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The effects of the mGluR5 antagonist MPEP and the mGluR2/3 antagonist LY341495 on rats' performance in the 5-choice serial reaction time task.

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Abstract

Schizophrenia is characterized by attentional deficits possibly associated with glutamate dysfunction. The role of postsynaptic metabotropic glutamate 5 (mGluR5) or presynaptic inhibitory mGluR2/3 on attention is currently unknown. We investigated the effects of the mGluR5 antagonist MPEP and the mGluR2/3 antagonist LY341495 on attention in the 5-choice serial reaction time task (5CSRTT), as well as on food intake to evaluate their effects on food motivation. The effects of pre-feeding and the muscle relaxant curare were examined to characterize the effects of alterations in motivation or the ability to perform the task, respectively. MPEP had no effect on accuracy but overall decreased performance in the 5CSRTT, including decreased speed of responding and decreased premature responses. *LY341495 had no significant effect on rats' performance in the 5CSRTT.* LY341495 decreased food intake in the home cage to a greater extent than MPEP. Curare decreased the speed of correct responding, reflecting motor impairment. Free feeding decreased overall performance, number of trials completed and number of head entries into the feeder, reflecting decreased motivation to perform the task. Thus, blockade of mGluR5, but not mGluR2/3, decreased overall responding without affecting accuracy in the 5CSRTT.

Keywords

attention; metabotropic glutamate receptors; MPEP; LY341495; schizophrenia; rat

Cognitive deficits are now regarded as a core feature of schizophrenia (Elvevag & Goldberg, 2000; Lewis et al., 2004), and include disturbances in selective attention (Mirsky, 1969; Carter et al., 1992; Hagan & Jones, 2005; an der Heiden & Hafner, 2000; Hughes et al., 2003) and working memory (Carter et al., 1996; Gold et al., 1997). Presently available pharmacological treatments produce little improvement in the cognitive and attentional deficits in schizophrenia patients.

Pharmacological blockade of *N*-methyl-*D*-aspartate (NMDA) receptors induced schizophrenia-like cognitive deficits in healthy subjects, and exacerbated positive and negative symptoms in schizophrenia patients (Krystal et al., 1994; Adler et al., 1999; Lahti et al.,

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2001), indicating that dysfunctions in glutamate neurotransmission contribute to the pathophysiology of schizophrenia (Krystal et al., 2003; Moghaddam, 2003, 2004; Tamminga, 1998). Glutamate mediates its actions via activation of both ionotropic and metabotropic (mGluR) receptors (Conn & Pin, 1997; Schoepp, 2001). There are synergistic interactions between postsynaptic NMDA receptors and mGluR5 indicated by electrophysiological and behavioral findings (Martin et al., 1997; Homayoun et al., 2004; Henry et al., 2002; Kinney et al., 2003; Campbell et al., 2004). Thus, it is predicted that mGluR5 antagonism would induce similar cognitive deficits to those induced by NMDA receptor blockade. By contrast, mGluR2/3 subtypes modulate glutamate neurotransmission through a presynaptic negative regulatory mechanism (Anwyl, 1999; Schoepp, 2001) suggesting that antagonists at mGluR2/3 would have the opposite behavioral effects to those of mGluR5 antagonists. Hence, antagonism at mGluR2/3 may improve cognitive function and, thus, might present a novel therapeutic strategy for treating cognitive impairments, including attentional deficits. Therefore, we explored whether blockade of mGluR5 would produce similar attentional deficits as NMDA receptor blockade, while mGluR2/3 blockade would produce improvement in attention.

Attentional performance was assessed in the 5CSRTT where detection of brief visual stimuli across five spatial locations served as a measure of sustained and divided attention (Carli et al., 1983; Robbins, 2002). Previous studies showed that the different NMDA receptor antagonists disrupted attentional performance in the 5CSRTT (for review, Chudasama & Robbins, 2004). It is not known whether mGluR5 blockade may induce similar deficits in the 5CSRTT as NMDA receptor blockade, and the effects of mGluR2/3 antagonists on attention have not been explored.

