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European Journal of Pharmacology 397 (2000) R1–R2

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Rapid communication

Lack of effect of LY314582 (a group 2 metabotropic glutamate receptor agonist) on phencyclidine-induced locomotor activity in metabotropic glutamate receptor 2 knockout mice

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Received 14 March 2000; accepted 31 March 2000

Abstract

In metabotropic glutamate receptor 2 ($mGlu_2$) knockout mice, the group 2 metabotropic glutamate receptor agonist LY314582 (20 mg/kg, i.p.), a racemate of LY354740, inhibits neither spontaneous nor phencyclidine (PCP)-induced (2.5 mg/kg, s.c.) locomotor activity. Since LY314582 attenuated spontaneous and PCP-induced locomotor activity in wild-type control mice, these data indicate that the effects of LY314582 are mediated via the $mGlu_2$ receptor and not via the $mGlu_3$ receptor.

Keywords: Glutamate; Metabotropic receptor; Mouse

Metabotropic glutamate (mGlu) receptors comprise a family of eight G protein-coupled receptor subtypes, which have been further classified into three groups based on sequence homology, second messenger coupling and pharmacological properties (Conn and Pin, 1997). Current knowledge of the pharmacology of these receptors, along with studies on their subcellular localization, as well as their physiological and pathological functions in the central nervous system, suggests that mGlu receptors provide suitable drug targets for psychiatric and neurological disorders (Knöpfel and Gasparini, 1996). Recently, LY354740 and its racemate LY314582 were identified as potent, selective and systemically active $mGlu_{2/3}$ receptor agonists (Monn et al., 1997), which served as useful in vivo pharmacological tools for elucidating the role of $mGlu_{2/3}$ receptors in multiple animal models. Moghaddam and Adams (1998) reported that LY354740 blocked phencyclidine (PCP)-induced increases in prefrontal glutamate levels and reduced PCP-induced locomotor activity. Since LY354740 is a group 2 receptor agonist, which includes the $mGlu_2$ and $mGlu_3$ receptor, it is currently unknown which receptor is particularly responsible for these effects. Therefore, we compared here the effect of LY354740 (used as its racemate, LY314582) on spontaneous and PCP-induced locomotor activity in $mGlu_2$ receptor knockout and wild-type control mice.

$MGlu_2$ receptor knockout mice (strain: 129SvJ × C57BL/6J; Yokoi et al., 1996) were bred and raised in the Novartis SPF-breeding facility. Male $mGlu_2$ receptor knock out mice (aged 12 weeks) and wild-type genotype-(129SvJ × C57BL/6J) and age-matched mice were housed under identical conditions (macrolon cages, 15 mice per cage) in a temperature-controlled room (22 ± 1°C) that was equipped with artificial illumination (0600–1800 h, lights on). The animals had access to water and food (Ecosan, Eberle Nafag, Gossau, Switzerland), ad libitum. Horizontal locomotor activity was quantified in transparent Plexiglas boxes (dimensions: $19 \times 31 \times 16$ cm) using the TSE Moti system (TSE, Bad Homburg, Germany). This

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0014-2999/00/$ - see front matter
PII: S0014-2999(00)00269-7

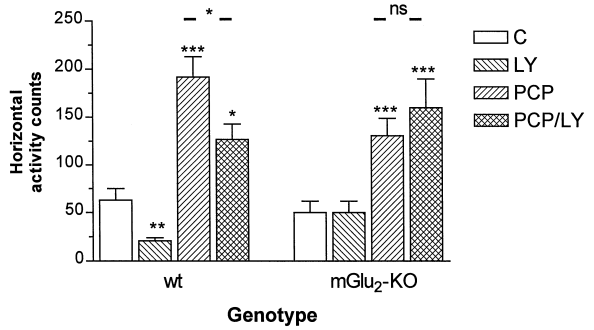

Fig. 1. Bars represent the mean (±S.E.M.) horizontal activity (tracked distance (arbitrary units)) recorded over 200 min following injection with PCP (2.5 mg/kg, s.c.) or vehicle (distilled water) in wild-type mice (wt) or in metabotropic glutamate receptor 2 knockout mice ($mGlu_2$-KO). The animals were pre-treated (−20′) with either LY314582 (=LY; 20 mg/kg, i.p.) or vehicle (distilled water). ($n = 17–23$ per group). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, ns = not significant. C = vehicle only.

system registers and computes interruptions of infrared light beams. The mice were individually placed in the test-boxes and injected with LY314582 (20 mg/kg, i.p.; racemate of LY354740) or vehicle (distilled water) and allowed to habituate in the cages for 20 min. The animals were then removed from their box and injected subcutaneously into the neck region with PCP (2.5 mg/kg) or vehicle (distilled water). The animals were immediately returned to their respective locomotor boxes and the (horizontal) locomotor activity was recorded for the next 200 min (Fig. 1). The results were statistically evaluated using a three-way analysis of variance (ANOVA; factors Genotype × PCP × LY314582) which was then followed by post-hoc intergroup tests, i.e. the Student *t*-test (Bonferroni corrected for multiple comparisons; SYSTAT 8.0®).

The ANOVA indicated a statistical significance for the factors PCP ($F = 47.960$, $P < 0.001$) and LY314582 ($F = 4.181$, $P < 0.05$). Significance was also found for the interaction Genotype × LY314582 ($F = 4.236$, $P < 0.05$) but not for the interaction Genotype × PCP ($F = 0.880$, $P > 0.05$) or PCP × LY314582 ($F = 0.477$, $P > 0.05$). The post-hoc analysis revealed that LY314582 inhibited (spontaneous) locomotor activity when injected alone ($P < 0.01$), as well as the PCP-induced locomotor activity ($P < 0.05$) in wild-type mice. None of these effects of LY314582 were seen in the $mGlu_2$ receptor knockout mice.

These data clearly indicate that the inhibition of both spontaneous and PCP-induced locomotor activity by the metabotropic glutamate receptor subtypes 2/3 agonist LY314582 are mediated by the $mGlu_2$ receptor.

Given that LY314582 already reduced spontaneous locomotor activity in the wildtype mice, it is debatable as to whether LY314582 is indeed counteracting PCP-induced hyperactivity or whether this rather reflects the final vector of both effects.

Acknowledgements

We sincerely thank C. Hunn for excellent technical assistance. Drs. C. Gentsch and A. Wrynn are thanked for critically reading the manuscript.

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