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Prevention of the Phencyclidine-Induced Impairment in Novel Object Recognition in Female Rats by Co-Administration of Lurasidone or Tandospirone, a 5-HT_{1A} Partial Agonist

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Hypoglutamatergic function may contribute to cognitive impairment in schizophrenia (CIS). Subchronic treatment with the *N*-methyl-D-aspartate receptor antagonist, phencyclidine (PCP), induces enduring deficits in novel object recognition (NOR) in rodents. Acute treatment with atypical antipsychotic drugs (APDs), which are serotonin (5-$HT)_{2A}$/dopamine D_2 antagonists, but not typical APDs, eg, haloperidol, reverses the PCP-induced NOR deficit in rats. We have tested the ability of lurasidone, an atypical APD with potent 5-HT_{1A} partial agonist properties, tandospirone, a selective 5-HT_{1A} partial agonist, haloperidol, a D_2 antagonist, and pimavanserin, a 5-HT_{2A} inverse agonist, to prevent the development of the PCP-induced NOR deficit. Rats were administered lurasidone (0.1 or 1 mg/kg), tandospirone (5 mg/kg), pimavanserin (3 mg/kg), or haloperidol (1 mg/kg) b.i.d. 30 min before PCP (2 mg/kg, b.i.d.) for 7 days (day1–7), followed by a 7-day washout (day8–14). Subchronic treatment with PCP induced an enduring NOR deficit. Lurasidone (1 mg/kg) but not 0.1 mg/kg, which is effective to acutely reverse the deficit due to subchronic PCP, or tandospirone, but not pimavanserin or haloperidol, significantly prevented the PCP-induced NOR deficit on day 15. The ability of lurasidone co-treatment to prevent the PCP-induced NOR deficit was enduring and still present at day 22. The preventive effect of lurasidone was blocked by WAY100635, a selective 5-HT_{1A} antagonists, further evidence for the importance of 5-HT_{1A} receptor stimulation in the NOR deficit produced by subchronic PCP. Further study is needed to determine whether these results concerning mechanism and dosage can be the basis for prevention of the development of CIS in at risk populations.
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INTRODUCTION

Intervening pharmacologically and in other manners during the prodromal stage of schizophrenia, primarily to prevent the onset of persistent psychosis and enduring cognitive impairment is a major goal of current strategies for reducing the disability associated with schizophrenia (Bilder *et al,* 1992; Klosterkötter *et al*, 2001). Intervention during this stage is intended to arrest or attenuate the progression of the underlying pathology (McGlashan and Fenton, 1993; Larson *et al,* 2010). Treatment of individuals in the prodromal period with atypical antipsychotic drugs (APDs) has been reported to reduce the rate of progression to first-episode psychosis in some high-risk indiviudals (Lee *et al,* 2005; Lieberman and Fenton, 2000; McGlashan *et al,* 2006; McGorry *et al,* 2008; Phillips *et al,* 2009; Ruhrmann *et al,* 2005; Salokangas and McGlashan, 2008). However, there are major concerns about this strategy, which include stigmatization, false positives, and metabolic and other side effects of the atypical APDs and stigmatization (Kaur and Cadenhead, 2010).

Even at the time of first diagnosis, deficits in multiple domains of cognition, including visual learning and declarative memory, are present in most patients with schizophrenia and are known to be a key factor leading to impaired work and social function (Saykin *et al,* 1991; Meltzer and McGurk, 1999). There is evidence that some of the atypical APDs, which are more potent serotonin $(5\text{-}HT)_{2A}$ than dopamine (DA) D_2 antagonists, including the novel atypical APD, lurasidone, are more effective than

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typical APDs to attenuate some of these deficits (Hagger *et al,* 1993; Meltzer and McGurk, 1999; Woodward *et al,* 2005; Harvey *et al,* 2011), although not all studies are in accord (Keefe *et al,* 2007). The development of novel adjunctive or stand alone treatments that can improve some domains of cognition in schizophrenia, accompanied by functional improvement, is currently a major goal of pharmacologic research (Buchanan *et al,* 2010).