The present studies investigated the effects of the mGluR5 antagonist MPEP and the mGluR2/3 antagonist LY341495 on rats' performance in the 5CSRTT. We also investigated: a) the effect of 24 hr access to food before the test to assess the effects of absence of motivation for food on 5CSRTT performance; b) the effects of MPEP and LY341495 on food intake in the home cage because performance on the 5CSRTT depends on motivation for food (Harrison et al., 1997; Grottick & Higgins, 2002; Bizarro & Stolerman, 2003); and c) the effects of curare, a neuromuscular blocker, to determine the effects of motor impairment on 5CSRTT performance. These studies allowed us to unambiguously interpret the pattern of effects seen after the pharmacological manipulations in the 5CSRTT.

Materials and methods

Subjects

Male Wistar rats (Charles River; Raleigh, NC) weighing 290–320 g at the beginning of the experiments were housed in groups of two (except in Experiment 3 when they were housed individually) in a humidity- and temperature-controlled vivarium on a reversed 12 hour light/dark cycle (lights on at 6 pm). A food restriction schedule of 20 g/rat per day was maintained throughout the training and testing periods, unless otherwise specified by the experimental design. Rats had *ad libitum* access to water throughout the course of the studies except during testing. Training and testing occurred during the dark phase of the cycle. All subjects were treated in accordance with the National Institutes of Health guidelines. All experimental protocols and animal facilities were in accordance with the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC).

Drugs

MPEP (6-methyl-2-[phenylethynyl]-pyridine) was purchased from ANAWA (Switzerland) and dissolved in saline (0.9% sodium chloride). LY341495 (2S-2-amino-2-[1S,2S-2-carboxycyclopropan-1-yl]-3-[xanth-9-yl]propionic acid) was purchased from Tocris Cookson

Inc (Ellisville, MO, USA) and dissolved in saline with a few drops (approximately 0.1 ml) of 1.0 M NaOH. d-Tubocurarine chloride (curare) was purchased from Sigma (St. Louis, MO, USA) and dissolved in saline. All drugs were administered intraperitoneally in a volume of 1 ml/kg. MPEP and LY341495 were administered with a pretreatment time of 30 minutes and curare with a pretreatment time of 15 minutes. Vehicle injections were either saline (control for MPEP and curare) or saline containing approximately 0.1 ml of 1.0 M NaOH (control for LY341495). All drug doses are reported as the salt.

Apparatus

All testing was conducted in a set of 12 nine-hole nosepoke boxes (Med Associates, St. Albans, VT). Each box consisted of a 25.5 cm width $\times$ 28.4 cm length $\times$ 28.7 cm height chamber enclosed in a sound-attenuated box with a ventilator fan providing air circulation and producing low level background noise. A 2.5 W, 24 V white house light was positioned on one wall of the chamber and was illuminated during each experimental session. The concavely curved rear wall of the chamber contained nine 2.5 cm² square apertures, 4 cm deep and 1.4 cm above floor level. Each aperture had a vertical infrared beam crossing the entrance that illuminated a photoelectric cell. Illumination of each aperture was provided by a 2.5 W bulb located at the rear of the aperture. Alternate apertures were blocked by a metal cover leaving five apertures open to register the subject's responses. Food pellets were delivered to a magazine tray, located on the wall opposite to the curved wall that contained the 5 apertures. The distance from each aperture to the magazine panel was 28.4 cm. Each apparatus was controlled and provided data collected through a MedAssociates interface to a PC computer.

The 5-choice serial-reaction time task procedure

The 5CSRTT procedure used was very similar to the procedure developed by Robbins and colleagues (Carli et al., 1983; Robbins, 2002). The subjects were given the opportunity to become familiar with the test box, feeding regimen, and response apertures prior to training and testing. Rats were initially trained to receive free food pellets from the magazine and the five response apertures during two 20 min sessions. Two additional sessions with pellets dispensed every 20 seconds for 20 min in the magazine preceded further training on the task.

