding vehicle/PCP control

maximal effect was observed approximately 4 h post-dosing. At this time, PCP-evoked total ambulations were inhibited by 78%, and fine movements were reduced by 45 and 42% at 2 and 4 h post-dosing, respectively (Fig. 1). LY379268 also reversed the decrease in time spent at rest elicited by PCP, with a maximal effect at 4 h. Significant effects were still present 8 h post-administration but inhibition of PCP activities by LY379268 was absent 24 h after dosing. Interestingly, 3 mg/kg LY379268 caused a significant increase in PCP-evoked total ambulations at the 24-h time point (144% of PCP control), however, no sig-

Table 1 Effect of oral (p.o.) administered LY379268 on basal motor activities. LY379268 was given 4 h prior to testing and motor activities measured for 1 h. Control animals (*O*) were administered p.o. water vehicle. Values are mean ± SE, 6 rats per treatment group

	Dose (mg/kg p.o.)	Total ambulations	Time at rest (s)	Fine movements
O		38±22	3467±21	256±41
LY379268	0.3	27± 8	3475±36	254±73
	1	35± 9	3469±15	254±26
	3	9± 3	3467±10	282±22
	10	5± 1	3430±22	148±43

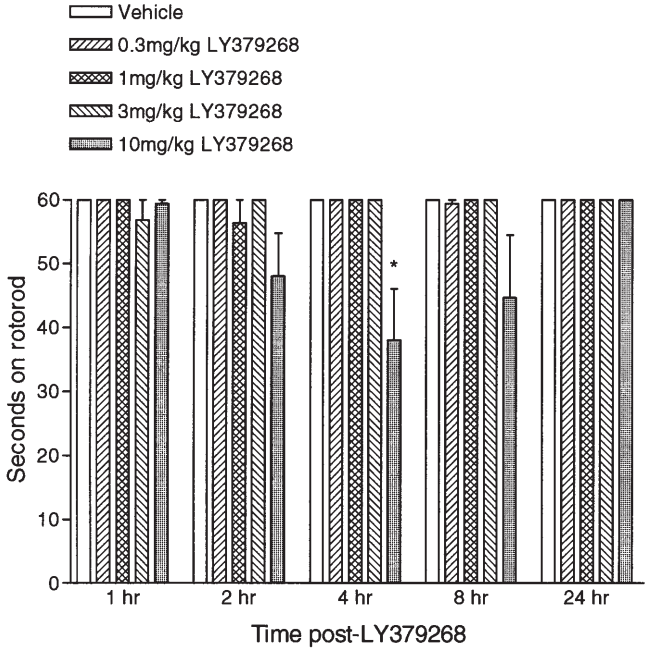

Fig. 3 Time course of the effect of LY379268 p.o. (at doses of 0.3, 1, 3, and 10 mg/kg) on rotorod performance of rats. Rats were administered vehicle or LY379268 (1 ml/kg) p.o. and then tested on the rotorod after 1, 2, 4, 8, or 24 h. Data (mean ± SEM) are presented as the time (s) spent on the rotorod, up to a maximum test period of 60 s; n=6 rats. *P<0.05 when compared to the corresponding vehicle control

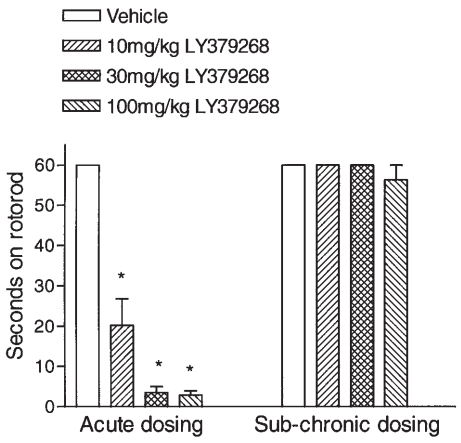

Fig. 4 Effect of multiple dosing with LY379268 p.o. (at doses of 10, 30, and 100 mg/kg) on rotorod performance of rats. Rats were given single, daily doses of vehicle or LY379268 (1 ml/kg) p.o. for 4 consecutive days and then tested on the rotorod 4 h following the dose on day 1 (acute) or day 4 (sub-chronic). Data (mean ± SEM) are presented as the time (s) spent on the rotorod, up to a maximum test period of 60 s; n=6 rats. *P<0.05 when compared to the corresponding vehicle control

nificant difference in time at rest was observed at 24 h and, furthermore, this increase was not observed with a dose of 10 mg/kg LY379268 (data not shown).