Hypoglutamatergic activity has been postulated to be a major cause of the cognitive impairment in schizophrenia (CIS; Goldman-Rakic and Selemon, 1997; Coyle, 2006). Important evidence that a deficit in glutamatergic function may be the basis for this component of schizophrenia is that the noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonists, such as phencyclidine (PCP), dizocilpine (MK-801), and ketamine, induce schizophrenia-like cognitive impairment in healthy subjects (Javitt and Zukin, 1991; Krystal *et al*, 1999). The effects of NMDA receptor antagonists on cognitive function in rodents and monkeys have been intensively studied as an animal model of CIS (Gunduz-Bruce, 2009). Acute or subchronic administration of PCP, MK-801, or ketamine to rodents produces cognitive impairments that model CIS, eg, novel object recognition (NOR; Neill *et al,* 2010, Meltzer *et al,* 2011). Acute administration of atypical APDs (eg, clozapine), but not the typical APD, haloperidol, has been reported to reverse cognitive deficits induced by subchronic PCP treatment in rat NOR (Grayson *et al,* 2007; Snigdha *et al,* 2010; Horiguchi *et al,* 2011a). We recently reported that selective 5-HT_{2A} inverse agonists (eg, pimavanserin) can potentiate the ability of sub-effective doses of several atypical APDs, including lurasidone, to ameliorate the PCP-induced NOR deficit (Snigdha *et al,* 2010). However, there are no reports that show a *preventive* effect of typical or atypical APDs.

Lurasidone is an atypical APD that has D_2, 5-HT_{2A}, and 5-HT_7 receptor antagonist properties, as well as being a potent 5-HT_{1A} partial agonist (Meyer *et al,* 2009; Ishibashi *et al,* 2010). We have recently reported that acute treatment with lurasidone ameliorates the subchronic PCP-induced NOR deficits in a 5-HT_{1A}- and 5-HT_7-dependent manner (Horiguchi *et al,* 2011b; Horiguchi and Meltzer, 2012).

Stimulation of 5-HT_{1A} receptors has been identified as a target for improving CIS, possibly by enhancing the release of cortical DA (Ichikawa *et al,* 2001, 2002). We have reported that the addition of tandospirone, a 5-HT_{1A} partial agonist (Hamik *et al,* 1990), to the ongoing treatment with typical APDs of patients with schizophrenia, improved executive function, verbal learning, and memory (Sumiyoshi *et al,* 2000, 2001a, b). We have also recently reported that acute administration of tandospirone or F15599, another 5-HT_{1A} agonist, improved the NOR deficit induced by subchronic PCP and WAY100635, a 5-HT_{1A} antagonist, blocked the acute attenuating effect of lurasidone (Horiguchi and Meltzer, 2012). These results indicate that acute stimulation of 5-HT_{1A} receptors is adequate to ameliorate the PCP-induced impairment in NOR.

The aim of the current study was to test the *preventive* effect of lurasidone, tandospirone, haloperidol, a typical APD, and pimavanserin, a 5-HT_{2A} inverse agonist, on the subchronic PCP-induced NOR deficit in rats. We also tested whether WAY100635, a 5-HT_{1A} antagonist, blocks the preventive effect of lurasidone.

MATERIALS AND METHODS

Animals

Thirty-four female Long-Evans (LE) rats (8 or 9 weeks old; Harlan Sprague Dawley, Indianapolis, IN, USA) were used as subjects for experiments 1–2 (rat group 1). Forty-three rats (rat group 2) were used for experiment 3. Twenty-six rats (rat group 3) were used for experiment 4. LE rats were housed in groups of three or four on a 12 h light/dark cycle. Food and water were available *ad libitum*. All experiments were conducted during the light phase in accordance with the Vanderbilt Animal Committee Regulations.

Drugs

Lurasidone and tandospirone were provided by Dainippon Sumitomo Pharma (Osaka, Japan). Pimavanserin was provided by Acadia Pharmaceuticals (Torrence, CA, USA). Haloperidol was obtained from Sigma-Aldrich (St Louis, MO, USA). WAY100635 was a gift from Wyeth Laboratories (Philadelphia, PA). PCP was supplied as a generous gift from the National Institute of Drug Abuse (Bethesda, MD, USA).

Lurasidone was dissolved in 0.5% methylcellulose, 0.2% Tween80. The other drugs were dissolved in distilled water. All drugs or vehicle were administered intraperitoneally (i.p.) in a volume of 1 ml/kg body.

Drug Treatment

LE rats (rat group 1) were randomly assigned to four groups. For each of these groups, the first injection (A) was given 30 min before the second injection (B) twice daily for 7 days (day1–7). Group 1 (control group), A; vehicle (saline), B; vehicle (saline). Group 2 (subchronic PCP group), A; vehicle, B; PCP (2 mg/kg). Group 3 (lurasidone 0.1 mg/kg + PCP group), A; lurasidone (0.1 mg/kg), B; PCP (2 mg/kg). Group 4 (lurasidone 1 mg/kg + PCP group), A; lurasidone (1 mg/kg), B; PCP (2 mg/kg).