Final Test Schedule—Each test session commenced with the illumination of the chamber by the house light and the delivery of a free food pellet. The collection of this pellet from the feeder started the first trial. After a fixed inter-trial interval (ITI) of 5 s, the light at the rear of one of the response apertures was illuminated for 0.75 s. Responses in this aperture within 5 s of illumination of the hole, the limited hold (LH), were recorded as correct responses and were rewarded by the delivery of a food pellet to the magazine. The correct response latencies measured from the initiation of the illumination of the aperture to the breaking of the appropriate photobeam were also recorded. Additional responses in the apertures prior to food collection, but after the initial response, were recorded as perseverative responses, and punished by a 5 s timeout period during which time the chamber was in darkness (house light and all other lights off). Further responding in the apertures during the time-out restarted this time-out period. The magazine latency was measured from the time the appropriate photobeam was broken to the entry to the feeder to collect the food pellet. Responses in a non-illuminated hole were recorded as incorrect responses and were punished by a time-out period, as were failures to respond within the 5 s limited hold period, which were recorded as omissions. Other panel responses during the ITI or time-out periods were also recorded and punished by a time-out period. A response in the feeder after the delivery of food (e.g., after correct response) or after a time-out period, initiated the next trial; while a feeder response after a premature response restarted the same trial. Each test session was terminated after either the completion of 100 trials (e.g., total number of correct responses + incorrect responses + omissions = 100 trials) or after 30 min elapsed, whichever occurred first. During each session the stimulus light

was presented an equal number of times in each of the five holes. Training started with the stimulus duration set at 30 s and the limited hold set at 60 s. These variables were altered on subsequent sessions until the target set of task parameters was implemented. These task parameters comprised the stimulus duration of 0.75 s and the limited hold of 5 s. The animals were considered to have reached criterion when performance of greater than or equal to 70% correct and less than 20% omissions on the target parameters was attained on five consecutive sessions. Approximately 40 training sessions were required before rats reached criterion performance in the task.

Performance on the task was assessed using the following measures:

1. Accuracy (the number of correct responses/number of correct + the number of incorrect responses).
2. The number of correct responses defined as the nose-poke responses in the same aperture as the stimulus light presentation during the limited hold period.
3. The number of incorrect responses defined as the nose-poke responses in a different aperture from the one where the stimulus light was presented during the limited hold period.
4. The number of omissions defined as no nose-poke response in any of the response apertures during the limited hold period.
5. Speed of responding: three measures of the speed of responding were recorded. a) the latency to respond correctly was measured from the onset of the visual stimulus to the response in the hole where the stimulus light appeared; b) the latency to respond incorrectly was measured from the onset of the visual stimulus to the response in the incorrect hole; and c) the magazine or “reward” latency was measured from the time of a correct response until the collection of the food pellet from the magazine.
6. Premature responses: total number of responses in any of the apertures during the ITI periods per session.
7. Perseverative responses: total number of responses in the apertures after a correct response and before collection of the food reward.

Data analyses

5CSRTT data were analyzed by repeated measures ANOVA with Drug dose as the within-subjects factor. Data on food intake were analyzed by repeated measures ANOVA with Drug dose and Time as the within-subjects factors. All post-hoc comparisons were conducted using the Newman-Keuls test after statistical significance in the ANOVAs (Winer, 1971). The level of significance was set at the $p < 0.05$ level.

Experimental procedures

Experiment 1: The effects of MPEP and LY341495 treatment on performance in the 5CSRTT—Naïve rats ($n=27$) were injected with MPEP (0, 1, 3, and 9 mg/kg, IP; $n=16$) or LY341495 (0, 0.25, 0.5, and 1.0 mg/kg, IP; $n=11$) 30 min before the session using a within-subjects Latin square design. Animals were administered drug injections once a week and tested in the 5CSRTT seven days a week.

Doses of MPEP, a relatively selective mGluR5 antagonist (Gasparini et al. 1999), were chosen based on our previous studies showing that the highest MPEP dose used here (9 mg/kg) decreased break points for food responding (Paterson & Markou, 2005), and based on literature findings showing that MPEP at higher doses is acting as an inhibitor of the norepinephrine transporter (e.g., Heidbreder et al., 2003). The LY341495 doses used were the most commonly

used dose in behavioral studies (e.g., Cartmell et al. 1999; Kenny et al. 2003; 1 mg/kg) and doses lower than this dose in order to maintain the selectivity for the mGluR2/3 (Kingston et al., 1998).

Experiment 2: The effects of free feeding on performance in the 5CSRTT

After the completion of Experiment 1, the same rats ($n=25$) were given 24 hr free access to food before testing in the 5CSRTT.

