The Selective Metabotropic Glutamate 2/3 Receptor Agonist MGS0028 Reverses Isolation Rearing–Induced Abnormal Behaviors in Mice

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Abstract. Isolation-induced abnormal behaviors are useful animal models for assessing potential anti-psychotic drugs. This study examined the effect of MGS0028, a selective metabotropic glutamate 2/3 receptor agonist, on abnormal behaviors such as hyperactivity, aggression, and deficits of prepulse inhibition in isolation-reared mice. MGS0028 attenuated hyperactivity and aggressive behaviors in isolation-reared mice. The agonist also reversed isolation rearing–induced deficits of prepulse inhibition. On the other hand, MGS0028 did not affect locomotor activity and prepulse inhibition in group-reared mice. These results suggest that the metabotropic glutamate 2/3 receptor agonist, MGS0028, is a potential compound for the treatment of psychiatric disorders.

Keywords: metabotropic glutamate 2/3 receptor, isolation rearing, behavior

Metabotropic glutamate 2/3 receptor (mGluR2/3) agonists inhibit amphetamine- and phencyclidine-induced hyperactivity. Moreover, they ameliorate the deficits of attention and working memory induced by N-methyl-D-aspartate (NMDA)-receptor antagonists. These findings suggest that activation of mGluR2/3 has a therapeutic potential for the treatment of schizophrenia (1). However, these models are not concerned with the environmental or developmental perspective in the etiology of schizophrenia. Rearing in social isolation from early life causes abnormal behaviors such as hyperactivity, aggressive behavior, deficits of prepulse inhibition (PPI), and cognitive impairments in rats and mice. Many of these behaviors strongly resemble core symptoms of schizophrenia (2). Moreover, anti-psychotic drugs such as risperidone and clozapine attenuate isolation rearing-induced aggressive behavior and PPI deficits in mice (3). We have recently shown that binding of the mGluR2/3 antagonist [3H]LY341495 in the prefrontal cortex and hippocampus was increased by isolation rearing in mice (4). This suggests that dysfunction of the glutamatergic system including mGluR2/3 contributes to the mechanisms for isolation rearing-induced abnormal behaviors. To study the therapeutic potential of mGluR2/3 ligands for psychiatric disorders, this study examined the effect of MGS0028, a potent and selective mGluR2/3 agonist (5, 6), on the abnormal behaviors of isolation-reared mice.

The experimental procedures concerning the use of
animals in this work were conducted according to the Guiding Principles for the Care and Use of Laboratory Animals approved by The Japanese Pharmacological Society. Three-week-old male ddY mice (Shimizu Laboratory Supplies Co., Ltd., Kyoto) were divided equally into isolation- and group-housed conditions at the same time. The isolation-reared and group-housed mice were housed for 6 weeks as previously reported (7). We used a total of 122 mice in all the experiments; different mice were used in each experiment. MGS0028 (Taisho Pharmaceutical Co., Saitama) was dissolved in saline (0.9% NaCl w/v) and adjusted to pH 7.4 with 0.5 M NaOH. The drug was injected at the volume of 10 mL/kg intraperitoneally. The doses of MGS0028 used here were selected referring to our previous study where the drug did not affect the spontaneous locomotor activity of group-reared mice (6).

Locomotor activity was measured using a digital counter system with an infrared sensor (Supermex®, Muromachi Kikai Co., Ltd., Tokyo). For assessing the effect of MGS0028 on aggressive behavior, two isolation-reared mice pretreated with the drug were placed in a neutral cage (24 × 17 × 12 cm), and the behaviors were videotaped for 20 min. In this experiment, we did not use group-reared mice because they did not show aggressive behaviors. The total time of aggressive behaviors (biting attacks, wrestling, lateral threats, and tail switching) and latency to the first attack were analyzed (7).

Acoustic startle responses were measured in a startle chamber (SR-LAB®; San Diego Instruments, San Diego, CA, USA) as described previously (8). After a background noise of 65 dB had been presented for a 5-min acclimation period, each mouse was exposed to four consecutive blocks with a total of 100 trials over the approximately 30-min test session. The maximum startle amplitude recorded during the 100-ms sampling window was used as the dependent variable. Startle amplitude was calculated as the average response to all of the pulse-alone trials. The amount of PPI was also calculated as a percentage score for each prepulse trial type. The following formula was used: \(\%\text{PPI} = 100 - \left(\frac{\text{startle response to prepulse-pulse trial}}{\text{startle response to pulse-alone trial}}\right) \times 100\).

Data for aggressive behavior and startle amplitude were analyzed using one-way and two-way analysis of variance (ANOVA), respectively, followed by the Tukey-Kramer test. Data for locomotor activity and PPI were analyzed using three-way ANOVA for rearing conditions and treatment as the intersubject factors and repeated measures with time or prepulse intensity as the intrasubject factor. A value of \(P < 0.05\) was considered statistically significant.