Rat group 2 were randomly assigned to five groups. For each of these groups, the first injection (A) was given 30 min before second injection (B) twice daily for 7 days (day1–7). Group 1 (control group), A; vehicle, B; vehicle. Group 2 (subchronic PCP group), A; vehicle, B; PCP (2 mg/kg). Group 3 (tandospirone 5 mg/kg + PCP group), A; tandospirone (5 mg/kg), B; PCP (2 mg/kg). Group 4 (haloperidol 1 mg/kg + PCP group), A; haloperidol (1 mg/kg), B; PCP (2 mg/kg). Group 5 (pimavanserin 3 mg/kg + PCP group), A; pimavanserin (3 mg/kg), B; PCP (2 mg/kg).

Rat group 3 were randomly assigned to three groups. For each of these groups, the first injection (A) and second injection (B) were given 45 min or 30 min, respectively, before the third injection (C) twice daily for 7 days (day1–7). Group 1 (control group), A; vehicle, B; vehicle, C; vehicle. Group 2 (subchronic PCP group), A; vehicle, B; vehicle, C; PCP (2 mg/kg). Group 3 (lurasidone 1 mg/kg + WAY100635 0.6 mg/kg + PCP group), A; WAY100635 (0.6 mg/kg), B; lurasidone (1 mg/kg), C; PCP (2 mg/kg).

Subsequently, animals were given a 7-day washout period (days 8–14) before NOR testing.

NOR Test

Testing was carried out according to a previously validated method (Snigdha *et al*, 2010). Briefly, all rats were habituated for 1 h to the NOR arena for three consecutive days (days 12–14) before the first NOR test. Rats were given a further 3-min habituation on the day of testing (days 15 or 21). After the 3-min habituation, the rats were given two 3-min trials (an acquisition trial and a retention trial) separated by a 1-min intertrial return to their home cage. During the acquisition trial, the animals were allowed to explore two identical objects (A1 and A2). During the retention trial, the animals explored a familiar object (A) from the acquisition trial and a novel object (B).

Behavior was recorded on video for blind scoring of object exploration. Object exploration is defined as an animal licking, sniffing, or touching the object with the forepaws while sniffing. The exploration time (s) of each object in each trial was recorded manually by the use of two stopwatches. The discrimination index (DI) [(time spent exploring the novel object−time spent exploring the familiar object)/total exploration time] was then calculated for retention trials.

If the exploration time in the aquisition or retention trials to either of two objects was <5 s, the data were excluded from analysis. This rarely occurred and did not affect the ability to complete the analysis using the data from the remaining animals of that group. All experimental groups consisted of six to nine rats.

Data Analysis

All data are expressed as the mean ± SEM ($n=6$–9 per group). Exploration data were analyzed by a two-way ANOVA followed by the pairwise comparison when a significant effect was detected by the ANOVA. This analysis was used to detect the interaction of drug treatment and object exploration as well as main effects. When a significant effect was found, further analysis by a *post hoc* Student's *t*-test was performed to compare the time spent exploring the novel and familiar object. DI data were analyzed using one-way ANOVA followed by the Bonferroni test when a significant effect was detected by the ANOVA.

RESULTS

Effect of Co-Administration of Lurasidone on Subchronic PCP-Induced NOR Deficit on Day 15 (Experiment 1)

In the aquisition trial, no significant differences in time spent exploring the two identical objects were observed in any group ($F_{7,54}=0.9$, $p>0.05$, Figure 1a). There were no significant effects of drugs on exploratory activity during the acquisition trial period ($F_{5,42}=0.64$, $p>0.05$ for Supplementary Figure 1, $F_{9,66}=0.6$, $p>0.05$ for Supplementary Figure 2, $F_{5,44}=0.48$, $p>0.05$ for Supplementary Figure 3) in any of the experiments (Supplementary Figures 1–3). In the retention phase, the time spent exploring the novel *vs* familiar objects was significantly different among the groups ($F_{7,54}=3.8$, $p<0.005$, Figure 1b). Using *post-hoc* analysis, vehicle-treated animals explored the novel object significantly longer than the familiar object ($p<0.05$, Figure 1b). The ability to discriminate novel and familiar objects was abolished by subchronic PCP treatment. Lurasidone (0.1 mg/kg) failed to prevent this deficit (Figure 1b). However, lurasidone (1 mg/kg) significantly attenuated the NOR deficit ($p<0.005$, Figure 1b). The model examining the group effect on DI was statistically significant ($F_{3,27}=5.7$, $p<0.005$, Figure 1c). In the *post-hoc* analysis, the DI was significantly reduced following subchronic PCP-treatment ($p<0.01$). Co-administration of 1 mg/kg lurasidone significantly prevented the PCP-induced reduction in DI ($p<0.01$), but 0.1 mg/kg lurasidone did not (Figure 1c).

