Behavioural Brain Research 301 (2016) 132–141

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Prolonged reversal of the phencyclidine-induced impairment in novel object recognition by a serotonin (5-HT)$_{1A}$-dependent mechanism

Masakuni Horiguchi[a,b,c], Masanori Miyauchi[a,c], Nichole M. Neugebauer[a], Yoshihiro Oyamada[a,c], Herbert Y. Meltzer[a,b,*]

[a] Division of Psychiatry and Behavioural Sciences, Northwestern University Feinberg School of Medicine, Chicago IL 60611, USA
[b] Division of Psychopharmacology, Vanderbilt University Medical Center, Nashville TN 37212, USA
[c] Sumitomo Dainippon Pharma Co., Ltd., Osaka 564-0053, Japan

HIGHLIGHTS

- Subchronic tandospironeinduced prolonged reversalof PCP-induced NOR deficit.
- Subchronic lurasidone, an atypical APD, induced prolonged reversal of NOR deficit.
- WAY100635, a5-HT1A antagonist, blocked the prolonged reversal of NOR by lurasidone.
- The reversal of the NOR deficit by lurasidone and tandospirone lasts several weeks.
- Lurasidone and tandospirone may induce metaplastic synaptic changes.

ARTICLE INFO

Article history:
Received 1 July 2015
Received in revised form 27 August 2015
Accepted 30 August 2015
Available online 3 September 2015

Keywords:
Phencyclidine
Novel object recognition
5-HT$_{1A}$
Lurasidone
Tandospirone
Cognitive impairment
Schizophrenia

ABSTRACT

Many acute treatments transiently reverse the deficit in novel object recognition (NOR) produced by subchronic treatment with the *N*-methyl-D-aspartate receptor non-competitive antagonist, phencyclidine (PCP), in rodents. Treatments which restore NOR for prolonged periods after subchronic PCP treatment may have greater relevance for treating the cognitive impairment in schizophrenia than those which restore NOR transiently. We examined the ability of post-PCP subchronic lurasidone, an atypical APD with potent serotonin (5-HT)$_{1A}$ partial agonism and subchronic tandospirone, a selective 5-HT$_{1A}$ partial agonist, to enable prolonged reversal of the subchronic PCP-induced NOR deficit. Rats treated with subchronic PCP (2 mg/kg, twice daily for 7 days) or vehicle, followed by a 7 day washout period were subsequently administered lurasidone or tandospirone twice daily for 7 days (day 15–21), and tested for NOR weekly for up to two additional weeks. Subchronic lurasidone (1, but not 0.1 mg/kg) or tandospirone (5, but not 0.6 mg/kg) significantly reversed the PCP-induced NOR deficit at 24 h and 7days after the last injection, respectively. The effect of lurasidone persisted for one more week (day 36, 14 days after the last lurasidone dose), while tandospirone-treated rats were able to perform NOR at 7, but not 14, days after the last tandospirone dose. Co-administration of WAY100635 (0.6 mg/kg), a 5-HT$_{1A}$ antagonist, with lurasidone, blocked the ability of lurasidone to restore NOR, suggesting that 5-HT$_{1A}$ receptor stimulation is necessary for lurasidone to reverse the effects of PCP. The role of dopamine, GABA and the MAPK/ERK signalling pathway in the persistent, but not indefinite, restoration of NOR is discussed.

1. Introduction

Deficits of variable severity in multiple domains of cognition, including executive function, attention, declarative, working, and semantic memory are present in most patients with schizophrenia and contribute to impaired work and social function [1,2]. The

Abbreviations: ANOVA, analyses of variance; APD, atypical antipsychotic drug; CIAS, cognitive impairment associated with schizophrenia; DA, dopamine; DI, discrimination index; DMSO, dimethyl sulfoxide; Glu, glutamate; HIP, hippocampus; ip, intraperitoneally; ITI, intertrial interval; LE, long-Evans; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; NMDAR, *N*-methyl-D-aspartate receptor; NOR, novel object recognition; PCP, phencyclidine; PFC, prefrontal cortex; SEM, standard error of the mean; 5-HT, 5-hydroxytryptamine.