LY379268 p.o. elicited a dose-dependent reversal of PCP-evoked motor activities (4 h post-dosing; Fig. 2). The MED of LY379268 p.o. was approximately 0.3 mg/kg, with ED_{50} values of 1.98 and 0.67 mg/kg, for the reversal of fine movements and total ambulations, respectively. At this time point, PCP-evoked fine movements were inhibited by 51 and 82% by 3 and 10 mg/kg LY379268 p.o., respectively. Furthermore, total ambulations were inhibited 78% by 3 mg/kg and completely abolished by 10 mg/kg LY379268 p.o. (Fig. 2). As shown in Table 1, basal motor activities (ambulations and fine movements) in this test were very low and variable, as the animals have been adapted to their cage. Also, as previously reported (Cartmell et al. 1999), basal activity is very modest (2 and 6% of the PCP-induced increases in ambulations and fine movements, respectively). In support of this, in a 60-min (3600 s) test session, animals spend >95% (>3400 s) of their time at rest. Doses of LY379268, up to 10 mg/kg p.o., had no significant effect on these basal activities (Table 1). However, as we have noted previously, higher doses of LY379268 (≥3 mg/kg) appear to reduce basal motor activities, but the variability of the response (particularly ambulations) precludes showing any significant reductions. Furthermore, when animals were given acute doses of LY379268 (3 or 10 mg/kg p.o.), and basal motor activities were measured 24 h later, no significant effects was observed when compared to animals treated with water vehicle (data not shown).

Thus, to test for possible motor impairment of the animals, their performance in a rotorod task was examined after acute oral LY379268. Doses up to 3 mg/kg LY379268 p.o. were without effect on the rotorod performance of the rats at all time points tested: 1, 2, 4, 8, and 24 h post-dosing (Fig. 3). However, 10 mg/kg LY379268 somewhat reduced rotorod performance at 2, 4, and 8 h post-dosing, although only the effect at 4 h was significant. At this time point, rats treated with 10 mg/kg LY379268 p.o. were only able to remain on the rotating rod for 38±8 s (n=6) in comparison with rats given vehicle or lower doses of LY379268 which were able to remain on the apparatus for the full 60-s test period (Fig. 3). In further agreement with the time course observed in the PCP motor activity study, motor impairment produced by 10 mg/kg LY379268 p.o. was absent 24 h after administration (Fig. 3).

The effects of multiple dosing with LY379268 p.o. on rotorod performance and inhibition of the PCP behavioral