Experiment 3: The effects of MPEP and LY341495 treatment on food intake in food-deprived rats—Naïve rats ($n=14$) were housed individually. The same rats were used to test the effects of MPEP (Latin square 1) and LY341495 (Latin square 2) on feeding behavior in this experiment. Animals were food deprived for 24 h before the test. On the test day (e.g., 24 h after the initiation of food deprivation), rats were injected with MPEP (0, 0.3, 1, 3, 6, 9 mg/kg, IP) or LY341495 (0, 0.25, 0.5, 1.0 mg/kg, IP) using a within-subjects Latin square design (different doses were administered on different days). Rats were placed into a clean cage to avoid possible undetected remains of food in the bedding and food deprived 24 h before the test. On the test day, rats received 40 g of standard food chow in the home cage 30 min after the drug injection. Food intake was measured 5, 30 and 90 min after the rats had access to food, as cumulative food intake by removing, weighing and returning back into the feeder food pellets at each time point. After the test, rats had *ad libitum* access to food until the next test. Animals were tested once a week, 2 h after the onset of the dark cycle.

Experiment 4: The effects of curare on performance in the 5CSRTT task

Naïve rats ($n=10$) were injected with curare (0, 15, 30, 60, 120 and 170 $\mu\text{g/kg}$, IP) 15 min before the session. *The first four doses (0–60 $\mu\text{g/kg}$) were administered in a within-subjects Latin square design and the highest curare doses of 120 and 170 $\mu\text{g/kg}$ were injected after the completion of the Latin square. Animals were injected with curare once a week, and tested in the 5CSRTT seven days a week 2 h after the onset of the dark cycle.*

Results

Experiment 1: The effects of MPEP and LY341495 treatment on performance in the 5CSRTT

Effects of MPEP—Overall MPEP administration decreased performance in the 5CSRTT without significant effect on response accuracy [$F(3,45)=2.78$, $p<0.52$, n.s.], although there was a trend for an effect at the highest MPEP dose tested (Fig. 1). The ANOVA revealed a significant decrease in the number of correct responses [$F(3,45)=15.48$, $p<0.001$] and a significant increase in omissions [$F(3,45)=9.91$, $p<0.001$] when MPEP was administered at the doses of 3 and 9 mg/kg (post-hoc test, $p<0.05$). The effects of MPEP on the number of incorrect responses were not significant, but there was a decrease in overall responding (see below). That is, premature [$F(3,45)=4.58$, $p<0.01$] and perseverative [$F(3,45)=4.9$, $p<0.01$] responses were decreased and these effects reached significance for the 9 mg/kg MPEP dose (post-hoc test, $p<0.05$). The overall speed of responding was decreased as reflected in significant increases in the latencies to correct [$F(3,45)=10.27$, $p<0.001$] and incorrect [$F(3,45)=8.47$, $p<0.001$] responses at the highest MPEP dose (9 mg/kg). There was no significant effect of MPEP treatment either on the magazine latency or on the number of head entries into the feeder (data not presented). Animals completed all available 100 trials independent of MPEP treatment.

Effects of LY341495—Overall LY341495 administration had no significant effect on most measures provided by the 5CSRTT (Fig. 2). There was only a significant decrease in premature responses [$F(3,30)=3.02$, $p<0.05$] revealed by ANOVA analyses, but not in the post-hoc test. Animals completed all available 100 trials independent of LY341495 treatment.

Experiment 2: The effects of free feeding on performance in the 5CSRTT

Free feeding did not change accuracy (Fig. 3) or speed of performance, such as latencies to correct and incorrect responses (data not shown). However, there were significant decreases in the number of correct, incorrect, premature and perseverative responses, and an increase in omissions (Fig. 3, two tailed t-test, $p < 0.001$). Further, there was 50% decrease in the number of trials completed and the number of head entries into the feeder. However, the magazine latency was not changed (data not shown).

Experiment 3. The effects of MPEP and LY341495 treatment on food intake in food-deprived rats

Effects of MPEP—The ANOVA revealed significant main effects of MPEP dose [$F(5,65) = 2.48$, $p < 0.05$] and Time [$F(2,26) = 364.57$, $p < 0.0001$], but no significant interaction effect. Post-hoc tests indicated that MPEP administration at the highest dose tested (9 mg/kg) significantly decreased food intake at the 5 and 30 min time points (Fig. 4A). There was no effect of MPEP treatment after 90 min of access to food.