Effect of Co-Administration of Lurasidone on Subchronic PCP-Induced NOR Deficit on Day 22 (Experiment 2)

In the retention trial, the time spent exploring the novel *vs* familiar objects was significantly different among the groups ($F_{5,42}=7.8$, $p<0.005$, Figure 2a). The *post-hoc* analysis revealed that vehicle-treated animals showed preference for the novel object ($p<0.005$, Figure 2a). PCP-treated rats did not show preference for the novel object (Figure 2a). Co-treatment with lurasidone (1 mg/kg) significantly attenuated the PCP-induced deficit ($p<0.005$, Figure 2a) demonstrating an enduring preventive effect on

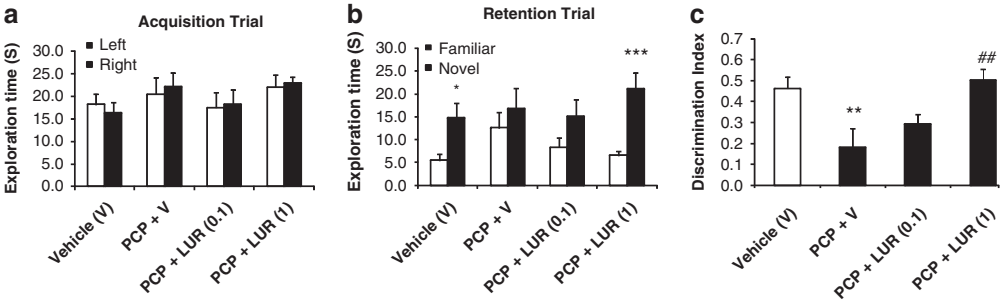

Figure 1 Effect of co-treatment with lurasidone (LUR, 0.1, 1 mg/kg) on PCP-induced cognitive impairment in NOR test on day 15. (a) Effect of LUR (0.1, 1 mg/kg, i.p.) on exploration of two identical objects in the aquisition trial in NOR test on day 15. Data are shown as mean ± SEM ($n=6$–9 per group). (b) Effect of LUR (0.1, 1 mg/kg, i.p.) on exploration of a novel and a familiar object in the retention trial in NOR test on day 15. Data are shown as mean ± SEM ($n=6$–9 per group). ***$p<0.001$, *$p<0.05$, significant difference in time spent exploring the novel compared with the familiar object. (c) Effect of LUR (0.1, 1 mg/kg, i.p.) on the DI on day 15. Data are shown as mean ± SEM ($n=6$–9 per group). **$p<0.01$, significant decrease in DI compared with the vehicle. $^{\#\#}p<0.01$, significant reversal in DI compared with PCP group.

