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ORIGINAL INVESTIGATION

The role of 5-HT$_{1A}$ receptors in phencyclidine (PCP)-induced novel object recognition (NOR) deficit in rats

M. Horiguchi · H. Y. Meltzer

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Abstract
Rationale Atypical antipsychotic drugs (APDs), many of which are direct or indirect serotonin (5-HT)$_{1A}$ agonists, and tandospirone, a 5-HT$_{1A}$ partial agonist, have been reported to improve cognition in schizophrenia.
Objectives and methods We tested the effect of 5-HT$_{1A}$ agonism, alone, and in combination with other psychotropic agents, including the atypical APD, lurasidone, in reversing the deficit in novel object recognition (NOR) induced by subchronic treatment with the non-competitive NMDA receptor antagonist, phencyclidine (PCP) (2 mg/kg, b.i.d., for 7 days).
Results Subchronic treatment with PCP induced a persistent NOR deficit. Lurasidone (0.1 mg/kg), a potent 5-HT$_{1A}$ partial agonist, 5-HT$_{2A}$ antagonist, and weaker D$_2$ antagonist, tandospirone (0.6 mg/kg), and the selective postsynaptic 5-HT$_{1A}$ agonist, F15599 (0.16 mg/kg), ameliorated the subchronic PCP-induced-NOR deficit. The 5-HT$_{1A}$ antagonist, WAY100635 (0.6 mg/kg), blocked the ameliorating effects of tandospirone and lurasidone. The combination of sub-effective doses of tandospirone (0.2 mg/kg) and lurasidone (0.03 mg/kg) also reversed the PCP-induced NOR-deficit. Buspirone, a less potent partial 5-HT$_{1A}$ agonist than tandospirone, was less effective. Co-administration of tandospirone (0.2 mg/kg) and pimavanserin (3 mg/kg), a relatively selective 5-HT$_{2A}$ receptor inverse agonist, did not reverse the effect of sub-chronic PCP on NOR. The D$_2$ antagonist, haloperidol, blocked the ameliorating effect of tandospirone on the PCP-induced deficit in NOR.
Conclusions These results indicate that 5-HT$_{1A}$ agonism is adequate to ameliorate the PCP-induced impairment in NOR and suggest further study of utilizing the combination of a 5-HT$_{1A}$ agonist and an atypical APD to ameliorate some types of cognitive impairment in schizophrenia.

Keywords Phencyclidine · Novel object recognition · Schizophrenia · 5-HT$_{1A}$ · Tandospirone · Lurasidone · F15599 · Buspirone · Cognition

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M. Horiguchi · H. Y. Meltzer
Division of Psychopharmacology,
Vanderbilt University Medical Center,
Nashville, TN 37212, USA

M. Horiguchi
Dainippon Sumitomo Pharma Co., Ltd.,
Osaka 564-0053, Japan

H. Y. Meltzer (✉)
Division of Psychopharmacology,
Vanderbilt University Medical Center,
1601 23rd Ave South, Suite 306,
Nashville, TN 37212, USA
e-mail: herbert.meltzer@vanderbilt.edu

Introduction

Moderate–severe deficits in multiple domains of cognition, including declarative memory, are present in schizophrenia (Kenny and Meltzer 1991; Saykin et al. 1991; Meltzer and McGurk 1999; Stone and Hsi 2011). Stimulation of 5-HT$_{1A}$ receptors has been identified as a target for improving cognitive impairment in schizophrenia (Meltzer 1999; Bantick et al. 2001). Post-mortem studies report increased density of 5-HT$_{1A}$ receptors in frontal and temporal cortices in schizophrenic patients (Burnet et al. 1996; 1997; Gurevich and Joyce 1997; Hashimoto et al. 1991; Simpson et al. 1996; Sumiyoshi et al. 1996). This is consistent with positron emission tomographic studies demonstrating in-

creased cortical 5-HT_{1A} receptor binding in schizophrenia (Kasper et al. 2002; Tauscher et al. 2002). Sumiyoshi et al. (2000; 2001a; 2001b) reported that the addition of tandospirone, a 5-HT_{1A} partial agonist, to ongoing treatment with typical antipsychotic drugs (APDs) improved executive function, verbal learning, and memory, suggesting that the upregulation of 5-HT_{1A} receptor density noted above may be a compensatory phenomenon to schizophrenia pathology. Sub-chronic treatment with phencyclidine (PCP), a noncompetitive *N*-methyl-D-aspartate receptor (NMDA-R) antagonist, has been reported to increase 5-HT_{1A} receptor binding in the medial–prefrontal and dorsolateral frontal cortex in the absence of changes in 5-HT_{2A} receptor binding in any brain region (Choi et al. 2009). This, too, may represent a compensatory process. Further, 5-HT_{1A} agonists, e.g., F15599, a preferential post-synaptic 5-HT_{1A} agonist (Maurel et al. 2007; Newman-Tancredi et al. 2009), improves cognition in rodents (see "Discussion").

There is conflicting evidence that atypical APDs are more effective than typical APDs in attenuating some cognitive deficits in schizophrenia (Hagger et al. 1993; Meltzer and McGurk 1999; Woodward et al. 2005; Keefe et al. 2007). Some atypical APDs, including aripiprazole, clozapine, and lurasidone, are 5-HT_{1A} partial agonists in vivo (Newman-Tancredi 2010). The increased dopamine (DA) release in medial prefrontal cortex (mPFC) induced by atypical APDs has been suggested to be due to 5-HT_{1A} receptor agonism as WAY100635, a 5-HT_{1A} antagonist, blocks the effect of atypical APDs to increase cortical DA release; 5-HT_{1A} agonists themselves enhance rat cortical DA efflux (Rollema et al. 1997; Ichikawa et al. 2001; 2002), leading to the suggestion that 5-HT_{1A} agonism-induced cortical DA release may play a role in the disputed ability of atypical APDs to improve cognitive function in schizophrenia (Ichikawa et al. 2002).