Effects of LY341495—The ANOVA revealed significant main effects of LY341495 dose [$F(3,39) = 5.57$, $p < 0.01$], and Time [$F(2,26) = 1426.86$, $p < 0.0001$], but no significant interaction effect. Post-hoc tests indicated no effect of LY341495 treatment after 5 min of access to food (Fig. 4B). However, LY341495 decreased food intake at the doses of 0.5 and 1 mg/kg after 30 min of access to food and at all doses tested at the 90 min time point.

Experiment 4: The effects of curare on performance in the 5CSRTT task

Suppression of operant performance was observed in 1 and 6 rats out of a group of 10 subjects when curare was injected at the doses of 120 and 170 $\mu\text{g/kg}$, respectively. Therefore, the ANOVA analyses included only those curare doses that did not grossly affect the rats' performance of the task (15–120 $\mu\text{g/kg}$; the one missing value for the 120 $\mu\text{g/kg}$ dose was replaced by the mean of the group). Curare administration overall decreased performance in the 5CSRTT without significant effect on response accuracy [$F(4,36) = 0.31$, n.s.] (Fig. 5). More specifically, the ANOVA revealed a significant decrease in the number of correct responses [$F(4,36) = 9.23$, $p < 0.001$], premature responses [$F(4,36) = 4.62$, $p < 0.05$] and a significant increase in omissions [$F(4,36) = 18.3$, $p < 0.001$] when curare was administered at the highest dose of 120 $\mu\text{g/kg}$ (post-hoc test, $p < 0.05$). The effects of curare on the number of incorrect ($F(4,36) = 2.5$, n.s.) and perseverative ($F(4,36) = 1.5$, n.s.) responses were not significant, but there was a trend for a decrease in these types of responses. The overall speed of responding was decreased as reflected in significant increases in the latencies to correct responses [$F(4,36) = 6.61$, $p < 0.001$]. There was no significant effect of curare treatment on the latencies to incorrect responses, magazine latency, the number of trials completed (e.g., all 100 trials were completed or non-significantly decreased) or the number of head entries into the feeder (data not shown).

Discussion

MPEP administration induced deterioration of behavioral performance, while LY341495 had no significant effect on 5CSRTT response measures (Figure 1 and Table 1). Both MPEP and LY341495 decreased food intake in the home cage in deprived rats, and this effect was larger after LY341495 administration. Further, either free feeding or curare administration, decreased overall behavioral performance without effects on accuracy. Curare administration decreased the speed of correct responding reflecting the effects of motor impairments. Free feeding significantly reduced most types of responses, as well as the number of trials completed and the number of head entries into the feeder reflecting a decrease in overall motivation to perform

the task. To facilitate the discussion of the effects of mGluR drug manipulations in the 5CSRTT, the effects of the muscle relaxant curare and pre-feeding are discussed first.

Effects of motor impairment on 5CSRTT performance

Curare, a neuromuscular blocker (Colquhoun et al., 1979; Katz & Miledi, 1973) without central nervous system effects because of its inability to cross the blood-brain barrier (Smith et al., 1947), produces motor impairment. As expected, curare increased correct response latency and omissions (see Table 1), measures associated with motor deficits (Robbins, 2002). *Curare did not affect accuracy, indicating no effects of general motor performance deficits on attention. At the highest curare dose used (170 µg/kg), 60% of the animals completed fewer than 10 trials or did not respond at all as their locomotion was noticeably suppressed suggesting that the curare doses used were within the range that produces muscle relaxation.*

The effects of food motivation on 5CSRTT performance

Decreased motivation for food involving 24 h free access to food did not affect accuracy or the magazine latency but decreased all response measures (Table 1). Further, free feeding resulted in a 50% decrease in the number of trials completed and decreases in the number of head entries into the feeder. Consistent with our findings, it has been shown previously that pre-feeding the rats before testing increased the number of omissions but did not change accuracy in the 5CSRTT (Carli & Samanin, 1992; Harrison et al., 1997; Grottick & Higgins, 2002; Bizarro & Stolerman, 2003). The magazine latency and the latency to respond have been shown to be increased after pre-feeding (Carli & Samanin, 1992; Harrison et al., 1997). However, in a recent study (Grottick & Higgins, 2002) and consistent with our results, the magazine latency and the latency to respond were not changed after pre-feeding, suggesting that the number of trials completed and the number of the head entries into the feeder, may more accurately reflect decreased motivation than increased latencies to magazine entry and to correct response.

