Habituation Deficits Induced by Metabotropic Glutamate Receptors 2/3 Receptor Blockade in Mice: Reversal by Antipsychotic Drugs

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ABSTRACT

Cortical metabotropic glutamate receptors (mGluRs) seem to be involved in habituation of simple stimulus-bound behaviors (e.g., habituation to acoustic startle or odor-elicited orienting response). Habituation deficits may contribute to the cognitive symptoms of schizophrenia. In the present study, male NMRI mice were injected with mGluR2/3 antagonist 2S-2-amino-2-(1S,2S-2-carboxycyclopropyl-1-yl)-3-(xanth-9-yl)propanoic acid (LY-341495) 30 min before being placed into novel arenas for automatic motor activity recording (2-h sessions). Administration of LY-341495 (1–10 mg/kg s.c.) dose-dependently prevented the habituation of the locomotor activity. Effects of LY-341495 (10 mg/kg) were fully and dose-dependently reversed by i.p. administration of haloperidol (0.03–0.3 mg/kg), clozapine (1–10 mg/kg), risperidone (0.01–0.1 mg/kg), olanzapine (0.3–3 mg/kg), aripiprazole (1–10 mg/kg), and sulpiride (3–30 mg/kg), each of which was given 15 min before the test. Effects of antipsychotic drugs were observed at the dose levels that did not affect spontaneous motor activity. LY-341495-induced delayed hyperactivity was also partially attenuated by lithium (50–200 mg/kg), amisulpiride (1–10 mg/kg), and the selective dopamine D3 antagonist trans-N-[4-[(2-6-cyano-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl][cyclohexyl]-4-quinolinecarboxamide (SB-277011A; 3–30 mg/kg). Administration of diazepam, imipramine, or several agonists and/or antagonists acting at various receptors that are thought to be relevant for antipsychotic treatment [e.g., 5-hydroxytryptamine (5-HT)2A, 5-HT3, and 5-HT6 antagonists; 5-HT1A agonist; D4 antagonist; CB1 antagonist; ampakines; and glycine transporter inhibitor] had no appreciable effects. Thus, behavioral deficits induced by mGluR2/3 blockade (such as delayed motor hyperactivity) are selectively reversed by clinically used antipsychotic drugs.
mGlur2/3 agonists such as LY-354740 blocks PCP-induced glutamate release, glutamate-dependent electrical activity of prefrontal cortex, and, perhaps even more importantly, it attenuates psychomotor activating and cognition-impairing effects of PCP (Moghaddam and Adams, 1998; Cartmell et al., 1999; Spooren et al., 2000; Lorrain et al., 2003; Homayoun et al., 2005). Based on these findings, it was proposed that mGlur2/3 agonists have antipsychotic potential, and some early clinical evidence suggests that these agents are capable of at least attenuating cognition-impairing effects of PCP-like psychotomimetics in humans (Krystal et al., 2005).

Conversely, blockade of cortical presynaptic mGlu receptors (groups II and III) facilitates release of glutamate (Schoepp, 2001) and therefore may be hypothesized to have some effects similar to those seen after administration of psychotomimetic compounds. However, this aspect of action of group II and III mGlu receptor antagonists remains largely unexplored.

Recent evidence indicates that mGlu receptors are involved in habituation of the cortical neurons to extraeceptive sensory stimulation. For example, Best et al. (2005) studied habituation to novel odor presentations using two independently recorded variables: heart rate-orienting response and electrical activity of anterior piriform cortex. Local application of cyclopropyl-4-phosphonophenylyglycine, an mGlu group III antagonist, retarded the habituation process. Unlike anterior piriform cortex (involved in olfactory processing), other cortical areas express also group II mGlu receptors, and one may expect similar habituation phenomena affected by group II mGlu receptors.