Hypoglutamatergic function in the frontal cortex and hippocampus has also been suggested to underlie the cognitive impairment in schizophrenia (Coyle 2006). The main evidence for such a deficit in glutamatergic function is that the NMDA-R antagonists, PCP, MK-801, and ketamine induce cognitive impairment in healthy subjects (Javitt and Zukin 1991; Krystal et al. 1999; Lahti et al. 2001; Newcomer et al. 1999) and increase psychosis in patients with schizophrenia (Lahti et al. 1995; 2001). Acute or subchronic administration of PCP and MK-801 has been reported to produce impairments in visual and learning memory, attention, reasoning and problem solving, working memory, and social cognition in rodents (see Neill et al. 2010 for review). Novel object recognition (NOR) is a possible analog of declarative memory in humans (Neill et al. 2010). Atypical APDs, but not the typical APD haloperidol, have been reported to reverse cognitive deficits induced by sub-chronic PCP treatment in NOR (see Meltzer et al. 2011 for review). We have recently reported that the ability of sub-effective doses of atypical APDs to reverse the NOR deficit in sub-chronic PCP-treated rats is potentiated by the 5-HT_{2A} inverse agonists, as well as the mGluR2/3 agonist, LY379268 (Snigdha et al. 2010; Horiguchi et al. 2011a). Moreover, the effect of atypical APDs to improve the PCP-induced NOR deficit is blocked by haloperidol, a D_2 receptor antagonist (Snigdha et al. 2010).

The aim of this study was to examine the effect of 5-HT_{1A} agonism on cognitive impairment in NOR induced by sub-chronic PCP treatment and its interaction with a variety of other mechanisms of interest for NOR. Experiments were carried out using the 5-HT_{1A} partial agonist tandospirone, alone and in combination with the selective 5-HT_{1A} antagonist WAY100635, the 5-HT_{2A} inverse agonist pimavanserin, the novel atypical APD lurasidone (which is itself a 5-HT_{1A} partial agonist), and the D_2 antagonist, haloperidol. We also studied the effect of another 5-HT_{1A} partial agonist, buspirone, and a preferential post-synaptic 5-HT_{1A} agonist, F15599, to reverse the effects of sub-chronic PCP.

Materials and methods

Animals

Eighty-six female Long–Evans (LE) rats from two separate batches (8–9 weeks old) (Harlan Sprague Dawley, Inc, Indianapolis, IN, USA) were used in the NOR experiment. The first 43 rats (rat group 1) were used for NOR experiments 1 to 4 and the second 43 rats (rat group 2) were used for NOR experiments 5 to 7. LE rats were housed in groups of three or four on a 12-h light/dark cycle. All experiments were conducted during the light phase. Food and water were available ad libitum. All experiments were conducted in accordance with 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). Buspirone and haloperidol were obtained from Sigma-Aldrich (St Louis, MO, USA). PCP was supplied as a generous gift from the National Institute of Drug Abuse. F15599 was obtained from Pierre Fabre (Castres, France). WAY100635 was a gift from Wyeth Laboratories (Philadelphia, PA, USA). Lurasidone and F15599 were solubilized in 0.5 % methylcellulose, 0.2 % Tween80. The other drugs were dissolved in distilled water. All drugs or

vehicle were administered intraperitoneally (i.p.) at a volume of 1 mL/kg body weight.

Drug treatment

LE rats in group 1 were randomly assigned to two treatment groups: nine were treated with vehicle (saline, i.p.) and the remainder were treated with PCP (2 mg/kg i.p.) twice daily for 7 days. Rats in group 2 were randomly assigned to two treatment groups: 19 were treated with vehicle (saline, i.p.) and the remainder were treated with PCP (2 mg/kg i.p.) twice a day for 7 days. Subsequently, animals were given a 7-day washout period prior to NOR testing (Grayson et al. 2007; Snigdha et al. 2010). Each rat was tested four times in the NOR paradigm with a 7-day washout period between each of the test sessions. This multiple-treatment regimen has previously been shown to not effect results when compared to testing rats only once and is preferred on humane and economic grounds. The criterion for continuing to test rats was exploration time in the acquisition and retention phases to either of two objects ≥ 5 s. If a rat did not explore at least 5 s in either of these two phases, its data were excluded from analysis. This rarely occurred and did not affect the ability to complete the analysis using data from the remaining animals of that group. All experimental groups consisted of six to nine rats.

NOR test

Testing was carried out according to a previously validated method (Snigdha et al. 2010). All rats were habituated for 1 h to the test environment and NOR arena for three consecutive days prior to the first NOR test. Rats were given a further 3-min habituation on the day of testing. After the 3-min habituation period, 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 objects exploration. Object exploration was defined by animal's 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 calculated for the retention trials.

Data analysis

All data are expressed as mean ± S.E.M. (n=6–9 per group). Exploration data were analyzed by a repeated-measures two-way ANOVA followed by pair-wise comparison when a significant effect was detected by ANOVA. DI data were analyzed by one-way ANOVA followed by Bonferroni test when a significant effect was detected by ANOVA.

Results

Effect of tandospirone in subchronic PCP-treated rats (experiment 1)

In the acquisition trial, no significant differences in time spent exploring the two identical objects were observed in any group (Fig. 1a). There were no significant effects of drugs during the acquisition trial period in any of the experiments ("Electronic supplementary material", Figs. S1, S2, S3, S4 and S5). In the retention phase, vehicle-treated rats explored the novel object significantly longer than the familiar objects (p<0.01; Fig. 1b). The ability to discriminate novel and familiar objects was abolished by subchronic PCP treatment (Fig. 1b). Tandospirone 0.6 mg/kg, but not 0.2 mg/kg, significantly attenuated the NOR deficit (p<0.01; Fig. 1b). Co-administration of tandospirone (0.6 mg/kg) with WAY100635 (0.6 mg/kg) abolished the ability of tandospirone to reverse the PCP-induced deficit (Fig. 1b). The DI was significantly reduced following subchronic PCP treatment (p< 0.01; Fig. 1c). Tandospirone 0.6 mg/kg, but not 0.2 mg/kg, significantly reversed the PCP-induced reduction in DI (p< 0.01; Fig. 1c). Futhermore, the effect of tandospirone (0.6 mg/kg) was significantly antagonized by 0.6 mg/kg WAY100635 (p<0.01; Fig. 1c). Tandospirone 0.6 mg/kg significantly increased the total exploration time in the acquisition and retention phase in the PCP-treated rats (p< 0.05 and p<0.01, respectively; Fig. 1a, b).