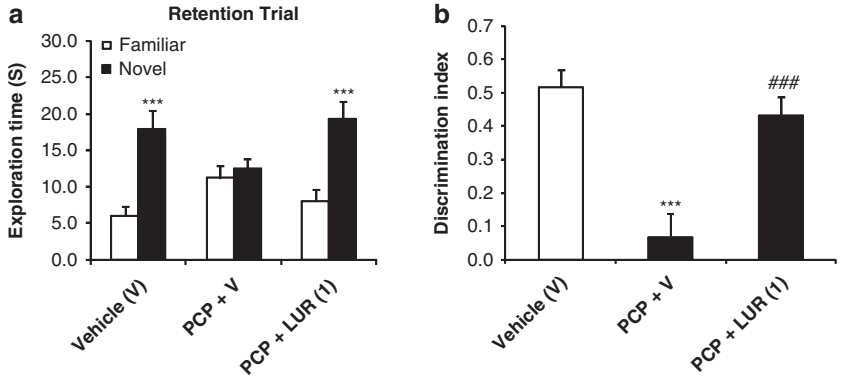

Figure 2 Effect of co-treatment with lurasidone (LUR, 0.1, 1 mg/kg) on PCP-induced cognitive impairment in NOR test on day22. (a) Effect of LUR (0.1, 1 mg/kg, i.p.) on exploration of a novel and a familiar object in the retention trial in NOR test on day 22. Data are shown as mean ± SEM ($n = 7$–9 per group). ***$p < 0.001$, significant difference in time spent exploring the novel compared with the familiar object. (b) Effect of LUR (0.1, 1 mg/kg, i.p.) on the DI on day 22. Data are shown as mean ± SEM ($n = 7$–9 per group). ***$p < 0.001$, significant decrease in DI compared with the vehicle. ###$p < 0.001$, significant reversal in DI compared with PCP group.

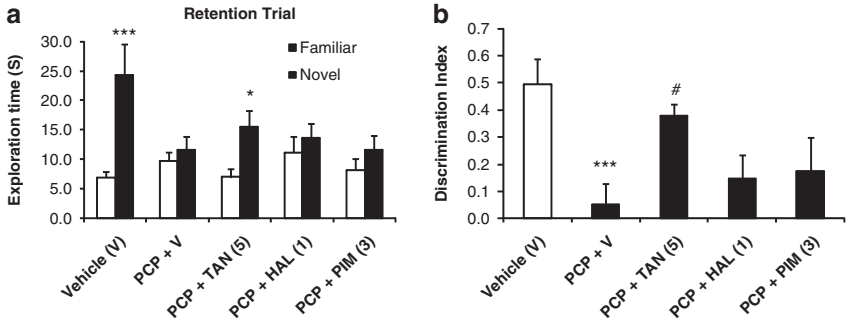

Figure 3 Effect of co-treatment with tandospirone (TAN, 5 mg/kg), haloperidol (HAL, 1 mg/kg), and pimavanserin (PIM, 3 mg/kg) on PCP-induced cognitive impairment in NOR test on day15. (a) Effect of TAN, HAL, and PIM (5, 1, and 3 mg/kg, respectively, i.p.) on exploration of a novel and a familiar object in the retention trial in NOR test on day 15. Data are shown as mean ± SEM ($n = 7$–9 per group). ***$p < 0.001$, *$p < 0.05$, significant difference in time spent exploring the novel compared with the familiar object. (b) Effect of TAN, HAL, and PIM (5, 1, and 3 mg/kg, respectively, i.p.) on the DI on day 15. Data are shown as mean ± SEM ($n = 7$–9 per group). ***$p < 0.001$, significant decrease in DI compared with the vehicle. #$p < 0.05$, significant reversal in DI compared with PCP group.

the PCP-induced NOR deficit. Statistical analysis showed the model examing the group effect on DI was significant ($F_{2,21} = 14.8$, $p < 0.005$, Figure 2b). Examing the *post-hoc* test, it was revealed that subchronic PCP-treatment significantly reduced the DI ($p < 0.005$, Figure 2b). Co-administration of lurasidone (1 mg/kg) prevented the reduction of DI ($p < 0.005$, Figure 2b).

Effect of Co-Administration of Tandospirone, Haloperidol, or Pimavanserin on Subchronic PCP-Induced NOR Deficit on Day 15 (Experiment 3)

In the retention trial, the time spent exploring the novel *vs* familiar objects was significantly different among the groups ($F_{9,66} = 3.8$, $p < 0.005$, Figure 3a). Using *post-hoc* analysis, it was found vehicle-treated rats showed exploratory preference for the novel object ($p < 0.005$, Figure 3a). In PCP-treated rats, there was no significant difference between the time spent exploring the novel and the familiar object (Figure 3a). Tandospirone (5 mg/kg) significantly prevented the PCP-induced NOR deficit ($p < 0.04$; Figure 3a). Neither haloperidol 1 mg/kg nor pimavanserin 3 mg/kg prevented this deficit (Figure 3a). The model examining the group effect on DI was statistically significant ($F_{4,33} = 4.5$, $p < 0.01$, Figure 3b). In the *post-hoc* analysis, the DI was significantly reduced following subchronic PCP-treatment ($p < 0.005$). Co-treatment with 5 mg/kg tandospirone ($p < 0.05$), but not 1 mg/kg haloperidol or 3 mg/kg pimavanserin, significantly improved the DI reduction (Figure 3b).