The Best et al. (2005) study focused on simple odor-induced habituation, but there are a number of more complex habituation processes. Schizophrenic patients are known to demonstrate deficits in habituation, perseverative behaviors, and various forms of behavioral inflexibility, all of which are described under different experimental conditions but nevertheless may have common neurobiological mechanisms (Ridley, 1994; Cools et al., 2000). Administration of psychotomimetic drugs such as PCP is also known to facilitate perseverative behaviors and impair behavioral flexibility and habituation both in humans and laboratory animals (Crider, 1997; Thompson and Disterhoft, 1997; Jentsch et al., 2000; Abdul-Monim et al., 2003; Ludewig et al., 2003; Klamer et al., 2004). Therefore, if the blockade of presynaptic cortical mGlu receptors (group II) is expected to have psychotomimetic potential, the range of its behavioral effects should also include habituation deficits.

It was reported that acute administration of the mGlu2/3 receptor antagonist LY-341495 stimulates locomotor activity in laboratory animals (O'Neill et al., 2003). When the time course of the effects of LY-341495 on motor activity is analyzed, one could notice that this compound does not enhance the activity levels above the initial levels but rather forces the motor activity to stay at the same level throughout the observation period. In control animals (treated with saline instead of LY-341495), exposure to the novel activity recording environment results in the initial exploratory activity followed by fairly rapid decrease in activity. In contrast, animals pretreated with LY-341495 do not demonstrate such a decrease over time, and their motor activity remains stable and elevated compared with the saline-treated controls (Fig. 1).

The main hypothesis behind this study was that effects of LY-341495 on locomotor activity reflect impaired habituation processes and may be reversed by antipsychotic drug treatment. To that end, various typical and atypical antipsychotics were administered together with LY-341495 before the test session and the motor activity was analyzed for the 2nd hour of the 2-h session, a period when the differences between LY-341495 and saline-treated animals were seen most reliably and consistently. In addition, several other drugs representing either novel antipsychotic principles or nonantipsychotic drug classes were tested.

Materials and Methods

Animals. Drug and experimentally naive male NMRI mice (6 weeks old at the time of testing) were purchased from Janvier (Le Genest-St-Ise, France). Animals were housed in groups of eight in Macrolon Type 3 cages (43 × 28 × 15 cm, length × width × height) under standard laboratory conditions, 21 ± 1°C and 40–70% humidity, with ad libitum access to food and water. Experimental procedures were approved by the Animal Welfare Office (Ludwigshafen, Germany) and were performed in accordance with the recommendations and policies of the United States National Institutes of Health Principles of Laboratory Animal Care (1996 edition). Animal housing and experiments were conducted in the facilities with full Association for Assessment and Accreditation of Laboratory Animal Care accreditation. All experiments were performed during the light phase of 12-h daylight cycle (lights on at 5:30 AM).

Drugs. Haloperidol, clozapine, risperidone, amisulpride, ketanserin tartrate, imipramine hydrochloride, dizapam, 8-hydroxy-2-[din-propylamino] tetratin (8-OH-DPAT), MDL-72222, lithium chloride, and methamphetamine hydrochloride were purchased commercially. Other compounds were synthesized internally: olanzapine, aripiprazole, sulpiride, LY-341495, CX-516, LY-392098, L-741626, SB-277011A, NBQX, SSR-504734, SR-141716A, and sodium valproate.

Compounds were prepared in sterile saline (amisulpride, ketanserin, imipramine, lithium, and methamphetamine), water (SSR-504734 and valproate), water that was slightly acidified by the addition of HCl (haloperidol, clozapine, risperidone, sulpiride, olanzapine, MDL-72222, and MDL-100907) or 0.05% ascorbic acid (8-OH-DPAT), 1% Tween 80 in sterile water (SR-141716A), or 0.5% hydroxypropylmethylcellulose in sterile water (LY-341495, aripiprazole, dizapem, LY-392098, L-741626, SB-277011A, NBQX, and CX-516).

All solutions and suspensions were prepared fresh daily and injected in a volume of 5 ml/kg. With the exception of LY-341495 and methamphetamine, which were administered s.c., all compounds were injected i.p.

For each compound to be coadministered with LY-341495, dose selection was based on the in-house evidence of specific pharmacodynamic activity. More specifically, compounds were tested up to the dose levels that produced no severe attenuation of spontaneous motor activity in previous in-house experiments. For all compounds, doses refer to the base forms.