Effect of buspirone and F15599 in subchronic PCP-treated rats (experiment 2)

In the retention trial, vehicle-treated rats showed preference for the novel object (p<0.01; Fig. 2a). PCP-treated rats did not show preference for the novel object (Fig. 2a). Buspirone (1 mg/kg) did not affect the exploration times of the PCP-treated rats. However, 0.3 mg/kg buspirone increased the amount of time the rats spent exploring the novel object (p<0.01; Fig. 2a). F15599 (0.16 mg/kg) significantly reversed the PCP-induced NOR deficit (p< 0.01; Fig. 2a). Subchronic PCP treatment significantly reduced the DI compared with control rats (p<0.01, Fig. 2b). Buspirone (1 mg/kg) did not affect the PCP-induced reduction in DI (Fig. 2b). Buspirone (0.3 mg/kg) produced a higher DI score in the vehicle-treated group as compared to the PCP-treated group (0.343±0.121 vs. 0.129±

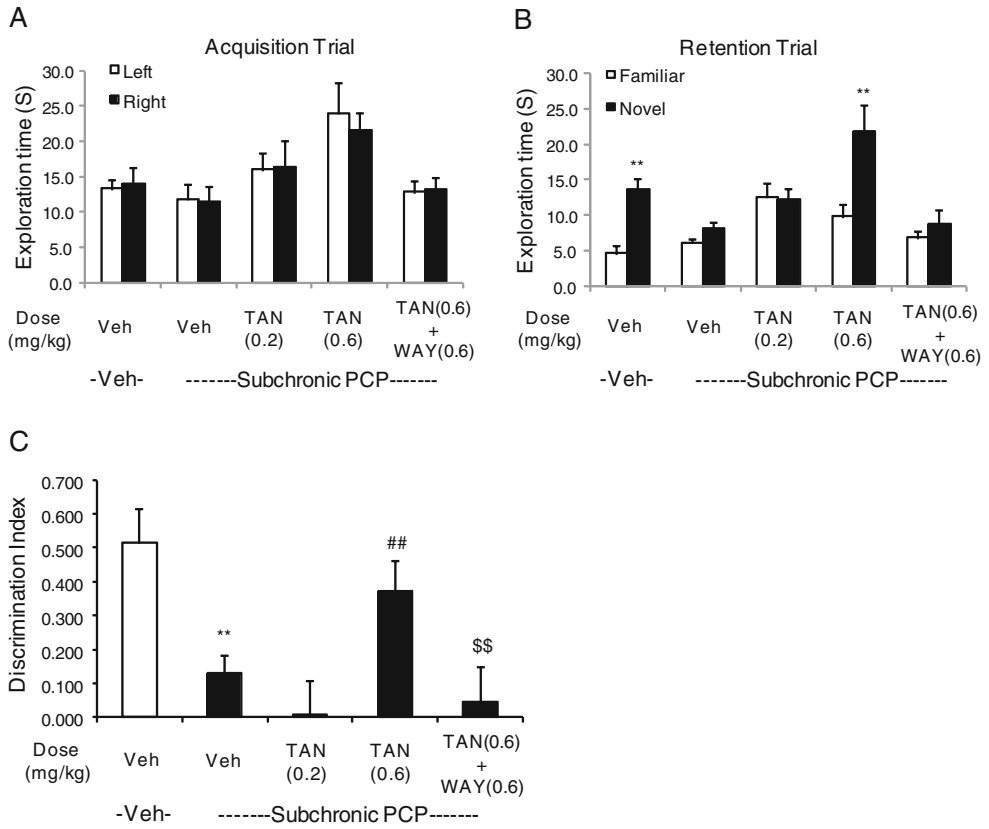

Fig. 1 Effect of tandospirone (*TAN*, 0.2, 0.6 mg/kg) and TAN (0.6 mg/kg) plus WAY100635 (*WAY*, 0.6 mg/kg) on PCP-induced cognitive impairment in NOR test. **a** Effect of TAN (0.2, 0.6 mg/kg) and TAN (0.6 mg/kg) plus WAY (0.6 mg/kg) on exploration of two identical objects in the aquisition trial. Data are shown as mean ± S.E.M. (n=7–9 per group). **b** Effect of TAN (0.2, 0.6 mg/kg) and TAN (0.6 mg/kg) plus WAY (0.6 mg/kg) on exploration of a novel and a familiar object in the retention trial. Data are shown as mean ± S.E.M. (n=7–9 per group). **p<0.01, significant difference in time spent exploring the novel compared with the familiar object. **c** Effect of TAN (0.2, 0.6 mg/kg) and TAN (0.6 mg/kg) plus WAY (0.6 mg/kg) on the DI. Data are shown as mean ± S.E.M. (n=7–9 per group). **p<0.01, significant decrease in DI compared with the vehicle. $^{\#\#}p$<0.01, significant reversal in DI compared with PCP group. $^{\$\$}p$<0.01, significant decrease in DI compared with PCP and 0.6 mg/kg TAN-treated group

0.060), but statistical analysis showed no significance difference in DI between buspirone (0.3 mg/kg) versus vehicle administered to PCP-treated rats (Fig. 2b). A dose of 0.16 mg/kg F15599 significantly improved the PCP-induced DI reduction (p<0.05; Fig. 2b). Buspirone 1 mg/kg significantly enhanced the total exploration time compared with the PCP-treated rats in the acquisition and retention ephase (p<0.05; Fig. 2b; "Electronic supplementary material", Fig. S1).

Effect of lurasidone and WAY100635 in subchronic PCP-treated rats (experiment 3)

In the retention trial, vehicle-treated rats showed exploratory preference for the novel object (p<0.01) and subchronic PCP treatment abolished the preference (Fig. 3a). Lurasidone (0.1 mg/kg) significantly reversed the PCP-induced NOR deficit (p<0.01; Fig. 3a). However, lurasidone (0.1 mg/kg) plus WAY100635 did not improve the NOR deficit (Fig. 3a). WAY100635 (0.6 mg/kg), by itself, did not affect the exploration times of the PCP-treated rats (Fig. 3a). The DI was significantly reduced following subchronic PCP treatment (p<0.01), and 0.1 mg/kg lurasidone significantly improved the DI reduction (p<0.01; Fig. 3b). Co-administration of 0.1 mg/kg lurasidone with 0.6 mg/kg WAY100635 or 0.6 mg/kg WAY100635 alone did not improve DI reduction (Fig. 3b).