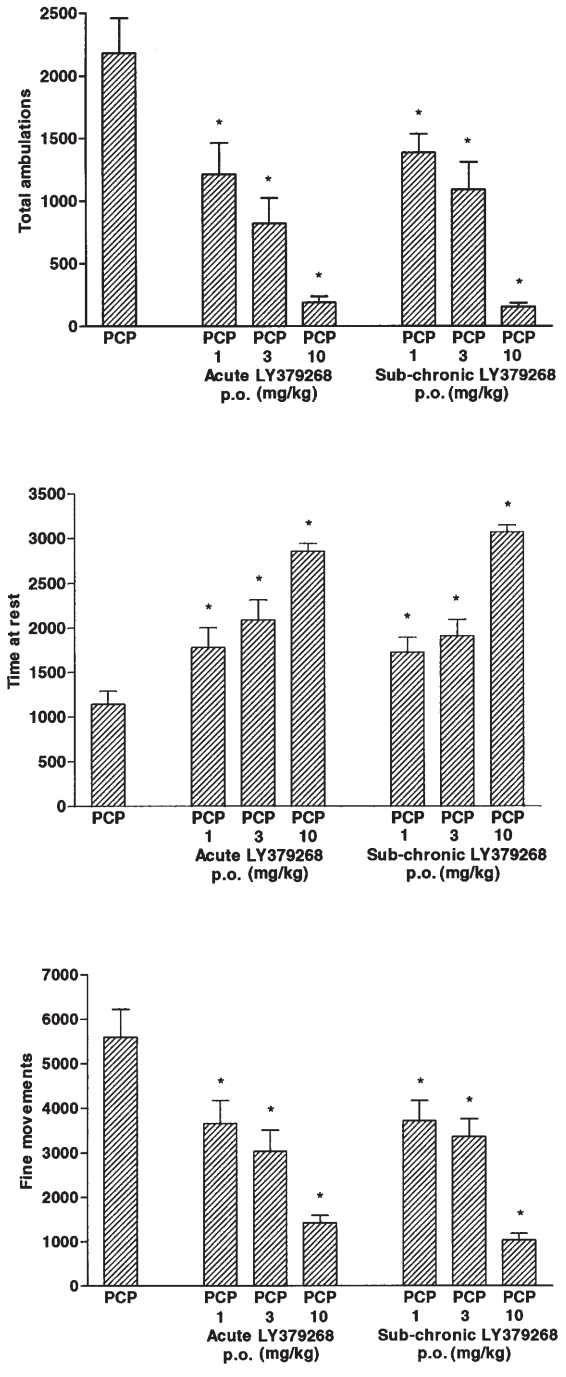

Fig. 5 Comparison of acute versus multiple (subchronic) dosing with LY379268 p.o. (at doses of 1, 3, or 10 mg/kg) on PCP (5 mg/kg s.c.)-evoked motor activities measured in an automated activity monitor. Rats were given single, daily doses of vehicle ('acute') or LY379268 ('subchronic') (1 ml/kg) p.o. for 3 consecutive days. On day 4, rats tested for acute and subchronic administration were all given LY379268 p.o. (at doses of 1, 3, or 10 mg/kg). Control PCP rats were given vehicle p.o. for 4 days. All rats were challenged with PCP (5 mg/kg s.c.) 4 h after the final dose on day 4. Motor activities were then monitored for the subsequent 60 min. Data (mean ± SEM) are presented as total number of behaviors expressed during 60 min; n=8 rats. *P<0.05 when compared to the corresponding vehicle/PCP control

response were also determined. Rats were dosed for 4 consecutive days with high doses of LY379268 (10, 30, or 100 mg/kg p.o.). As shown in Fig. 4, 4 h after dosing on day 1 all three doses produced significant motor impairment; rats given 10 mg/kg LY379268 p.o. could only remain on the rotorod for 20±7 s (n=6). Higher doses of 30 and 100 mg/kg LY379268 p.o. caused even more marked effects on performance, rats fell from the rotating rod after approximately 3 s. However, after single p.o. doses of LY379268 (either 10, 30, or 100 mg/kg) given once daily for 4 consecutive days, tolerance to the LY379268-induced motor impairment developed. When tested 4 h following the final dosing on day 4, none of the rats were impaired by LY379268, and all rats were able to complete the 60-s test period.

The influence of multiple dosing with LY379268 p.o. was also examined on the ability of the compound to reverse PCP (5 mg/kg)-evoked motor activities. Following p.o. administration of either vehicle or LY379268 (at doses of 1, 3, or 10 mg/kg) for 4 days, rats were challenged with PCP (5 mg/kg s.c.) 4 h after the final dose on day 4. Figure 5 shows that the animals which received vehicle on days 1–3 and an acute administration of LY379268 p.o. on day 4 reversed total ambulations and fine movements evoked by PCP with ED_{50} values of 1.45 and 2.70 mg/kg, respectively. Similarly, those animals that received four daily doses of LY379268 were also able to reverse the motor activities of PCP with ED_{50} values 1.88 and 2.14 mg/kg for total ambulations and fine movements, respectively.

Discussion

LY379268 is a potent, selective agonist at mGlu2/3 receptors, with potencies at these receptors in the low nanomolar range (Monn et al. 1999). The compound shows more than 100-fold selectivity for group II mGlu receptors, only activating group III receptors at concentrations greater than 100 nM (Monn et al. 1999). LY379268 is without effect on NMDA, AMPA, kainate, or group I mGlu receptors (Monn et al. 1999). In this study the effect of oral administration of LY379268 was investigated in the PCP model of psychosis, using automated motor activity monitors. Furthermore, the influence of subchronic exposure on the therapeutic index of LY379268 p.o. was also examined.