Figure 1A shows the effect of MGS0028 on isolation rearing–induced hyperactivity. MGS0028 at doses of 0.1 and 0.3 mg/kg did not affect the spontaneous locomotor activity of group-reared mice. Locomotor activity in a...
novel environment was higher in the isolation-reared mice than the group-reared mice, and the isolation-induced hyperactivity was inhibited by MGS0028. Repeated measures three-way ANOVA revealed the main significant effects of prepulse intensity \([F_{1,130} = 75.419, P < 0.0001]\), rearing \([F_{1,30} = 5.231, P = 0.0294]\) and treatment \([F_{2,30} = 6.815, P = 0.0036]\). There was a significant interaction between rearing and treatment \([F_{2,30} = 7.097, P = 0.0030]\).

Figure 1B shows the effect of MGS0028 on aggressive behaviors in isolation-reared mice. The total time of aggressive behaviors was significantly attenuated by MGS0028 at the dose of 0.3 mg/kg, but not 0.1 mg/kg \([F_{2,18} = 6.493, P = 0.0075]\). Short latent attacks of isolation-reared mice were also improved by MGS0028 (0.3 mg/kg) \([F_{2,18} = 5.800, P = 0.0114]\). Figure 2 shows the effect of MGS0028 on PPI deficits of the acoustic startle response in isolation-reared mice. PPI of the acoustic startle response was less in the isolation-reared mice than the group-reared mice at all three prepulse levels, and the PPI deficits were reversed by MGS0028 (0.3 mg/kg) (Fig. 2A). Repeated measures three-way ANOVA revealed the main significant effects of prepulse intensity \([F_{2,80} = 37.429, P < 0.0001}\), rearing \([F_{1,40} = 6.356, P = 0.0158}\), and treatment \([F_{1,40} = 5.163, P = 0.0285}\). There was a significant interaction between rearing and treatment \([F_{1,40} = 4.502, P = 0.0401]\). On the other hand, neither isolation rearing nor MGS0028 treatment affected the baseline startle responses (Fig. 2B). Two-way ANOVA revealed no main significant effects of the rearing \([F_{1,40} = 0.424, P > 0.05}\) and treatment \([F_{1,40} = 0.238, P > 0.05}\), and there was no significant interaction between rearing and treatment \([F_{1,40} = 0.702, P > 0.05}\).

This study demonstrated that the mGluR2/3 agonist MGS0028 inhibited hyperactivity and aggressive behaviors in isolation-reared mice. The anti-hyperactivity of MGS0028 was observed in amphetamine- and phencyclidine-induced hyperactivities (1). Previous neurochemical studies suggest that modulation of the monoaminergic and glutamatergic systems may be involved in the effect of the mGluR2/3 agonist (6, 9, 10), but the exact mechanism for the anti-hyperactivity in isolation rearing–induced hyperactivity is not known. Concerning the anti-aggressive effect, we have previously shown that the 5-HT2 receptor antagonist ritanserin inhibited isolation rearing–induced aggressive behaviors in mice (7). Marek et al. (11) reported that mGluR2/3 agonists suppressed the induction of excitatory postsynaptic potentials/currents via activation of 5-HT2A receptors in layer V pyramidal cells of the medial prefrontal cortex. Furthermore, González-Maeso et al. (12) have shown that mGlut2 and 5-HT2A receptors are co-localized in the cortex and the mGlut2 receptors interact through specific transmembrane helix domains with the 5-HT2A receptors to form functional and physiological complexes in brain cortex. They also showed that activation of mGlutR2/3 reverses the head-twitch responses in mice induced by the 5-HT2A/C receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane. Taken together, it is likely that regulation of 5-HT2A receptor function may be involved in the anti-aggressive effect of MGS0028.

Isolation rearing has been given considerable attention as an animal model of sensorimotor gating deficits in schizophrenia, as it has a developmental perspective (8). The present study shows that MGS0028 reverses isolation rearing–induced PPI deficits in mice. Furthermore, Jones et al. (13) have recently reported that LY379268, another mGluR2/3 agonist, reverses hyperlocomotion...
and object recognition memory deficits in isolation-reared rats. These findings suggest the potential role of mGluR2/3 in the treatment of PPI deficits and/or cognitive impairment in schizophrenia. On the other hand, previous studies showed that mGluR2/3 agonists did not affect PPI deficits induced by psychotomimetic compounds such as apomorphine and phencyclidine (1, 14). The exact reason for the difference is not known, but the previous study shows a similar difference that the effect of donepezil on PPI deficits depends on the model used (8). Concerning the clinical studies on mGluR2/3, one study showed a significantly greater improvement of both positive and negative symptoms in schizophrenia (15), while the other showed an inconclusive result (16).

In conclusion, the present study showed that the mGluR2/3 agonist MGS0028 inhibits hyperactivity and aggressive behaviors and improves PPI deficits in isolation-reared mice. These findings, taken together with the recent findings in isolation-reared rats (13), suggest a potential role of mGluR2/3 agonists in the treatment of psychiatric disorders such as schizophrenia.

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References