Effect of tandospirone in combination with lurasidone or pimavanserin in subchronic PCP-treated rats (experiment 4)

In the retention trial, vehicle-treated rats showed exploratory preference for the novel object (p<0.01) and this preference was abolished in the PCP-treated rats (Fig. 4a). Tandospirone (0.2 mg/kg) plus 0.03 mg/kg lurasidone, but not 0.03 mg/kg lurasidone alone, reversed the PCP-induced deficit (p<0.01; Fig. 4a). A dose of 0.2 mg/kg tandospirone plus 3 mg/kg pimavanserin did not affect the exploration times of the PCP-treated rats (Fig. 4a). Subchronic PCP

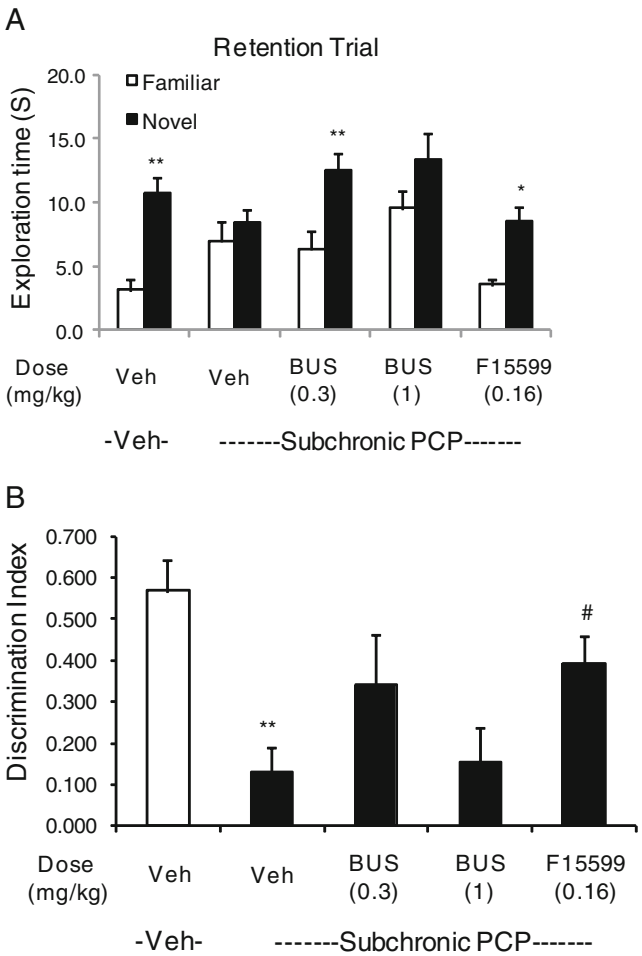

Fig. 2 Effect of buspirone (*BUS*, 0.3, 1 mg/kg) and F15599 (0.16 mg/kg) on PCP-induced cognitive impairment in NOR test. **a** Effect of BUS (0.3, 1 mg/kg) and F15599 (0.16 mg/kg) on exploration of a novel and a familiar object in the retention trial. Data are shown as mean ± S.E.M. (n=7–9 per group). **p<0.01, *p<0.05, significant difference in time spent exploring the novel compared with the familiar object. **b** Effect of BUS (0.3, 1 mg/kg) and F15599 (0.16 mg/kg) on the DI. Data are shown as mean ± S.E.M. (n=7–9 per group). **p<0.01, significant decrease in DI compared with the vehicle group. $^{\#}p$<0.05, significant reversal in DI compared with PCP group

treatment significantly reduced the DI (p<0.01; Fig. 4b). Lurasidone (0.03 mg/kg) did not reverse the reduction of the DI. However, 0.2 mg/kg tandospirone in combination with 0.03 mg/kg lurasidone, but not with 3 mg/kg pimavanserin, improved the subchronic PCP-induced DI reduction (p<0.01; Fig. 4b).

Effect of buspirone in combination with lurasidone in subchronic PCP-treated rats (experiment 5)

In the retention trial, vehicle-treated rats showed preference for the novel object (p<0.01; Fig. 5a). WAY100635 did not affect the exploration times of the control rats (Fig. 5a). PCP-treated rats did not show preference for the novel object and buspirone (0.1 mg/kg) did not affect the exploration times of the PCP-treated rats (Fig. 5a). Moreover, 0.1 mg/kg buspirone in combination with 0.03 mg/kg lurasidone did not improve the PCP-induced NOR deficit (Fig. 5a). WAY100635 did not affect the DI in control rats (Fig. 5b). Subchronic PCP significantly reduced the DI (p< 0.01; Fig. 5b). Buspirone (0.1 mg/kg) alone or with 0.03 mg/kg lurasidone did not affect the PCP-induced DI reduction (Fig. 5b).