* Corresponding author at: Division of Psychiatry and Behavioural Sciences, Northwestern University Feinberg School of Medicine, 303 E, Chicago Avenue Ward 7-002, Chicago, IL 60611, USA. Tel.:+1 312 503 0309; fax: +1 312 503 0466.
http://dx.doi.org/10.1016/j.bbr.2015.08.040
0166-4328/

E-mail address: h-meltzer@northwestern.edu (H.Y. Meltzer).

cognitive impairment associated with schizophrenia (CIAS) precedes the onset of psychosis, is persistent, and gradually worsens during chronic stages of the illness [2]. There is evidence that some of the atypical APDs which are more potent serotonin (5-HT)$_{2A}$ than dopamine (DA) D_2 antagonists, including the atypical APD, lurasidone [3–5], are more effective than typical APDs in attenuating some of these deficits [6–9], although not all studies are in accord [10]. With the exception of amisulpride, atypical APDs are direct or indirect 5-HT$_{1A}$ agonists, which may contribute to their cognitive enhancing effects [11,12]. Consistent with this, tandospirone, a 5-HT$_{1A}$ partial agonist [13], with anxiolytic properties [14], has been reported to augment the efficacy of antipsychotic drugs to improve CIAS [15].

The development of novel treatments that can improve some domains of cognition in schizophrenia as adjunctive therapy to antipsychotic drugs is currently a major goal of pharmacologic research [16]. Alterations in glutamatergic and GABAergic neurotransmission have been postulated to be a major cause of CIAS [17–19], making treatments that might address any such abnormalities major targets for adjunctive treatment of CIAS as add-ons to APDs [8]. Important evidence that a deficit in glutamatergic function may be the basis for CIAS is that noncompetitive *N*-methyl-D-aspartate receptor (NMDAR) antagonists, e.g., phencyclidine (PCP), dizocilpine (MK-801), and ketamine induce schizophrenia-like cognitive impairment in healthy subjects [20,21]. This has stimulated the study of the effects that NMDAR antagonists have on cognitive function in rodents and monkeys as an animal model of CIAS [22].

The administration of acute and, particularly, subchronic PCP, MK-801, or ketamine to rodents produces impairment in novel object recognition (NOR), a possible model of the declarative memory deficit in CIAS [23–25]. NOR is principally dependent upon hippocampal and prefrontal cortical function [25], interactive brain regions thought to be critically important to the pathophysiology of CIAS [26]. Acute administration of atypical APDs (e.g., amisulpride, clozapine, lurasidone, olanzapine, risperidone), but not the typical APD, haloperidol, has been reported to reverse the subchronic PCP-induced impairment rat NOR [23,27–29]. We recently reported that a single dose of several selective 5-HT$_{1A}$ agonists, tandosprione [13] and F15599 [30], also reverses the subchronic PCP-induced NOR deficit. Further, tandospirone potentiated the ability of a subeffective dose of lurasidone to ameliorate the subchronic PCP-induced NOR deficit [31]. Tandospirone alone, and in combination with the atypical APD, blonanserin, has been reported to improve exectuive function in marmosets [32]. Finally, the combination of subeffective doses of tandospirone, pimavanserin, a 5-HT$_{2A}$ inverse agonist, and haloperidol, a D_2 antagonist, but not any two of these three mechanisms, can prevent the deficit in NOR produced by subchronic PCP treatment and acute administration of all three prior to acquistion can restore NOR in subchronic PCP-treated rats [33]. Elsworth et al. reported that subchronic PCP decreased the number of excitatory spine synapses in layers II, III and V of rat PFC and that olanzapine, 1.5 mg/kg, i.p., acutely, restored the spines at 90 min after olanzapine [34]. Oral administration of olanzapine, 8 mg/kg, for three weeks, starting at one week after the last PCP injection, with sacrifice immediately after the last dose of olanzapine, demonstrated restoration of normal spine density. However, there are no reports which show prolonged reversal of the subchronic PCP-induced deficit in NOR post-PCP withdrawal following repeated administration of atypical APDs, 5-HT$_{1A}$ agonists, or other mechanisms. Prolonged reversal would be expected to have greater translational value than transient reversal.