The effects of MPEP and LY341495 on food intake in the home cage

Both MPEP and LY341495 significantly decreased food intake in the home cage, indicating that there was a decrease in motivation for food that *may have contributed to their effects on attentional performance. Consistent with this finding it has been reported that mGluR5 knockout mice ate significantly less compared to the wild type mice when re-fed after overnight food deprivation, while in rats, MTEP decreased night-time food intake in a dose-related manner without rebound feeding (Bradbury et al., 2005). These findings suggest that mGluR5 receptors are involved in feeding behavior.* However, LY341495 decreased food intake more than MPEP, while it had no significant effect on most 5CSRTT response measures. *Further, the profile of effects induced by MPEP in the 5CSRTT differed from the profile induced by reduced food motivation. Specifically, free feeding significantly reduced the number of trials completed and head entries, while MPEP had no effect on these measures.* Therefore, it is possible, but highly unlikely, that the decreases in responding induced by MPEP are attributable to the effects of MPEP on the animal's hunger state or ability to consume food.

Effects of MPEP and LY341495 on 5CSRTT performance

Attentional performance—Our findings suggest partial and subtle involvement of the mGluR5 in attentional processes reflected in significant MPEP-induced decreases in the number of correct responses, but without having an effect on accuracy. Further, the number of omissions was significantly increased after MPEP administration. It has been previously shown that the NMDA receptor antagonist PCP increased omissions and decreased choice accuracy in rats (Jin et al., 1997) and mice (Greco et al., 2005), and exacerbated these effects in neonatal hippocampal lesioned rats, an experimental manipulation that induces aspects of schizophrenia

in rats (Le Pen et al., 2003). Similar attentional deficits were also seen after systemic or central administration of different NMDA receptor antagonists (Higgins et al., 2003; Murphy et al., 2005; Mirjana et al., 2004), but their effects on accuracy were more robust compared to MPEP indicating that the mGluR5 may play a modulatory role in attentional processes, consistent with their modulatory role in glutamate transmission (Conn & Pin, 1997; Schoepp, 2001).

Surprisingly, LY341495 had no significant effect on accuracy in the 5CSRTT. Lack of improvement in attention by LY341495 administration may be due to a ceiling effect because of the initially high level of accuracy/correct responses and low level of incorrect responses and omissions after extensive training in the 5CSRTT. Consistent with this notion, LY341495 improved performance during acquisition of spatial learning in the Morris water maze task (Higgins et al., 2004) but there was no effect on working memory in a forced choice delayed-alternation task on a T-maze (Gregory et al., 2003), a delayed non-matching-to-position task (Higgins et al., 2004) and a spatial discrimination task (Gregory et al., 2003) after learning had occurred. Interestingly, administration of LY379268, a mGluR2/3 agonist, rather than an antagonist, also had no significant effect on accuracy in the 5CSRTT task in C57BL/6 and DBA/2J mice (Greco et al., 2005). However, there was a trend for accuracy to be slightly increased in the less accurate DBA/2J mice compared to the more accurate C57BL/6 mice indicating that the initial level of accuracy may be important for detection of improved performance. Thus, the possibility remains that mGluR2/3 may be involved in attentional process when performance is deteriorated, and further experiments are needed to address this point. In conclusion, it appears that blockade of mGluR2/3 enhances learning processes during acquisition of a task while having no effects on working memory and attentional tasks after task acquisition.

