Behavioural Brain Research 238 (2013) 36–43

Contents lists available at SciVerse ScienceDirect

Behavioural Brain Research

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

Research report

D_1 receptor agonists reverse the subchronic phencyclidine (PCP)-induced novel object recognition (NOR) deficit in female rats

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HIGHLIGHTS

- D_1 agonist, SKF38393, improved the NOR deficit induced by subchronic PCP in rats.
- The effect of D_1 agonism on this NOR deficit follows an inverted U-shape curve.
- 5-HT_{1A} and mGluR2/3 signaling may contribute to the efficacy of D_1 agonism.

ARTICLE INFO

Article history:
Received 21 February 2012
Received in revised form
14 September 2012
Accepted 18 September 2012
Available online 24 September 2012

Keywords:
Phencyclidine
Novel object recognition
Schizophrenia
D_1 receptor
SKF38393
Cognition

ABSTRACT

Development of dopamine (DA) D_1 receptor agonists is a priority to improve cognitive impairment in schizophrenia (CIS). This study examined the dose–response relationship of the selective D_1 agonist, SKF38393 (0.5–40 mg/kg), to reverse the deficit in novel object recognition (NOR), an analog of declarative memory in man, produced by subchronic phencyclidine (PCP), an N-methyl-D-aspartate (NMDA) receptor non-competitive antagonist, and the ability of the D_1 antagonists, SCH23390 (0.05 mg/kg) and SKF83566 (0.15 mg/kg), to impair NOR in normal Long-Evans female rats. We also examined the ability of tandospirone, a serotonin (5-HT)$_{1A}$ receptor partial agonist, and LY341495, a mGluR2/3 receptor antagonist, to potentiate or block the effects of SKF38393 on NOR, respectively. SKF38393 reversed the persistent NOR deficit produced by subchronic PCP; the dose–response curve for SKF38393 was an inverted U-shape, with the peak effect at 6 mg/kg. SKF83566 and SCH23390 impaired NOR in normal rats. Co-administration of sub-effective doses of SKF38393 (0.25 mg/kg) and tandospirone (0.2 mg/kg) improved the PCP-induced NOR deficit, while LY341495 (1 mg/kg) blocked the ameliorating effect of SKF38393 (6 mg/kg), respectively. These data provide the first evidence that the reversal of the PCP-induced NOR deficit by D_1 agonism has an inverted U-shaped dose–response curve and that 5-HT_{1A} and mGluR2/3 receptor signalling facilitates the efficacy of D_1 agonism to improve these deficits. These data suggest that although D_1 agonists may be useful to improve CIS, these agents, particularly higher doses, may also worsen cognitive function in some patients, because of an inverted U-shaped dose response curve.

1. Introduction

Moderate-severe deficits in multiple domains of cognition, including declarative memory, are present in schizophrenia [1–4]. Atypical antipsychotic drugs (APDs), which are often more potent serotonin (5-HT)$_{2A}$ than dopamine (DA) D_2 antagonists, are effective to partially ameliorate some of these deficits in some patients There is controversy as to whether the effect of the atypical APDs to improve cogntion in schizophrenia is equivalent to, or superior to, that of the typical APDs. For example, some measures of cognitive function were improved to an equivalent extent in a randomized double-blind study of patients with schizophrenia, after switching to olanzapine, quetiapine or risperidone, all of which

Abbreviations: ANOVA, analysis of variance; APD, antipsychotic drugs; CIS, cognitive impairment in schizophrenia; DA, dopamine; DI, discrimination index; LE, Long-Evans; mGluR2/3, metabotropic glutamate 2/3 receptor; NMDA, N-methyl-D-aspartate; NOR, novel object recognition; PCP, phencyclidine; PFC, prefrontal cortex; 5-HT, serotonin.

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http://dx.doi.org/10.1016/j.bbr.2012.09.030

are atypical APDs, or to perphenazine, a typical APD [5], but in another well-designed randomized trial in chronic schizophrenia patients, global cognitive function was reported to improve significantly more with olanzapine or risperidone treatment than with haloperidol, a typical APD [8], although the effect is modest in most [3,6–8].

Acute or subchronic administration of the N-methyl-D-aspartate (NDMA) receptor non-competitive antagonists phencycline (PCP) and dizocilpline (MK-801) have been reported to produce impairments in visual and learning memory, attention, reasoning and problem solving, working memory, and social cognition in rodents [9,10]. Hypoglutamatergic function in the frontal cortex and hippocampus is postulated to be a major factor in the pathophysiology of cognitive impairment in schizophrenia (CIS) [11]. The main evidence for a deficit in glutamatergic function contributing to CIS is that PCP, as well as two other NMDA receptor antagonists, e.g. dizocilipine (MK-801) and ketamine, induce schizophrenia-like cognitive impairments in healthy subjects [12,13] and increase psychosis in patients with schizophrenia [14,15]. Post-mortem and genetic studies also support this hypothesis [16]. 5-HT_{2A} inverse agonists, e.g. M100907 or pimavanserin, by themselves, did not improve the PCP-induced NOR deficit in rodents, but they did potentiate the ameliorating effects of atypical APDs [9,17]. 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 serotonin (5-$HT)_{1A}$ agonist, tandospirone, as well as the metabotropic glutamate 2/3 receptor (mGluR2/3) agonist, LY379268 [18,19]. Moreover, the mGluR2/3 antagonist, LY341495 blocked the effect of clozapine to improve subchronic PCP-induced NOR deficit [18].