Lurasidone has DA D_2, 5-HT$_{2A}$, and 5-HT$_7$ receptor antagonist properties, as well as potent 5-HT$_{1A}$ partial agonism [3,35]. Acute treatment with lurasidone ameliorates the subchronic PCP-induced NOR deficits in a 5-HT$_{1A}$ and 5-HT$_7$ dependent manner [23,31]. We reported that co-administration of lurasidone with PCP (twice daily for 7 days) prevented the NOR deficit induced by subchronic PCP [31]. The preventive effect of lurasidone was blocked by the selective 5-HT$_{1A}$ agonist, WAY100635 [36,37], further evidence for the importance of 5-HT$_{1A}$ receptor stimulation in the NOR deficit produced by subchronic PCP [31]. We have reported that augmentation of APDs with tandospirone improved executive function, verbal learning, and memory [38–40]. However, it is important to note that there is evidence that WAY100635-induced 5-HT$_{1A}$ receptor antagonism improves, while 5-HT$_{1A}$ agonism impairs, memory and learning in rodents [41,42], possibly suggesting that the effects of 5-HT$_{1A}$ receptor signalling on learning, and memory may have differential outcomes in normal compared to subchronic PCP-treated animals. However, the effects of 5-HT$_{1A}$ agonism to improve, and for WAY100635 to impair, cognitive function has also been noted in enhancing the ability of the mGluR2/3 agonist, LY379268, to block MK-801-induced impairment in rat NOR [43].

In order to test this model's ability to identify treatments for CIAS that would be enduring, the principal goal of this study was to determine whether subchronic treatment with lurasidone or tandospirone post-PCP induces prolonged reversal of the subchronic PCP-induced NOR deficit, and if so, for how long, as the deficit in NOR produced by subchronic PCP is indefinite in rats [24] and mice [25]. We determined whether the doses of these drugs needed for prolonged reversal were the same as those required for acute reversal. Further, we determined whether the ability of lurasidone to produce prolonged reversal of the subchronic PCP-induced deficit was dependent on signalling through the 5-HT$_{1A}$ receptor by co-administration of WAY100635, a 5-HT$_{1A}$ antagonist, prior to lurasidone.

2. Material and methods

2.1. Animals

One hundred two female Long-Evans (LE) rats (8 or 9 weeks old) (Harlan Sprague Dawley, Inc, Indianapolis, IN, USA) were used. 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 National Institutes of Health guidelines for animal research and approved by the Animcal Care Committee at Northwestern University and the Vanderbilt animal committee regulations.

2.2. Drugs

Lurasidone and tandospirone were provided by Sumitomo Dainippon Pharma (Osaka, Japan). WAY100635 was a gift from Wyeth Laboratories (Philadelphia, PA, USA). 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 weight.

2.3. Drug treatment

LE rats were randomly assigned to two treatment groups and were treated with either vehicle (saline, i.p.) or PCP (2 mg/kg, i.p.) twice daily for 7 days (day 1–7). Subsequently, animals were given a 7-day washout period (day 8–14) during which they remained undisturbed in the home cage. To study the subchronic effects, lurasidone (0.1 and 1 mg/kg), tandospirone (0.6 and 5 mg/kg), and WAY100635 (0.6 mg/kg) were then administrated to the PCP-treated rats twice daily for 7 consecutive days (day 15–21; Fig. 1).