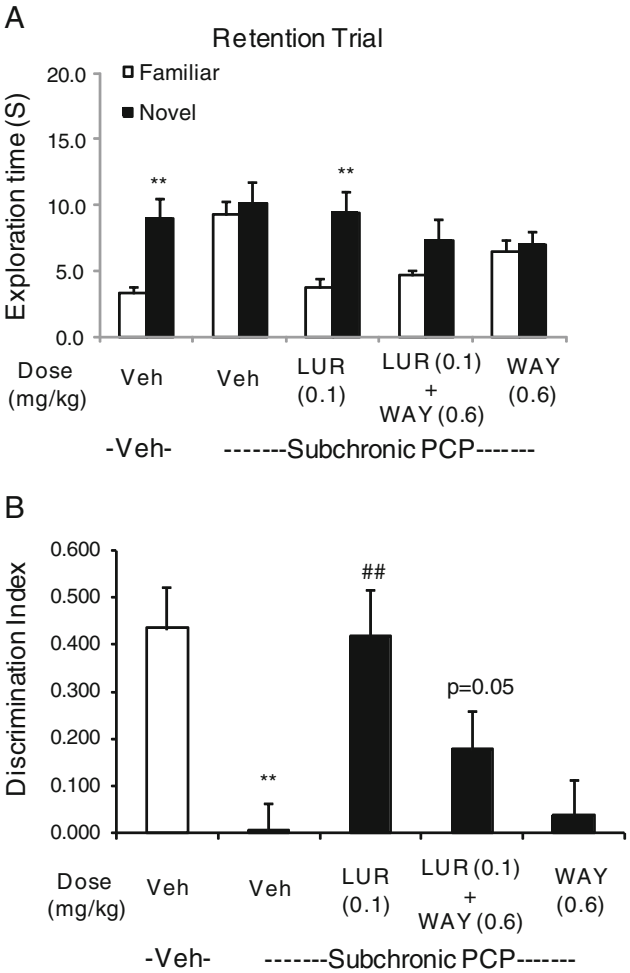

Fig. 3 Effect of lurasidone (*LUR*, 0.1 mg/kg), LUR (0.1 mg/kg) plus WAY100635 (*WAY*, 0.6 mg/kg), and WAY (0.6 mg/kg) on PCP-induced cognitive impairment in NOR test. **a** Effect of LUR (0.1 mg/kg), LUR (0.1 mg/kg) plus WAY (0.6 mg/kg), and WAY (0.6 mg/kg) on exploration of a novel and a familiar object in the retention trial. Data are shown as mean ± S.E.M. (n=6–8 per group). **p<0.01, significant difference in time spent exploring the novel compared with the familiar object. **b** Effect of LUR (0.1 mg/kg), LUR (0.1 mg/kg) plus WAY (0.6 mg/kg), and WAY (0.6 mg/kg) on the DI. Data are shown as mean ± S.E.M. (n=6–8 per group). **p<0.01, significant decrease in DI compared with the vehicle group. $^{\#\#}p$<0.01, significant reversal in DI compared with PCP group. LUR (0.1 mg/kg) plus WAY (0.6 mg/kg)-treated group tend to reduce the DI compared with LUR (0.1 mg/kg)-treated group (p=0.050)

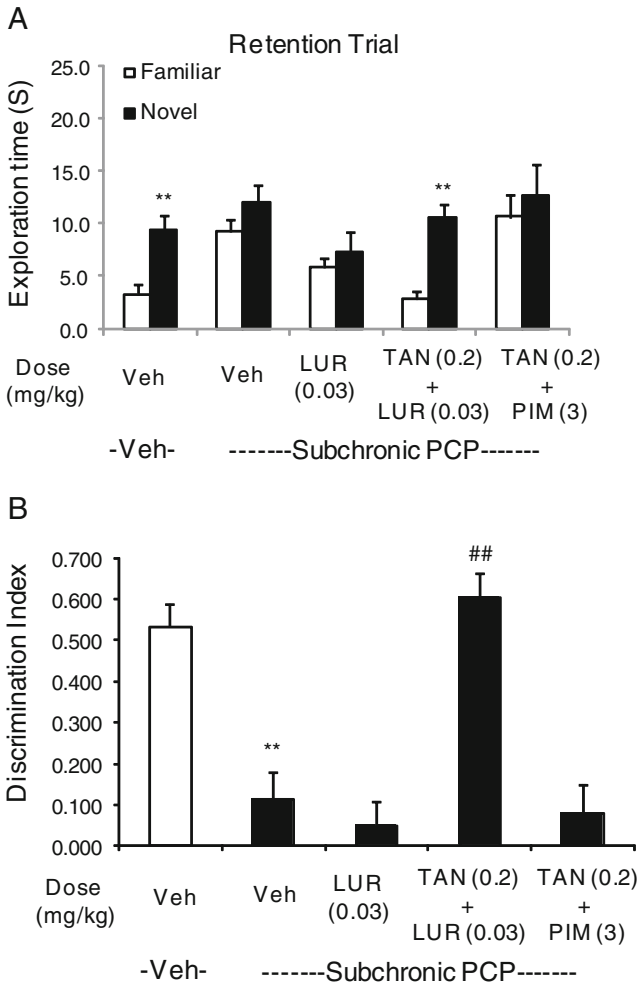

Fig. 4 Effect of lurasidone (*LUR*, 0.03 mg/kg), tandospirone (*TAN*, 0.2 mg/kg) plus LUR (0.03 mg/kg), and TAN (0.2 mg/kg) plus pimavanserin (*PIM*, 3 mg/kg) on PCP-induced cognitive impairment in NOR test. **a** Effect of LUR (0.03 mg/kg), TAN (0.2 mg/kg) plus LUR (0.03 mg/kg), and TAN (0.2 mg/kg) plus PIM (3 mg/kg) on exploration of a novel and a familiar object in the retention trial. Data are shown as mean ± S.E.M. (n=6–8 per group). **p<0.01, significant difference in time spent exploring the novel compared with the familiar object. **b** Effect of LUR (0.03 mg/kg), TAN (0.2 mg/kg) plus LUR (0.03 mg/kg), and TAN (0.2 mg/kg) plus PIM (3 mg/kg) on the DI. Data are shown as mean ± S.E.M. (n=6–8 per group). **p<0.01, significant decrease in DI compared with the vehicle group. $^{\#\#}p$<0.01, significant reversal in DI compared with PCP group

Effect of tandospirone or lurasidone in combination with haloperidol in subchronic PCP-treated rats (experiment 6)

In the retention trial, vehicle-treated rats explored the novel significantly more than the familiar object (p<0.01) and subchronic PCP treatment abolished the preference (Fig. 6a). Lurasidone (0.1 mg/kg) or tandospirone (0.6 mg/kg) in combination with 0.1 mg/kg haloperidol did not improve the NOR deficit (Fig. 6a). The DI was significantly reduced following subchronic PCP treatment (p<0.01), and lurasidone (0.1 mg/kg) or tandospirone (0.6 mg/kg) in combination with 0.1 mg/kg haloperidol did not improve the PCP-induced reduction in DI (Fig. 6b).