Procedures. Animals were brought from the animal facility into the experimental room and allowed to acclimatize for at least 30 min. Then animals were weighed and injected s.c. with LY-341495 or its vehicle and placed back to their home cages. Thirty minutes later, animals were put in a novel Macrolon Type 3 cage, which was placed in a ActiMot frame (TSE Systems, Bad Homburg, Germany; nine photo beams along x-axis and five photo beams along y-axis). Standard test session lasted 2 h.

To evaluate the effects of LY-341495 on motor activity of mice habituated to the test environment, mice were first placed into the test arena as described above and their activity was recorded for 60 min. At the end of this habituation period, mice received s.c. injec-
tions of LY-341495 or its vehicle; they were immediately returned to the test arena, and the recording continued for another 2 h.

For pharmacological characterization of the delayed hyperactivity induced by LY-341495, separate groups of mice received first injections of LY-341495 or its vehicle and 15 min later were injected i.p. with the test compound or its vehicle (mice were returned to the home cages after these injections). Fifteen minutes after the last injection, mice were placed into the test arena for 2 h.

To evaluate the pharmacological specificity of the delayed hyperactivity induced by LY-341495, separate set of experiments, mice were pretreated with methamphetamine (2 mg/kg s.c.) instead of LY-341495. The dose of methamphetamine was chosen because it produces long-lasting hyperactivity that was seen during the entire 2-h session. Thus, motor activity of the LY-341495-treated mice during the 2nd hour of the test could be compared with that of methamphetamine-treated subjects. In all other respects, the methamphetamine studies were identical to the experiments with LY-341495.

After the completion of the experiments, built-in ActiMot analysis of the recorded activity yielded the total counts of beam breaks. Unless indicated otherwise, each treatment group included 10 mice. Each mouse was used only once.

**Data Analyses.** Data were subjected to a set of two- and three-way analyses of variance (ANOVAS; General Linear Model) with repeated measures on time whenever needed (SAS Institute, Cary, NC). Independent variables included 1) time (data in Figs. 1 and 2), 2) dose of LY-341495 (Figs. 1–4) or methamphetamine (Fig. 3), and 3) dose of the test drug (Figs. 2–4). Whenever indicated by ANOVA, post hoc comparisons were conducted using Dunnett’s test. To determine ED₅₀ values for the effects of tested compounds, quantal data were quantified by calculating the proportion of rats in each treatment group with the recorded dependent variable value smaller than a 5th percentile of corresponding vehicle group data. Subsequently, these quantal data were analyzed using the probit regression procedure.

**Results**

Administration of LY-341495 produced significant and dose-dependent effects on motor activity [main effect of LY-341495 dose: \(F(3,28) = 5.1, P < 0.01\); Fig. 1, left]. These effects were most pronounced during the 2nd half of the session. Starting from the time point 50 min, motor activity of animals treated with LY-341495 was significantly higher than that of vehicle-treated controls. Two-way ANOVA revealed significant interaction between factors time and LY-341495 dose \(F(69,644) = 5.7, P < 0.01\), confirming absence of time-dependent decay in motor activity in LY-341495-treated mice. At the highest dose level of 10 mg/kg, LY-341495-treated animals remained more active than vehicle-treated controls until the end of the 120-min session.

In a separate set of experiments, animals were placed into the activity monitors for a habituation period of 1 h, and then they were challenged with LY-341495 (Fig. 1, right). In these mice, vehicle injection itself elevated motor activity for a short period of time. In contrast, after the injection of LY-341495 motor activity remained elevated until the end of the session [main effect of LY-341495: \(F(3,36) = 11.9, P < 0.01\); time by LY-341495 dose interaction: \(F(69,828) = 4.0, P < 0.01\)].

Based on these findings, a LY-341495 dose of 10 mg/kg was chosen for subsequent experiments, as this dose results in the most reliable and consistent habituation deficits and allow to conduct experiments with the sample size of 10 mice per group. In addition, analysis of the time course of the LY-341495 effects indicated that the hyperactivity was delayed until the end of the 1st hour. As shown in Fig. 2, sulpiride (30 but not 3 or 10 mg/kg) restored normal habituation pattern of spontaneous motor activity impaired by LY-341495 in NMRI mice [main effect of sulpiride: \(F(3,72) = 6.4, P < 0.01\)], and these effects were seen almost exclusively during the 2nd half of the session.