Effect of Co-Administration of WAY100635 Plus Lurasidone on Subchronic PCP-Induced NOR Deficit on Day 15 (Experiment 4)

In the retention trial, the time spent exploring the novel *vs* familiar objects was significantly different among the groups ($F_{5,44} = 3.0$, $p < 0.02$, Figure 4a). Using *post-hoc* analysis, it was found that the vehicle-treated rats showed preference for the novel object ($p < 0.005$); this preference was abolished by subchronic PCP-treatment (Figure 4a). WAY100635 (0.6 mg/kg) plus lurasidone (1 mg/kg) did not prevent this deficit (Figure 4a). The model examing the group effect on DI was statistically significant ($F_{2,22} = 4.4$, $p < 0.05$, Figure 4b). In the *post-hoc* analysis, the DI was significantly reduced following subchronic PCP-treatment

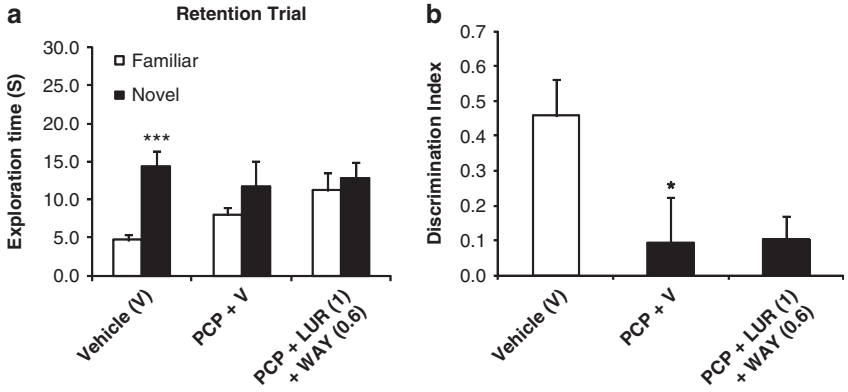

Figure 4 Effect of co-treatment with WAY100635 (WAY, 0.6 mg/kg) plus lurasidone (LUR, 1 mg/kg) on PCP-induced cognitive impairment in NOR test on day 15. (a) Effect of WAY (0.6 mg/kg, i.p.) plus LUR (1 mg/kg, i.p.) on exploration of a novel and a familiar object in the retention trial in NOR test on day 15. Data are shown as mean ± SEM ($n = 7$–9 per group). ***$p < 0.001$, significant difference in time spent exploring the novel compared with the familiar object. (b) Effect of WAY (0.6 mg/kg, i.p.) plus LUR (1 mg/kg, i.p.) on the DI on day 15. Data are shown as mean ± SEM ($n = 7$–9 per group). *$p < 0.05$, significant decrease in DI compared with the vehicle.

($p < 0.05$). Treatment with 0.6 mg/kg WAY100635 and 1 mg/kg lurasidone did not improve the reduction in the DI (Figure 4b).

DISCUSSION

NOR is a possible analog of declarative memory in humans (Winters *et al,* 2010) and a frequently studied model of CIS. In this study, we again confirmed that subchronic administration of PCP produces a severe deficit in NOR and that the co-treatment with lurasidone, an atypical APD with 5-HT_{1A} partial agonism, or with tandospirone, a selective 5-HT_{1A} agonist, prevented the NOR deficit induced by subchronic PCP. On the other hand, haloperidol, a typical antipsychotic with selective D_2 antagonist properties, or pimavanserin, a selective 5-HT_{2A} inverse agonist, did not prevent the PCP-induced deficit in NOR.

This is the first demonstration of the preventive effect of an atypical APD (lurasidone), or a 5-HT_{1A} partial agonist (tandospirone) on subchronic PCP-induced disruption in NOR in rats. We also found that the preventive effect of lurasidone lasted at least 14 days after the final PCP injection (on day 22). It has been reported that lurasidone has cognitive benefits in some animal models of CIS, in which other APDs were ineffective or even worsened the impairment in cognition (Ishiyama *et al,* 2007; Enomoto *et al,* 2008). Lurasidone was reported to be somewhat more effective than ziprasidone to improve general cognitive function in patients with schizophrenia in a double-blind study of 21 days duration (Harvey *et al,* 2011). In the present experiment, co-administration of lurasidone, 0.1 mg/kg, did not show the preventive effect, although acute treatment with this dose of lurasidone can reverse the subchronic PCP-induced NOR deficit (Horiguchi *et al,* 2011a, b). Acute treatment with lurasidone, 0.1 mg/kg, is sufficient to temporarily reverse the subchronic PCP-induced NOR deficit 30 min after administration, but when co-administration with subchronic PCP, this dose is insufficient to prevent the cognitive impairment in NOR induced by the subchronic PCP regimen. These results are inconsistent with several other preclinical reports using risperidone, suggest that lower doses of risperidone might be effective in some animal models of psychosis (Piontkewitz *et al,* 2011; Richtand *et al*, 2006). Thus, risperidone, at a dose of 0.045 mg/kg per day attenuated the abnormally elevated locomotor response to amphetamine following hippocampal lesions and behavioral abnormalities in the offsprings of poly I:C mother mice (Piontkewitz *et al,* 2011; Richtand *et al,* 2006). Our results suggest that for lurasidone or other atypical APDs higher doses than those needed to prevent recurrence of psychosis might be needed to impact CIS.