Discussion

The major findings of this study are that the 5-HT_{1A} partial agonist, tandospirone, and the preferential post-synaptic 5-HT_{1A} agonist, F15599, significantly reversed the subchronic PCP-induced deficit in NOR. Pretreatment with WAY100635, a 5-HT_{1A} antagonist, blocked the ability of tandospirone and lurasidone, a novel atypical APD with

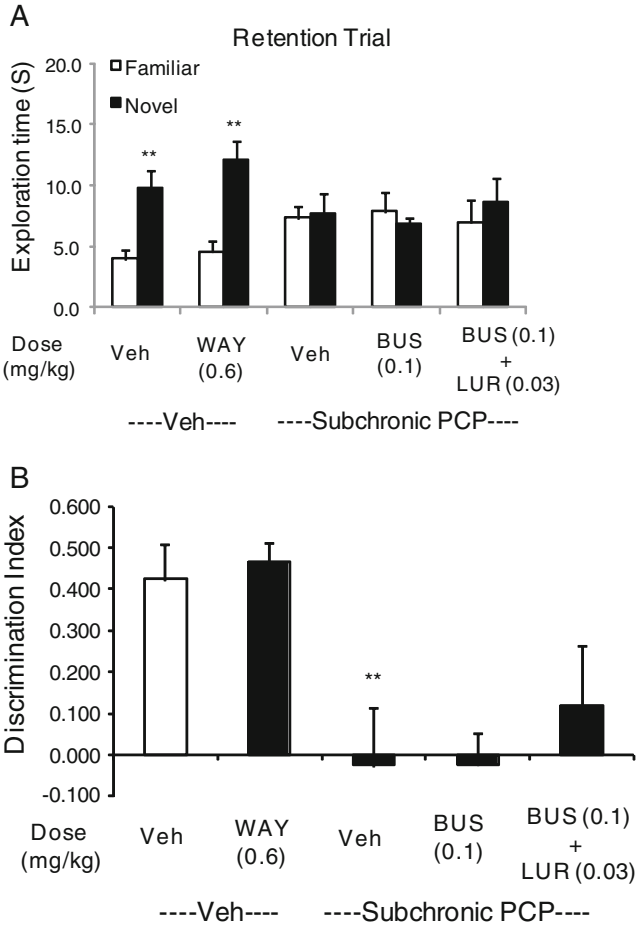

Fig. 5 Effect of WAY100635 (*WAY*, 0.6 mg/kg) on control rats and buspirone (*BUS*, 0.1 mg/kg) and BUS (0.1 mg/kg) plus lurasidone (*LUR*, 0.03 mg/kg) on PCP-induced cognitive impairment in NOR test. **a** Effect of WAY (0.6 mg/kg) to control rats and BUS (0.1 mg/kg) and BUS (0.1 mg/kg) plus LUR (0.03 mg/kg) on exploration of a novel and a familiar object in the retention trial. Data are shown as mean ± S.E.M. (n=6–8 per group). **p<0.01, significant difference in time spent exploring the novel compared with the familiar object. **b** Effect of WAY (0.6 mg/kg) to control rats and BUS (0.1 mg/kg) and BUS (0.1 mg/kg) plus LUR (0.03 mg/kg) on the DI. Data are shown as mean ± S.E.M. (n=6–8 per group). **p<0.01, significant decrease in DI compared with the vehicle group

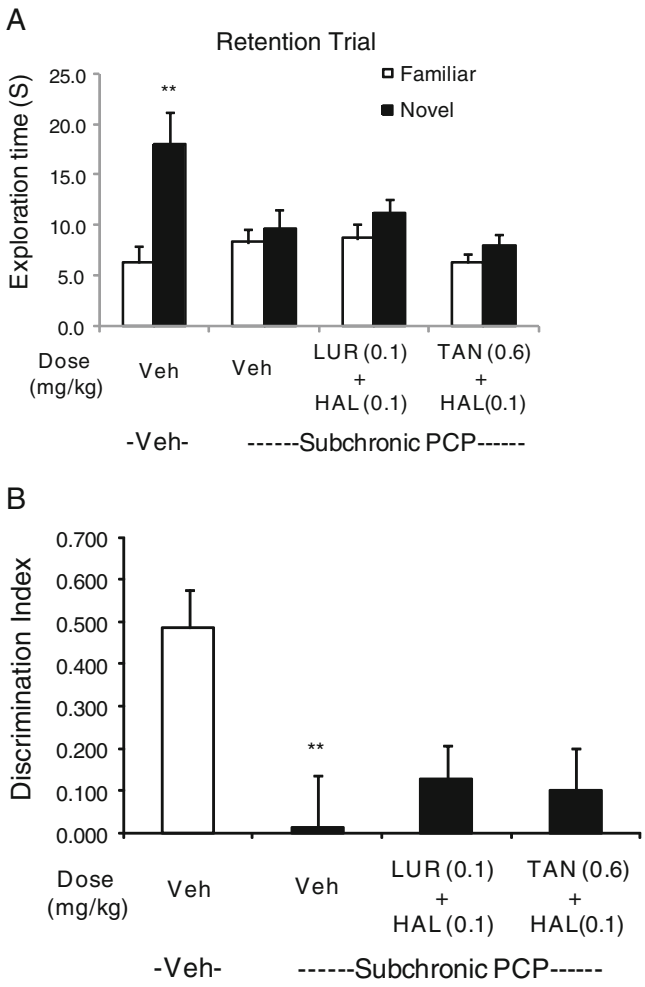

Fig. 6 Effect of lurasidone (*LUR*, 0.1 mg/kg) plus haloperidol (*HAL*, 0.1 mg/kg) and tandospirone (*TAN*, 0.6 mg/kg) plus HAL (0.1 mg/kg) on PCP-induced cognitive impairment in NOR test. **a** Effect of LUR (0.1 mg/kg) plus HAL (0.1 mg/kg) and TAN (0.6 mg/kg) plus HAL (0.1 mg/kg) on exploration of a novel and a familiar object in the retention trial in NOR test. Data are shown as mean ± S.E.M. (n=7–9 per group). **p<0.01, significant difference in time spent exploring the novel compared with the familiar object. **b** Effect of LUR (0.1 mg/kg) plus HAL (0.1 mg/kg) and TAN (0.6 mg/kg) plus HAL (0.1 mg/kg) on the DI. Data are shown as mean ± S.E.M. (n=7–9 per group). **p< 0.01, significant decrease in DI compared with the vehicle group