We have previously shown that LY379268 s.c. attenuates PCP (5 mg/kg s.c.)-evoked total ambulations and fine movements with ED_{50} values around 1.5 mg/kg for both activities (Cartmell et al. 1999). Moreover, a dose of 3 mg/kg LY379268 s.c. inhibited the PCP-elicited increase in motor activities by 80–90%. Therefore, in the present study we used this dose to test the oral time course of LY379268. The actions of LY379268 p.o. were time-dependent, the maximal effects of the compound were observed 4 h post-dosing. Significant inhibitions of PCP motor behaviors by LY379268 were maintained 8 h post-

administration but were absent after 24 h. This time course agrees with the maximal impairment of rotorod performance by 10 mg/kg LY379268, which was also observed after 4 h. However, this effect of LY379268 on the rotorod was not due to the development of catalepsy, as p.o. LY379268 up to 30 mg/kg did not produce significant immobility on a vertical wire grid (measured as described by Kronthaler and Schmidt 1998) in comparison to the positive control haloperidol (1 mg/kg; data not shown). The absence of any significant inhibitory effects of LY379268, in the PCP model or in the rotorod test, 24 h after dosing, indicate that the actions of the compound (at least up to doses tested in this study) are reversible and are unlikely to be mediated via a toxic mechanism. Four hours after oral dosing, the ED_{50} values of LY379268 for the inhibition of PCP-evoked total ambulations and fine movements were 0.67 and 1.98 mg/kg, respectively, values very similar to those obtained for after 30 min s.c. pretreatment of LY379268.

The significant increase in total ambulations evoked by 5 mg/kg PCP, 24 h following p.o. dosing with 3 mg/kg LY379268 might reflect a sensitization of receptors mediating this effect. However, this increase (although significant) was relatively small (ca 30% increase) and was only observed in one of the parameters measured. In particular, there were no significant changes in the time spent at rest or fine movements at this time point in the same animals. Furthermore, this effect was not dose related, as we did not observe an increase in PCP ambulations 24 h following a p.o. dose of 10 mg/kg LY379268. In addition, LY379268 per se (3 or 10 mg/kg p.o.) did not produce any increases in spontaneous motor movements 24 h following acute administration. Collectively, these data indicate that acute doses of LY379268 do not produce substantial sensitization to PCP.

The reduction of PCP motor behaviors by LY379268 is not mediated via sedative or ataxic actions of the compound as 3 mg/kg LY379268, a dose that reduced PCP-evoked total ambulations by 80%, did not impair rats when tested on the rotorod apparatus, even 4 h after dosing. However, although all motor behaviors tested were fully reversed by 10 mg/kg LY379268, this dose did cause some degree of motor impairment. Similar sedative/impairing effects of antipsychotic drugs, such as haloperidol are well known (Asper et al. 1973; Rastogi et al. 1982). However, unlike LY379268, with which impairment of rotorod performance occurred only at doses greater than those required to inhibit PCP-evoked motor activities, doses of haloperidol active in the PCP motor activities model also caused severe sedation/motor impairment of rats (Cartmell et al. 1999). Moreover, a number of studies have shown tolerance to the reduction in basal locomotor activity and induction of catalepsy by haloperidol following repeated administration. Rastogi et al. (1982) showed that treatment with 2 mg/kg i.p. haloperidol for 20 days reversed the reduction in spontaneous locomotor activity following acute administration. Furthermore, administration of 1.5 mg/kg p.o. haloperidol for 21 days resulted in a reversal of catalepsy evoked by an acute dose of haloperidol (Asper et al. 1973). Therefore, to determine whether tolerance to the motor impairment produced by high doses of LY379268 would develop, we tested the effects of multiple p.o. treatments with high doses of LY379268 which caused impairment after acute administration. After 4 days of single, daily doses of 10, 30, or 100 mg/kg LY379268 p.o., the acute motor impairment caused by these doses of LY379268 was no longer produced, even up to a dose of 100 mg/kg LY379268. The ability of the rats to remain on the rotorod for the entire test period after 4 days of dosing was not due to a longer practice time or increased learning acquisition (rats were tested on each of the 4 days). Initial tests showed that animals treated with vehicle on days 1–3, but which were given an acute dose of 10 mg/kg p.o. LY379268 on day 4 were also impaired when tested on the rotorod (data not shown).