The results in this study are consistent with the acute reversal studies in which atypical APDs, including lurasidone and the 5-HT_{1A} agonist, tandospirone, but not pimavanserin or haloperidol, are effective reversing PCP-induced cognitive deficits (Grayson *et al,* 2007; Snigdha *et al,* 2010; Horiguchi *et al,* 2011a, b; Horiguchi and Meltzer, 2012). It is of interest to compare these results from acute reversal studies with studies in mice that showed a subchronic PCP (10 mg/kg)-induced NOR deficit in mice and examined the ability of subsequent subchronic administration of APDs to reverse the impairment (Hashimoto *et al,* 2005; Hagiwara *et al,* 2008; Nagai *et al,* 2009; Tanibuchi *et al,* 2009). This deficit was recovered by *subsequent* subchronic (14 days) administration of clozapine (5 mg/kg, i.p.), but not haloperidol (0.1 mg/kg, i.p.; Hashimoto *et al,* 2005). This deficit was also subsequently improved by subchronic treatment with perospirone or aripiprazole both of which are 5-HT_{1A} partial agonists (Hagiwara *et al,* 2008; Nagai *et al,* 2009). Tanibuchi *et al* (2009) reported that subsequent treatment with quetiapine, another atypical APD with 5-HT_{1A} partial agonism, also reversed the subchronic PCP-induced deficit in mice. On the other hand, in rat NOR, McKibben *et al* (2010) reported that treatment with risperidone (0.5 mg/kg, i.p.) twice daily for 10 days, beginning 3 days before the start of PCP administration (2 mg/kg, i.p., b.i.d. for 7 days), did not show a protective effect against the NOR deficit induced by subchronic PCP. More studies with other atypical APDs are needed to better understand the role of atypical APDs on cognitive impairments in NOR induced by subchronic PCP. These results suggest that at least some atypical APDs (eg, lurasidone) may be effective to prevent the development of

cognitive impairmant in individuals who at high risk for schizophrenia.

Stimulation of 5-HT_{1A} receptors has been identified as a target for improving CIS (Meltzer, 1999). In this study, not only lurasidone but also the 5-HT_{1A} agonist, tandospirone, showed the preventive effect on subchronic PCP-induced NOR deficit. Moreover, WAY100635, a selective 5-HT_{1A} antagonist, blocked the preventive effect of lurasidone, thereby demonstrating the involvement of 5-HT_{1A} agonism in the effect of lurasidone. As mentioned above, these results are consistent with the acute studies with 5-HT_{1A} agonists in this model (Horiguchi and Meltzer, 2012). These data suggest that tandospirone by itself or as an add on treatment with an atypical APD might have value to prevent the development of CIS. The 5-HT_{1A} agonists, eg, tandospirone, have a lower side effect burden than most atypical APDs, especially of the metabolic variety (Feighner and Boyer, 1989). It is noteworthy that lurasidone shares important structural similarities with tandospirone, and that lurasidone is also a 5-HT_{1A} partial agonist (Meltzer *et al,* 2011).

