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Rapid communication

LY354740 affects startle responding but not sensorimotor gating or discriminative effects of phencyclidine

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Abstract

LY354740 {(1*S*,2*S*,5*R*,6*S*)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylate monohydrate}, a selective group II metabotropic glutamate (mGlu) receptor agonist, was recently reported to attenuate the behavioral effects of phencyclidine (PCP) in rats. In the present study, LY354740 failed to attenuate the discriminative stimulus properties of PCP and its disruption of prepulse inhibition of the acoustic startle response, at a dose range which decreased startle responding. The suggestion that mGlu group II receptor activation induces antipsychotic effects may be premature.

Keywords: Drug discrimination; Glutamate receptor, Metabotropic; Schizophrenia

The glutamate hypothesis of schizophrenia is largely based on the ability of the noncompetitive glutamate receptor antagonist phencyclidine (PCP) to mimick positive and negative symptoms of schizophrenia (Javitt and Zukin, 1991). It was recently reported that the potent and selective group II metabotropic glutamate (mGlu) receptor agonist LY354740 {(1*S*,2*S*,5*R*,6*S*)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylate monohydrate, Schoepp et al., 1997} attenuated some behavioral and biochemical effects induced by PCP in rats; and it was suggested that activation of these receptors may provide a new approach for the treatment of schizophrenia (Moghaddam and Adams, 1998). The present study evaluated the effects of LY354740 in a sensorimotor gating model of schizophrenia, in which PCP was used to disrupt prepulse inhibition of the acoustic startle reflex in rats (Bakshi et al., 1994). Prepulse inhibition refers to the phenomenon that presentation of a non-startle-eliciting stimulus (prepulse) shortly before an intense startling stimulus (pulse) results in activation of an inhibitory process that attenuates ('gates') the startle response. In addition, it was tested whether pretreatment with LY354740 was able to attenuate the effects of PCP in rats trained to discriminate PCP from vehicle. Compounds which are able to attenuate or block the PCP cue may have antipsychotic potential (for discussion, see Koek, 1999).

Male Spraque–Dawley rats (180–220 g), housed under a 12-h light–dark schedule (light on at 0900 h), were submitted to a prepulse inhibition paradigm essentially as described by Bakshi et al. (1994). The following trial types were presented as broadband stimuli of 20-ms duration: no stimulus, 120 dB, and prepulses that were 3, 6 and 12 dB above a 70-dB background and presented 100 ms before the pulse. Stimuli were presented 10 times in a random sequence, except for 120 dB, where five additional pulses at the beginning and the end of the test session were given. Percentage prepulse inhibition was calculated as follows: $100 - [100 \times (\text{amplitude on prepulse trial}/\text{amplitude on pulse trial})]$. PCP (2 mg/kg, s.c., *t*-15 min, dissolved in saline) induced a disruption of prepulse inhibition [$F(1,404) = 640.87$, $P < 0.001$; Fig 1]. LY354740 (0.01–10 mg/kg, i.p., *t*-45 min, synthesized by the Chemistry Department of Bayer, Leverkusen, Germany; dissolved in saline and a drop of NaOH) had no effect on percent prepulse inhibition when tested alone, and failed to reverse the disruption of prepulse inhibition induced by PCP (2 mg/kg; Fig. 1). A false negative finding due to inappropriate dosing is unlikely as LY354740 significantly ($P < 0.01$) decreased startle responding at 0.01 and 1 mg/kg.

A group of male Wistar rats ($n = 8$), housed under similar conditions, with the exception that they were kept

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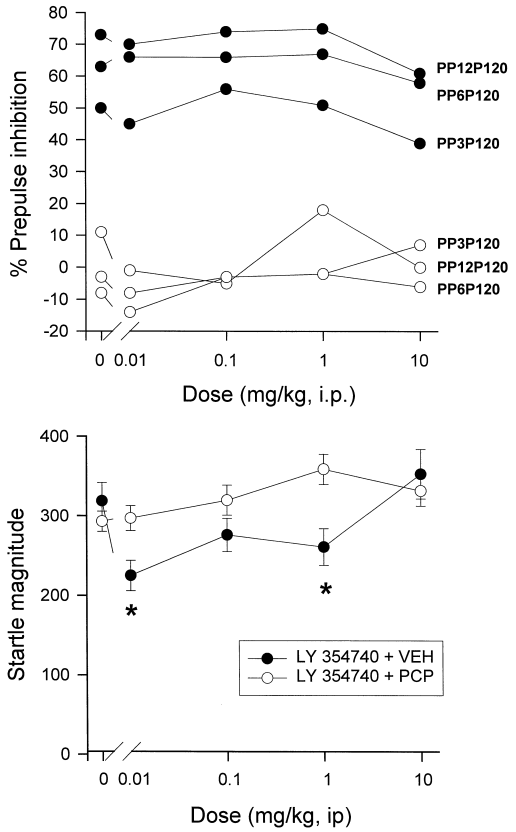

Fig. 1. Upper panel: Effects of LY354740 on prepulse inhibition of the acoustic startle response and on PCP-induced disruption of prepulse inhibition in rats. Analysis of variance (ANOVA) indicated that PCP (2 mg/kg, s.c.), but not LY354740, affected percent prepulse inhibition ($P < 0.001$). Pretreatment with LY354740 failed to affect PCP-induced disruption of prepulse inhibition. Lower panel: Effects of LY354740 on startle responding. ANOVA indicated that LY354740 (0.01 and 1 mg/kg, i.p.), but not PCP, affected startle responding. $n = 10–20$ rats/group. Abbreviations: PP3P120: 3-dB prepulse followed by 120-dB pulse (likewise for PP6P120 and PP12P120); VEH: vehicle. * $P < 0.01$ vs. vehicle–vehicle treatment group.

at about 80% of their free-feeding weight by restricting daily amount of food, was trained to discriminate PCP (2 mg/kg, i.p., *t*-15 min) from saline in a standard 2-lever fixed-ratio:10 food-reinforced procedure (according to De Vry and Jentzsch, 1998). LY354740, (0.1–10 mg/kg, i.p.) injected 30 min before PCP (2 mg/kg), induced 87.5% drug lever selections at 0.1 mg/kg (five out of six rats tested selected the PCP-appropriate lever), and 100% drug lever selections at both 1 and 10 mg/kg; indicating that pretreatment with the mGlu group II receptor agonist did not block the PCP cue. LY354740 (10 mg/kg, $n = 3$) did also not generalise to the discriminative stimulus properties of PCP.

LY354740 (10 mg/kg, i.p.) was previously reported to attenuate some other behavioral effects induced by PCP, such as locomotor stimulation and working memory deficits (Moghaddam and Adams, 1998). The present study, therefore, suggests that the behavioral effects of PCP are differentially affected by mGlu group II receptor activation. As far as reversal of PCP-induced disruption of sensorimotor gating and attenuation of the PCP cue reflect potential antipsychotic efficacy (for discussion, see Bakshi et al., 1994; Koek, 1999), our data do not support the hypothesis that activation of group II mGlu receptors results in antipsychotic effects (Moghaddam and Adams, 1998). Interestingly, Moore et al. (1999) recently reported that LY354740 (2.5–10 mg/kg, i.p.) dose-dependently decreased exploratory behavior; suggesting that the attenuating effects on PCP-induced locomotor stimulation (as reported by Moghaddam and Adams, 1998) may be confounded by such unconditioned effects on locomotor behavior. Further assessment of the effects mGlu group II receptor agonists in other animal models of schizophrenia will be required in order to substantiate the hypothesis that such compounds consist of a new class of antipsychotics.

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