Since effects of LY-341495 were most pronounced during the 2nd half of the session and this was when the effects of the test compounds were expected, for the sake of clarity and brevity, results of other experiments are presented as cumulative motor activity score during the 2nd half of the session.

As shown in Fig. 3 (left), haloperidol, clozapine, and risperidone reversed effects of LY-341495 on motor activity [main effects of the test drug dose: \(F(3,69) = 18.8, P < 0.01\); \(F(3,70) = 7.0, P < 0.01\); \(F(3,72) = 9.8, P < 0.01\), respectively]. For haloperidol, there were found significant main effects of haloperidol dose on motor activity of mice treated with vehicle instead of LY-341495 [main effect of haloperidol dose: \(F(3,72) = 11.9, P < 0.01\)]

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**Fig. 1.** Effects of LY-341495 on locomotor activity of NMRI mice. LY-341495 (1, 3, or 10 mg/kg) or its vehicle (0.5% hydroxypropylmethylecellulose) was injected either 30 min before (left panels) or 60 min (right) after the start of the session. Motor activity was recorded for 2 h after LY-341495 administration. \(n = 8\) to 10 per data point.
F(3,36) = 6.1, P < 0.01]. However, post hoc Dunnett’s test did not reveal significant differences between any haloperidol-treated groups and corresponding vehicle control. For clozapine and risperidone, attenuation of LY-341495-induced effects was observed at the dose levels that had no effects on motor activity of vehicle-pretreated mice during the 2nd half of the session. Accordingly, two-way ANOVA revealed significant test drug by LY-341495 interactions [haloperidol: F(3,69) = 9.4, P < 0.01; clozapine: F(3,70) = 11.9, P < 0.01; risperidone: F(3,72) = 12.1, P < 0.01].

In a separate set of experiments, mice pretreated with methamphetamine demonstrated robust increases in motor activity that remained elevated throughout the entire 2-h session. To enable direct comparisons with the experiments with LY-341495, total motor activity over the 2nd hour of the methamphetamine test was analyzed. It was found that haloperidol and clozapine but not risperidone attenuate late methamphetamine-induced hyperactivity [Fig. 3, right; test drug by methamphetamine interactions: F(3,72) = 13.9, P < 0.01; F(3,72) = 9.2, P < 0.01; and F(3,72) = 2.2, N.S., respectively]. Haloperidol attenuated methamphetamine-induced hyperactivity at the same dose levels (0.1 and 0.3 mg/kg) that were found to inhibit delayed hyperactivity induced by LY-341495. In contrast, clozapine attenuated methamphetamine-induced hyperactivity only at the highest dose level (10 mg/kg) and had virtually no effects at lower doses.

Selective reduction of LY-341495-induced effects was also noted in animals treated with olanzapine, aripiprazole, amisulpride, lithium, dopamine D3 receptor antagonist SB-277011A, and the D2-preferring dopamine receptor antagonist L-741626 [Fig. 4; main effects of the test drug dose: F(3,72) = 5.2, P < 0.01; F(3,71) = 18.6, P < 0.01; F(3,72) = 2.8, P < 0.05; F(3,71) = 3.5, P < 0.05; F(3,72) = 3.3, P < 0.05; and F(3,72) = 4.5, P < 0.01, respectively]. For these compounds, two-way ANOVA confirmed that motor activity in the presence of LY-341495 was affected more than the spontaneous motor activity [test drug by LY-341495 interactions: F(3,72) = 9.4, P < 0.01; F(3,71) = 12.2, P < 0.01; F(3,72) = 2.6, P = 0.058; F(3,71) = 2.9, P < 0.05; F(3,72) = 4.2, P < 0.01; and F(3,72) = 2.8, P < 0.05, respectively].