Speed of responding—Similarly to curare administration, MPEP administration increased response latencies suggesting some motor impairment. However, no effect of MPEP on locomotor or exploratory behavior (Tatarczynska et al., 2001; Henry et al., 2002; Homayoun et al., 2004) and rotarod performance (Spooren et al., 2000; Tessari et al., 2004) was reported. Thus, MPEP does not appear to have robust non-specific motor effects, although decreased all types of responding *may be partially attributable to slight motor effects*. Decreased response latencies may also reflect decreased motivation to perform the task. Published findings indicated that MPEP has no effect on food self-administration on a fixed ratio 5 schedule of reinforcement (Paterson et al., 2003), saccharin consumption (Schachtman et al., 2003) or acquisition of a food-motivated spatial task (Petersen et al., 2002). In a more complex motivational task, MPEP decreased breakpoints for food self-administration on a progressive ratio schedule of reinforcement (Paterson & Markou, 2005). Therefore, possible effects of MPEP on motivation for food may only be revealed in complex tasks such as progressive ratio schedules or 5CSRTT. Finally, magazine latency, as a traditional measure for food motivation (Robbins, 2002; Carli & Samanin, 1992; Harrison et al., 1997), was not affected either by MPEP (present study) or by pre-feeding (present study; Grottick & Higgins, 2002). Importantly, the number of trials completed and head entries into the feeder were not affected after MPEP administration, further indicating that MPEP-induced decreases in response speed cannot be fully attributed to decreased food motivation.

LY341495 had no significant effect on response latencies in the 5CSRTT (present study) or locomotor activity at the dose of 1 mg/kg (O'Neill et al., 2003; Cartmell et al., 1999).

Impulsive/compulsive behavior—Besides sustained attention, the 5CSRTT measures some aspects of inhibitory behavioral control measured by premature responses (impulsive behavior) or perseverative responses (compulsive behavior, Evenden, 1999; Robbins, 2002). In the present study, MPEP administration decreased both premature and perseverative responses, opposite to the effects of the NMDA antagonists PCP, Ro63-1908 or MK-801

administration (Jin et al., 1997; Murphy et al., 2005; Higgins et al., 2003). These decreases seen after MPEP administration can be attributed to non-specific motoric and/or sedative effects. *LY341495 had no effects either on the numbers of premature or perseverative responses.*

Neural mechanisms—The mechanism of action of MPEP may include a noncompetitive NMDA receptor blockade in addition to mGluR5 blockade (O’Leary et al., 2000). Similar to the effects of NMDA receptor antagonists, blockade of mGluR5 with MPEP-induced impairments in spatial working memory and instrumental learning (e.g., Homayoun et al., 2004), and potentiated behavioral effects of different NMDA receptors antagonists (Campbell et al., 2004; Homayoun et al., 2004; Henry et al., 2002). The mGluR2/3 are localized predominantly presynaptically and serve as auto-receptors that regulate transmitter release (Shigemoto et al., 1997; Cartmell & Schoepp, 2000; Kew & Kemp, 2005). It has been suggested that mGluR2/3 antagonists have minimal effects under baseline conditions as extrasynaptic glutamate levels are low under physiological conditions (Javitt, 2004). Accordingly, the mGluR2/3 antagonist LY341495 did not affect significantly the rats’ performance in the 5CSRTT under baseline conditions. However, lack of significant effect of LY341495 does not preclude an important functional role of these receptors during pathological conditions when endogenous neurotransmitter levels are excessively elevated or decreased. Further, the noradrenergic system is involved in arousal, vigilance and attention (Aston-Jones et al., 1999; Harley, 1987). Blockade of mGluR5 resulting in reduced extracellular norepinephrine levels (Page et al., 2005; however, see Heidbreder et al., 2003) may contribute to the small attentional deficits seen in the 5CSRTT (present study, Ruotsalainen et al., 1997; Sirvio et al., 1994) as well as to the sedative and anxiolytic effects of MPEP measured in a variety of anxiety tests (Spooren et al., 2000; Pietraszek et al. 2005). Finally, in the 5CSRTT, elevated serotonin levels are associated with impaired response accuracy, while reduced serotonin levels are associated with increased impulsive behavior (Robbins, 2002; Harrison et al., 1997; Koskinen & Sirvio, 2001; Winstanley, et al., 2004a,b). MPEP administration did not modify serotonin levels in the cerebral cortex (Lee & Croucher, 2003) indicating that the serotonin system may not be involved in the effects of MPEP in the 5CSRTT. By contrast, LY341495 increased the firing rate of dorsal raphe nucleus serotonergic neurons and increased extracellular levels of serotonin in the rat medial prefrontal cortex (Kawashima et al., 2005), but in the present study, LY341495 had no effect on accuracy or impulsivity, possibly indicating that LY341495-induced increases in serotonin levels were not sufficient to improve performance or task demands were already too high to detect such improvements.