potent 5-HT_{1A} partial agonist properties (Ishibashi et al. 2010), to reverse the deficit in NOR produced by subchronic PCP. Co-administration of sub-effective doses of tandospirone and lurasidone also reversed the impairment in PCP-treated rats, but no such synergy was noted with the combination of sub-effective doses of buspirone, a less efficacious 5-HT_{1A} agonist than tandospirone. The combination of sub-effective doses of tandospirone with pimavanserin, a selective 5-HT_{2A} inverse agonist, did not ameliorate the PCP-induced NOR deficit. On the other hand, co-administration of 0.1 mg/kg haloperidol, a D_2 antagonist, blocked the ameliorating effect of both 0.6 mg/kg tandospirone and 0.1 mg/kg lurasidone, consistent with previous evidence that blockade of D_2 receptors beyond a limited extent has negative consequences on reversing the effect of atypical APDs on the PCP-induced deficit (Snigdha et al. 2010).

Deficits in declarative memory are among the most common and severe of all cognitive impairments in schizophrenia (Stone and Hsi 2011). The subchronic PCP-induced deficit in NOR has been suggested to provide a useful animal model of declarative memory (see Meltzer et al. 2011 for review). Some clinical studies indicate that atypical APDs which are 5-HT_{2A}/D_2 antagonists and direct or indirect 5-HT_{1A} agonists improve declarative memory in schizophrenic patients, not due to a practice effect (Meltzer and Sumiyoshi 2008). It has been reported that atypical APDs, but not the typical APD, haloperidol, reverse the NOR deficit produced by the subchronic PCP treatment employed here (Grayson et al. 2007; Snigdha et al. 2010; Horiguchi et al. 2011a; 2011b). The findings of the present study, along with these previous findings, provide additional support for the conclusion that this model can differentiate between typical and atypical APDs and may be valuable for identifying the mechanisms relevant to the etiology and treatment of cognitive dysfunction in schizophrenia. A potential limitation of this study is that the same animals were used for up to four times, separated by a 7-day washout period, raising the possibility of a carryover effect. The 7-day interval should be sufficient to wash out any residual drug. This design, which has been used in previous studies, requires the use of fewer animals for research purposes and is, thus, both more humane and cost-effective. The procedure has previously been validated by conducting the same experiment as the first in one group of animals and the last in another group of animals and finding no difference in results (Snigdha et al. 2010). This indicates that this subchronic PCP treatment regimen (2 mg/kg, i.p., twice a day for 7 days) induces a stable and persistent impairment in NOR and that single doses of agents only temporarily reverse the adverse effects of subchronic PCP (Grayson et al. 2007; Snigdha et al. 2010).

This is the first report describing the effects of 5-HT_{1A} partial agonists on the subchronic PCP-induced NOR deficit. Both tandospirone and F15599 significantly improved the PCP-induced NOR deficit. Furthermore, the efficacy of tandospirone was antagonized by the 5-HT_{1A} antagonist, WAY100635, suggesting that stimulation of 5-HT_{1A} receptors is the likely basis for the improvement produced by 5-HT_{1A} agonists in the PCP-induced NOR deficit. Our results are in accordance with other studies showing that 5-HT_{1A} agonists improve PCP- or amphetamine-induced cognitive impairment (Stevens et al. 2006; Winstanley et al. 2003). Depoortère et al. (2010) reported that F15599 partially alleviated PCP-induced impairment in working and reference memory and cognitive flexibility in a rat reversal learning task and the post-

synaptic preference of F15599 could be important for its procognitive profile. Further studies will be needed to clarify the effect of pre- and post-synaptic 5-HT_{1A} receptors on the cognitive impairment of schizophrenia. The atypical APDs, aripiprazole and perospirone, both 5-HT_{1A} receptor partial agonists, improved the PCP-induced NOR deficit in ICR mice, and the ameliorating effect of these atypical APDs was also blocked by WAY100635 (Hagiwara et al. 2008; Nagai et al. 2009). Moreover, Snigdha and Neill (2008) reported that PCP-induced deficits in social behaviors were reversed by aripiprazole and WAY100635 prevented the reversal of social behavior deficits observed with aripiprazole. F15063, a compound with 5-HT_{1A} agonism, attenuated PCP-induced social interaction impairments owing to its 5-HT_{1A} agonist activity (Depoortère et al. 2007). Our results support the view that 5-HT_{1A} agonism is an effective means to attenuate the action of PCP (Depoortère et al. 2007). The clinical relevance of our findings is supported by previous studies from this laboratory (see "Introduction"). By contrast, tandospirone has been reported to impair explicit memory function in demented patients (Yasuno et al. 2003). The results reported here suggest that the combined administration of tandospirone with lurasidone may be a means to potentiate their ability to improve cognitive impairment in patients with schizophrenia.

Lurasidone, a novel atypical APD which is a 5-HT_{1A} partial agonist (Ishibashi et al. 2010; Meyer et al. 2009), has been previously shown to improve the PCP-induced NOR deficit in female rats (Horiguchi et al. 2011a; 2011b). We have now found that WAY100635 blocked the effect of lurasidone to improve the PCP-induced NOR deficit. Moreover, a sub-effective dose of tandospirone in combination with a sub-effective dose of lurasidone, but not with the 5-HT_{2A} inverse agonist, pimavanserin, improved the PCP-induced NOR deficit. The dose of pimavanserin used in these studies, a dose that achieves nearly complete 5-HT_{2A} receptor occupancy (Vanover et al. 2006), was based on previous microdialysis experiments showing the potentiation of DA and ACh efflux in the rat brain when administered in combination with subthreshold doses of APDs (Kuroki et al. 1999; Ichikawa et al. 2002; Li et al. 2005). These results demonstrate that 5-HT_{1A} agonism contributes to the ability of lurasidone to ameliorate the subchronic PCP-induced deficit on NOR. Clinically, the combination of a sub-effective dose of lurasidone, or perhaps other atypical APDs, with a 5-HT_{1A} partial agonist may permit lower doses of the atypical APD, thereby decreasing the side effect burden associated with a full dose.