Postmortem studies have reported that the density of 5-HT_{1A} receptors is increased in frontal and temporal cortices in schizophrenia (Burnet *et al,* 1996, 1997; Gurevich and Joyce, 1997; Hashimoto *et al,* 1991; Simpson *et al,* 1996; Sumiyoshi *et al,* 1996). Positron emission tomography studies confirm an increase in cortical 5-HT_{1A} receptor binding in schizophrenia (Kasper *et al,* 2002; Tauscher *et al,* 2002). Subchronic treatment with PCP has been reported to increase 5-HT_{1A} receptor binding in the medial- and dorsolateral-frontal cortex (Choi *et al,* 2009). Microdialysis studies report that acute administration of PCP increases cortical 5-HT release (Etou *et al,* 1998; Martin *et al,* 1998; Millan *et al,* 1999; Adams and Moghaddam, 2001; Amargós-Bosch *et al*, 2006). This effect is blocked by clozapine and olanzapine but not haloperidol (Amargós-Bosch *et al*, 2006). It is possible that lurasidone and tandospirone, through their 5-HT_{1A} agonist properties, suppress cortical 5-HT release, thereby blocking effects of PCP related to 5-HT release that lead to interference with NOR.

Haloperidol and pimavanserin did not show a preventive effect in this model. As mentioned above, these results are in agreement with the lack of effectiveness of these drugs to acutely reverse the effects of subchronic PCP on NOR (Grayson *et al,* 2007; Snigdha *et al,* 2010). Subchronic treatment with haloperidol also did not reverse the NOR deficit induced by subchronic PCP in mice (Hashimoto *et al,* 2005; Nagai *et al,* 2009). Haloperidol (1 mg/kg) has been reported to reverse PCP-induced morphologic deficits in the auditory system, but not to reverse PCP-induced decreases in prefrontal cortical GABAergic interneurons in rats (Cochran *et al,* 2003). Pimavanserin (3 mg/kg) has been shown to achieve essentially 100% 5-HT_{2A} receptor occupancy (Vanover *et al,* 2006) and potentiated the ability of sub-effective doses of atypical APDs to reverse the NOR deficit induced by subchronic PCP (Snigdha *et al,* 2010). It is noteworthy that haloperidol and pimavanserin effectively block acute NMDA receptor antagonist (eg, PCP, MK-801)-induced hyperlocomotion, considered a model of psychosis (Maurel-Remy *et al,* 1995; Vanover *et al,* 2006; Gardell *et al,* 2007). Ritanserin, another 5-HT_{2A} inverse agonist, was able to block the ability of PCP to increase cortical 5-HT efflux (Amargós-Bosch *et al*, 2006). Co-administration of haloperidol or pimavanserin with PCP was ineffective in restoring performance in the NOR test in subchronic PCP-treated rats, indicating that D_2 or 5-HT_{2A} receptor blockade alone is insufficient to reverse cognitive impairment induced by subchronic PCP treatment, unlike the blockade of the effect of acute PCP or MK-801 on locomotor activity.

It has been reported that subchronic PCP induces a reduction in the density of paravalbumin-containing GABAergic interneurons in the hippocampus in both male and female rats (Abdul-Monim *et al*, 2007; Jenkins *et al*, 2008). A number of groups have conducted studies investigating the neuroprotective effects of atypical APDs. Chronic PCP treatment decreases parvalbumin mRNA expression and chronic administration of clozapine, but not haloperidol, reversed the PCP-induced decreases in parvalbumin mRNA expression in prefrontal cortical GABAergic interneurons (Cochran *et al,* 2003). Chronic treatment with olanzapine, but not haloperidol, has been reported to slow volume loss in the prefrontal cortex in a prefrontal cortical dopamine denervation model of schizophrenia (Wang and Deutch, 2008). Some clinical reports also suggest some atypical APDs may have a neuroprotective effect. A study of patients with first-episode schizophrenia reported that basal ganglia volume is increased in patients treated with risperidone (Massana *et al,* 2005). Treatment with risperidone increased the volume of gray matter in neuroleptic-naive patients (Molina *et al,* 2005). Further studies with lurasidone and tandospirone on the subchronic PCP-induced GABAergic interneuron deficit could provide valuable insight into the mechanism of subchronic PCP to induce cognitive impairment in rat NOR.

Female rats were used in this study primarily because they have been found to perform significantly better than male rats in the NOR task (Sutcliffe *et al,* 2007). Further, no effect of estrous cycle on performance in the NOR task has been found (Sutcliffe *et al,* 2007). Finally, female rats have been shown to differ in pharmacokinetics of PCP metabolism rendering them more sensitive to PCP than males, because of slower metabolism and higher PCP tissue levels (Nabeshima *et al,* 1984).

In conclusion, these results indicate that lurasidone or tandospirone, but not haloperidol, a typical APD, nor pimavanserin, may prevent the development of cognitive impairment in individuals who are at the risk for schizophrenia or related disorders with cognitive impairment, eg, bipolar disorder.

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