In conclusion, blockade of mGluR5 appears to primarily decrease all types of responding and speed of responding, without significantly affecting accuracy, contrary to our prediction. These effects may be partially attributable to decreased motivation for food, or sedative or motor impairments. Neurobiologically, these effects of MPEP may be attributed to decreased glutamate neurotransmission and/or decreased noradrenergic transmission. Although it was originally hypothesized that antagonists at mGluR2/3 would enhance attentional performance, administration of LY341495 had no significant effect on most measures in the 5CSRTT. Lack of performance improvement by LY341495 can be explained by a potential “ceiling effect” because of the high level of performance under baseline conditions. Thus, the present findings do not preclude the possibility that mGluR2/3 antagonists may have beneficial effects in states that involve dysregulation of glutamate function, as those seen in schizophrenia. The present studies promote our understanding of the function of mGlu receptors in attentional and cognitive processes with relevance to cognitive deficits seen in schizophrenia.

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Figure 1.

The effects of MPEP treatment on performance in the 5CSRTT. Data are presented as mean $\pm$ s.e.m. of absolute values (the number of correct, incorrect, premature and perseverative responses, the number of omissions and response latencies). Latencies are presented in seconds. Accuracy is presented as percent of the number of correct responses/(number of correct + number of incorrect responses)*100. Asterisks denote statistically significant differences between MPEP- and saline-treated rats (***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$).

Figure 2.

The effects of LY341495 treatment on performance in the 5CSRTT. Data are presented as mean $\pm$ s.e.m. for absolute values (the number of correct, incorrect, premature and perseverative responses, the number of omissions and response latencies). Latencies are presented in seconds. Accuracy is presented as percent of the number of correct responses/(number of correct + number of incorrect responses)*100. Asterisk indicates a main effect of LY341495 on premature responses in the ANOVA.

Figure 3.

The effects of free-feeding on performance in the 5CSRTT. Data are presented as mean $\pm$ s.e.m. of absolute values (the number of correct, incorrect, premature and perseverative responses, the number of omissions and response latencies). Latencies are presented in seconds. Accuracy is presented as percent of the number of correct responses/(number of correct + number of incorrect responses)*100. Asterisks denote statistically significant differences between baseline performance during the food deprivation state and the test after the 24 hr access to food (Student t-test, ***, $p<0.001$). Bsl=baseline; test=assessment of performance after 24 h of free-feeding.

Figure 4.

The effects of MPEP (panel A) and LY341495 (panel B) treatment on food intake in food-deprived rats. Data are presented as mean $\pm$ s.e.m of grams of food consumed. Asterisks denote statistically significant differences between MPEP- or LY341495- and saline-treated rats (**, $p < 0.01$; *, $p < 0.05$).

Figure 5.

The effects of curare treatment on performance in the 5CSRTT. Data are presented as mean $\pm$ s.e.m. for absolute values (the number of correct, incorrect, premature and perseverative responses, the number of omissions and response latencies). Latencies are presented in seconds. Accuracy is presented as percent of the number of correct responses/(number of correct + number of incorrect responses)*100. Asterisks denote statistically significant differences between curare- and saline-treated rats (*, $p < 0.05$).

Table 1

Summary of the effects of drug- and non-drug manipulations on 5CSRTT performance.

Parameter	LY341495	MPEP	Curare	Free feeding
Accuracy	ns	Ns	ns	ns
Correct responses	ns	↓	↓	↓
Incorrect responses	ns	Ns	ns	↓
Omissions	ns	↑	↑	↑
<u>Speed of responding</u>				
Latency to correct response	ns	↑	↑	ns
Latency to incorrect response	ns	↑	ns	ns
Latency to reward	ns	ns	ns	ns
<u>Impulsive/compulsive behavior</u>				
Premature responses	↓	↓	↓	↓
Perseverative responses	ns	↓	ns	↓
<u>Additional measures</u>				
Trials completed	ns	ns	ns	↓
Head entries into the feeder	ns	ns	ns	↓

Abbreviations: ns – non-significant effect; ↑ - increase, ↓ - decrease