There were several other compounds tested that had no appreciable effects when tested in combination with LY-341495 (data not shown; Table 1).

Discussion

Previous studies have observed that laboratory animals treated with mGlur2/3 antagonists such as LY-341495 demonstrate higher motor activity compared with the control vehicle-treated animals (O’Neill et al., 2003). It was suggested that effects of mGlur2/3 antagonists on motor activity are likely to be qualitatively different from that seen after administration of psychostimulant drugs. The present study confirms that hypothesis. Most importantly, LY-341495-treated animals do not express true hyperactivity. First, motor activity in these animals is never enhanced beyond the levels observed during the early portions of the session. In the control subjects, motor activity is subject to rapid habituation over the 1st hour, whereas LY-341495-treated mice do not exhibit such habituation and motor activity stays virtually unchanged for the entire 2-h observation period. Second, after 1-h habituation period, injection of LY-341495 did not induce motor hyperactivity either. In fact, the injection procedure itself (i.e., in the vehicle-treated group) enhanced motor activity that returned to baseline levels within 10 to 15 min. LY-341495 seemed to turn this temporary increase in motor activity into a more permanent increase, an observation that is again consistent with the idea that LY-341495 impairs habituation of simple exploratory motor behaviors.

Habituation is one of the most basic learning phenomena (Thompson and Spencer, 1966), and impaired habituation may characterize a number of psychopathological states, such as schizophrenia (Ludewig et al., 2003; Klamer et al., 2004). The present study aimed to evaluate mGlur2/3-dependent habituation by testing its sensitivity to antipsychotic drugs as well as variety of other drugs. Initially, three well established antipsychotics, haloperidol, clozapine, and risperidone, were tested against delayed hyperactivity induced by LY-341495. All three drugs reversed effects of LY-341495 at the dose levels efficacious in other antipsychotic screening tests. It is important to note that at least for clozapine and risperidone, interactions with LY-341495 were not due to the nonspecific motor deficits. Indeed, LY-341495-induced effects were attenuated at the dose levels that had no effects on spontaneous activity. This was clearly true for clozapine and risperidone and less so for haloperidol, which had significant effects on spontaneous activity (indicated by ANOVA main effects) although the post hoc Dunnett’s test did not reveal significant differences between any haloperidol-treated groups and the corresponding vehicle control. For haloperidol, these results seem to be in line with the previously reported data by O’Neill et al. (2003) who observed that haloperidol attenuated motor hyperactivity in mice treated with another mGlur2/3 antagonist, LY-366457, but only at the doses that significantly suppressed spontaneous locomotion. In the present study, analysis of the interactions between LY-341495 and test drug factors confirmed that clozapine and risperidone (but not haloperidol) differentially affected LY-341495-induced and spontaneous activity.
However, these arguments may not be sufficient because levels of drug-induced activity are much higher than that of spontaneous activity and, therefore, rate-dependence phenomenon may be argued to explain the observed pattern of effects (Dews and Wenger, 1977). To address this issue, this study compared activity in animals pretreated with LY-341495 with that induced by methamphetamine. Because clozapine and risperidone seemed to be less potent against delayed methamphetamine-induced hyperactivity, one may argue that the effects of clozapine and risperidone in LY-341495-treated mice are not due to nonspecific motor impairments. However, at present, it is not possible to extend this conclusion to haloperidol, which seemed to be equally effective in LY-341495 and methamphetamine experiments.

Olanzapine, aripiprazole, sulpiride, and amisulpride also attenuated LY-341495-induced effects at doses that did not affect spontaneous activity. Thus, all seven clinically used antipsychotic drugs were effective in LY-341495-treated mice. Since all clinically used antipsychotic drugs usually score positive in classical tests (e.g., conditioned avoidance response, apomorphine-induced climbing, and amphetamine-induced hyperlocomotion), the present results do not necessarily point at LY-341495-induced delayed hyperactivity as a novel valuable test for antipsychotic drug screening. To establish it as such, one would need to demonstrate additional benefits brought about by this test compared with the classical tests. For example, neurochemistry of LY-341495-induced behaviors is different from that for dopaminergic psychostimulants. Thus, LY-341495 is expected to modify behavior via mechanisms that would favor detection of novel antipsychotic principles.