Interestingly, Asper et al. (1973) showed that, in addition to the tolerance to catalepsy, a reduction in the ability of haloperidol to inhibit apomorphine-evoked stereotypic behavior also occurred after repeated dosing. In untreated rats, apomorphine elicited compulsive gnawing behavior with an ED_{50} value of approximately 0.4 mg/kg. This value increased to 1.2 mg/kg following one dose of 2 mg/kg p.o. haloperidol, showing that an acute dose of haloperidol inhibited this effect of apomorphine. However, after dosing with 2 mg/kg haloperidol for 14 days, the dose of apomorphine required to evoke gnawing in 50% animals was reduced to around 0.6 mg/kg, indicating that the effects haloperidol in this model were substantially reduced after repeated administration. Furthermore, an even more marked tolerance to the effects of the neuroleptic, loxapine (2 mg/kg p.o.), was also observed, with ED_{50} values for apomorphine of 6.5 and 1.5 mg/kg following acute and subchronic doses of loxapine, respectively (Asper et al. 1973). In contrast to the reduced effects of the typical neuroleptics, haloperidol and loxapine, on apomorphine-evoked stereotypies after subchronic treatment, the present data show that the inhibition of PCP-elicited motor activities by LY379268 was maintained after repeated treatment. ED_{50} values obtained for the reversal of PCP-evoked total ambulations and fine movements were essentially unchanged for acute versus subchronic (4 days) p.o. administration of LY379268.

For classic neuroleptics it has been proposed that the development of tolerance to the sedative effects of these compounds is necessary in order for the therapeutic actions to occur, and thus is the reason for their therapeutic latency (Freed 1988). Freed (1988) has hypothesized that a compensatory reduction in glutamatergic transmission may be linked to the development of tolerance to neuroleptic sedative effects, and this may be responsible for their therapeutic action in schizophrenia. While initial sedation by neuroleptics is associated with acute dopaminergic antagonism, tolerance to neuroleptic sedation which occurs following their chronic administration may be due to the development of dopamine receptor supersensitization which eventually counteracts neuroleptic blockade of dopamine receptors. Interestingly, this ‘supersensitivity’

of dopamine receptors in the striatum may be associated with a 'subsensitivity' of glutamatergic synapses (Freed 1989; Freed et al. 1989). It is proposed that this suppression of glutamatergic transmission in certain synapses is responsible for the antipsychotic effects of neuroleptics. Consistent with this, acute addition or administration of mGlu2/3 agonists have been shown to reduce enhanced glutamate transmission via a presynaptic mechanism in various in vitro and in vivo models (see Introduction; Conn and Pin 1997). In particular, it was shown that PCP enhanced glutamate release in the prefrontal cortex (Moghaddam and Adams 1998) is suppressed by acute administration of a mGlu2/3 agonist. Therefore, unlike dopamine antagonists which require chronic administration and subsequent compensatory mechanisms to produce their therapeutic effects, mGlu2/3 agonists have a primary action on the glutamate system (i.e., presynaptic suppression of enhanced glutamate release). Nevertheless, further research is necessary to fully elucidate the cellular mechanisms underlying the potential antipsychotic actions of mGlu2/3 agonists.

In summary, studies here demonstrate that oral administration of LY379268 (0.3–3 mg/kg p.o.) dose-dependently reversed the motor behaviors induced by PCP, and these doses were not associated with motor impairment (as demonstrated on the rotorod test). Higher acute oral doses of LY379268 (≥10 mg/kg p.o.) produced motor impairment, but this effect was completely tolerated within 4 days of subchronic treatment. Interestingly, this tolerance to motor impairment induced by the higher doses of LY379268, was not associated with changes in LY379268 potency in reversing PCP-evoked motor activities. Thus, we show here that the therapeutic index of LY379268 in the PCP model was further increased by subchronic oral LY379268 treatment. Further studies are currently in progress to investigate the cellular mechanisms underlying the tolerance phenomenon to motor impairment by LY379268, and its implications to the potential antipsychotic actions of these agents.

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