D_1 receptor stimulation has been hypothesized to improve cognitive impairment in schizophrenia (CIS) [20–22]. D_1 receptors are more abundant than D_2 receptors in the prefrontal cortex (PFC) and have been implicated in working memory function in non-human primates, a key component of CIS [23,24]. Okubo et al. [25] reported downregulation of D_1 binding in the PFC of drug naive schizophrenic patients; this decrease was correlated with the severity of cognitive dysfunction and negative symptoms. Kosaka et al. [26] replicated the decrease in D_1 receptor density in the PFC of patients with chronic schizophrenia, but another study did not [27]. It is noteworthy that subchronic treatment with PCP using the same schedule of administration as utilized in this study, has been reported to decrease D_1 receptor binding and increase 5-HT_{1A} receptor binding in the medial-prefrontal and dorsolateral frontal cortex [28]. It has been reported that the DA D_1 antagonist SCH23390 can also block the ability of atypical APDs to facilitate pyramidal neuron NMDA receptor currents in rat prefrontal cortex (PFC), a possible basis for their ability to improve cognition [29]. The facilitation of cortical NMDA receptor-induced current by the atypical APD, asenapine, was also shown to be blocked by SCH23390 [30].

Stimulation of DA D_1 receptors in the PFC generally produces an 'inverted U-shape' dose–response curve [31]. Stimulation of D_1 DA receptor facilitates postsynaptic NMDA current, thereby increasing action potential firing in cortical layer V pyramidal neurons, whereas high concentrations of DA or D_1 agonists reduces NMDA-evoked current and postsynaptic potentials in pyramidal neurons [32]. In mice, rats and monkeys performing PFC-dependent working memory tasks, activation of D_1 receptors produces an inverted U-shape dose response curve, where either too little [24,33,34] or too much [35,36] D_1 receptor stimulation impairs performance. Thus, rat working memory is impaired both by blockade of D_1 receptors with SCH23390, a D_1 antagonist, as well as high doses of the D_1 agonist SKF81297 [36]. The marked impairment on working memory tasks in aged monkeys is improved by low doses of the selective D_1 agonist SKF81297 whereas higher doses worsened performance [37]. This inverted U-shape dose response has also been observed in humans performing PFC cognitive tasks [38,39]. Previous studies have demonstrated the procognitive effect of D_1 agonists on NMDA receptor antagonist-induced cognitive deficits in animal models without examination of the dose–response relationship (see Section 4). There have been no prior studies to our knowledge of the effect of D_1 receptor antagonists on NOR in normal rats.

The aim of this study was to determine the attenuating effect of SKF38393, a selective D_1 partial agonist, on the impairment in NOR. These data could be for value in planning any future D_1 agonist studies in man. We predicted that D_1 receptor blockade would induce an NOR deficit in normal rats. Finally, 5-HT_{1A} and mGluR2/3 receptor stimulation has been shown to contribute to reversal of subchronic PCP induced NOR deficit [18,19]. We predicted that D_1 receptor agonism would augment the ability of a 5-HT_{1A} partial agonist to reverse the effect of subchronic PCP on NOR while an mGluR2/3 antagonist would block the effect of a D_1 agonist to do the same.

2. Material and methods

2.1. Animals

Forty-three female Long-Evans (LE) rats (8–9 weeks old, Harlan Sprague Dawley, Inc, Indianapolis, IN, USA) were used in the NOR experiments 1–3 (rat group 1). Twenty-six rats were used for NOR experiments 4 (rat group 2). 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.

2.2. Drugs

Tandospirone ((3aR,4S,7R,7aS)-rel-Hexahydro-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-4,7-methano-1H-isoindole-1,3(2H)-dione citrate) was provided by Dainippon Sumitomo Pharma (Osaka, Japan). LY341495 ((2S)-2-Amino-2-[(1S,2S)-2-carboxycycloprop-1-yl]-3-(xanth-9-yl) propanoic acid), SCH23390 ((R)-(+)-7-Chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride), SKF38393 ((±)-1-Phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol hydrobromide) and SKF83566 (8-Bromo-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepin-7-ol hydrobromide) were obtained from Tocris Bioscience (Ellisville, MO, USA). PCP was supplied as a generous gift from the National Institute of Drug Abuse. PCP, SKF83566 and tandospirone were dissolved in distilled water. SCH23390 and SKF38393 were dissolved in saline. LY341495 was dissolved in a small amount of 0.1 M sodium hydroxide and then diluted with saline. All drugs or vehicle were administered intraperitoneally (i.p.), at a volume of 1 mL/kg body weight. LY341495 and SCH23390 were administrated 45 min before the NOR test and all other drugs were administrated 30 min before the NOR test.

2.3. Drug treatment

LE rats in group 1 were randomly assigned to two treatment groups: 9 were treated with vehicle (saline, i.p.) and the remainder were treated with PCP (2 mg/kg i.p.) twice daily for 7 days. Subsequently, animals were given a 7-day washout period prior to NOR testing [9,40]. Each rat was tested three 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 affect results when compared to testing rats only once and is preferred on humane grounds [9]. LE rats in group 2 were not treated with PCP and each rat was tested one time in the NOR paradigm. The criterion for continuing to test rats was exploration time in the acquisition and retention phases to either of two objects $\geq$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 6–9 rats.

2.4. NOR test

Testing was carried out according to a previously validated method [9,40]. 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.