It has been reported that 5-HT_{1A} agonism produces functional effects similar to those produced by 5-HT_{2A} antagonism (Meltzer and Huang 2008 for review). The results of this study indicate that the activation of 5-HT_{1A} receptors is sufficient to the subchronic PCP-induced deficits in NOR. In contrast, we have recently reported that 5-HT_{2A} inverse agonists do not improve the PCP-induced NOR deficits by itself but can restore the ability of a sub-effective dose of atypical APDs to attenuate these deficits (Snigdha et al. 2010). These results are in accordance with the microdialysis study. Tandospirone and F15599 enhanced cortical DA efflux which may contribute to improve cognition (Kuroki et al. 1999; Yoshino et al. 2002; Lladó-pelfort et al. 2010). On the other hand, 5-HT_{2A} inverse agonists alone have no effect on basal DA efflux but can regulate DA efflux when combined with the blockade of D_2 (Bonaccorso et al. 2002; Li et al. 2005). As previously mentioned, subchronic treatment with PCP increased 5-HT_{1A} receptor binding in the medial–prefrontal and dorsolateral–frontal cortex and decreased D_1 receptor density in the medial and lateral caudate-putamen, with no changes in any other brain regions nor any changes in 5-HT_{2A} or D_2 receptors in any brain region (Choi et al. 2009). The 5-HT_{1A} effect, which parallels the post-mortem data cited in the "Introduction", suggest the possibility that subchronic PCP treatment impairs cortical 5-HT release, leading to an upregulation of post-synaptic 5-HT_{1A} receptors, which may contribute to the efficacy of 5-HT_{1A} agonists in this model. It is noteworthy that the efficacy of clozapine to prevent PCP-induced desynchronization of PFC is dependent upon 5-HT_{1A} activation, but not 5-HT_{2A} blockade (Kargieman et al. 2011), a further evidence for the important role of 5-HT_{1A} agonism to ameliorate hypoglutamatergic deficits. The results reported here also indicate that the combination of 5-HT_{1A} partial agonism and 5-HT_{2A} antagonism is insufficient to reverse the PCP-induced NOR deficit. This indicates that some other component of atypical APDs other than 5-HT_{1A} partial agonism is needed to reverse the effect of subchronic PCP. We previously reported that haloperidol, 0.1 mg/kg, blocked the ability of risperidone to reverse the PCP-induced deficit in NOR (Snigdha et al. 2010). Similarly, the same dose of haloperidol also blocked the effect of lurasidone and tandospirone to improve NOR, indicating the importance of avoiding excessive blockade of D_2 receptors with 5-HT_{1A} agonists or atypical APDs that rely on serotonergic mechanisms for their efficacy.

While tandospirone clearly improved the PCP-induced NOR deficit, buspirone, 0.3 mg/kg, partially improved this deficit but a 1-mg/kg dose did not. Moreover, 0.1 mg/kg buspirone in combination with a sub-effective dose of lurasidone did not ameliorate the NOR deficit. These results parallel those from clinical studies in patients with schizophrenia, which reported that tandospirone (Sumiyoshi et al. 2001a; 2001b), but not buspirone, enhanced some cognitive domains, e.g., verbal learning and memory and executive function (Sumiyoshi et al. 2007; Piskulić et al. 2009). The differences between tandospirone and buspirone to affect the

PCP-induced deficit in NOR may be related to differences in intrinsic activity as 5-HT_{1A} receptor agonists. Tandospirone and F15599 are nearly full agonists at 5-HT_{1A} receptors (Tanaka et al. 1995; Newman-Tancredi et al. 1998; Maurel et al. 2007; Newman-Tancredi et al. 2009), whereas buspirone is a weaker 5-HT_{1A} partial agonist (Newman-Tancredi et al. 2009).

High doses of tandospirone (0.6 mg/kg) and buspirone (1 mg/kg) increased the total exploration time in both trials. A similar effect has been reported with pimavanserin and LY379268, a mGluR2/3 agonist (Snigdha et al. 2010; Horiguchi et al. 2011a). Additional studies are necessary to clarify the effect of 5-HT_{1A} agonists, 5-HT_{2A} inverse agonists, and mGluR2/3 agonists on exploration time in subchronic PCP-treated rodents.

The present study also evaluated the effect of the 5-HT_{1A} antagonist WAY100635 on NOR, by itself, in vehicle- and PCP-treated rats. WAY100635 alone did not affect the exploration times of vehicle-treated rats and did not improve the NOR deficit induced by PCP. Previous studies of the effects of WAY100635 in other animal models of cognitive function have produced conflicting results. Consistent with the findings of the present study, WAY100635 had no effect on PCP-induced NOR deficit in ICR mice and female rats (Hagiwara et al. 2008; McLean et al. 2009; Nagai et al. 2009). On the other hand, some previous animal studies have indicated that 5-HT_{1A} antagonists have beneficial effects on cognitive impairment induced by MK-801 or scopolamine (Pitsikas et al. 2003; Boast et al. 1999; Wedzony et al. 2000; Hirst et al. 2008). These conflicting results could be due to differences in mechanisms of MK-801 and scopolamine versus PCP and/or the acute administration of scopolamine and MK-801 in contrast to the subchronic PCP regimen of this study.

In conclusion, these results indicate that 5-HT_{1A} agonism is required for the amelioration of the PCP-induced impairment of NOR by some, but not all, atypical APDs which are 5-HT_{2A}/D_2 antagonists. Further, some 5-HT_{1A} agonists may be useful for treating cognitive deficits in schizophrenia.

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Conflicts of interest Herbert Y. Meltzer: consultant to Cypress, Dainippon Sumitomo Pharma, Janssen, Merck, and Pfizer and shareholder of SureGene, Bio Vail, and ACADIA. Masakuni Horiguchi: employed as a research scientist by Dainippon Sumitomo Pharma.

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