The present experiments studied effects of several novel, commonly discussed potential antipsychotic principles. Some of them are being developed as stand-alone therapies (5-HT2 and 5-HT3 antagonists, D3 and D4 antagonists, GlyT1 inhibitors, and CB1 antagonists); some are expected to be effective as add-ons (5-HT1A agonists, 5-HT6 antagonists, and ampakines).

GlyT1 inhibitors, CB1 antagonists, D4 antagonists, 5-HT3 antagonists, 5-HT1A agonists, and ampakines have no antipsychotic-like activity in classical dopaminergic antipsychotic tests such as apomorphine-induced climbing and conditioned avoidance response, and all failed to reverse effects of LY-341495 in the present study. In contrast, D2 dopamine receptor-prefering antagonist L-741626 (D2/D3 selectivity ratio = 10-fold; Bowery et al., 1996) readily antagonizes effects of both LY-341495 (present study) and amphetamine (Millan et al., 2000). Furthermore, lithium chloride, a mood-stabilizing agent, reverses a number of behavioral effects of amphetamine, including hyperlocomotion and acoustic start-
prepulse inhibition deficits (Ong et al., 2005), and, in the present study, it was found to attenuate delayed hyperactivity in LY-341495-treated subjects. Another antimanic agent, valproate, was ineffective against amphetamine-induced prepulse inhibition deficit (Ong et al., 2005) and did not interfere with the effects of LY-341495 on motor activity.

Thus, it seems that the ability of a drug to attenuate behavioral effects of the dopaminergic psychostimulants predicts reversal of LY-341495-induced motor effects. It is highly unlikely that LY-341495 has amphetamine-like properties because there is no evidence that it directly affects monoamine transport or stimulates dopamine receptors although local blockade of mGluR2/3 receptors increases extracellular dopamine levels in brain areas (Karasawa et al., 2006). In addition to that, blockade of mGluR2 receptors may induce a chain of neurochemical changes that includes stimulation of D2 dopamine receptors. Regardless, the latter could explain a rather selective action of the tested antipsychotics, all of which potently block D2-like dopamine receptors.

However, there are two sets of data that potentially argue against such explanation. First, selective dopamine D3 antagonist SB-277011A attenuated motor activity habituation failures induced by LY-341495. This effect was observed at the highest tested dose level (30 mg/kg), but one needs to note that at this dose level, SB-277011A produced no behavioral effects attributable to D2 receptor blockade (Reavill et al., 2000). Second, 5-HT2A antagonists such as MDL-100907 and ketanserin are capable of attenuating amphetamine-induced...
hyperactivity (Kehne et al., 1996) but were without any significant effects in the present study against motor effects induced by LY-341495, in agreement with the previous findings (O’Neill et al., 2003).

5-HT2A receptor blockade was also shown previously to facilitate acoustic startle habituation (Geyer and Tapas, 1988), and these data suggest that there are different forms of behavioral habituation with different neuropathological characteristics (e.g., mGlur group III receptors are likely to be involved in short-term habituation of the acoustic startle; Weber et al., 2002).

Normal habituation process was argued to depend on the intact working memory function, disturbance of which was suggested to be in the core of the cognitive impairment in schizophrenia (Silver et al., 2003). Interestingly, several of intact working memory function, disturbance of which was to be involved in short-term habituation of the acoustic startle (Terry et al., 1995).

These considerations lead to two alternative conclusions: either observed effects of LY-341495 have no relevance to cognitive deficits observed in schizophrenia or blockade of mGlur2/3 receptors results in cognitive deficits that are not well represented in schizophrenia research. Obviously, further studies will be necessary to address these issues.

In conclusion, LY-341495-induced habituation deficits may be relevant for the analysis of cognitive abnormalities in schizophrenia and were blocked by antipsychotic treatment. Together with antipsychotic-like activity of mGlur2/3 agonists, present data strengthen the evidence on involvement of mGlur2/3 receptors in pathophysiology of schizophrenia.

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