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Research report

Combined serotonin (5-HT)$_{1A}$ agonism, 5-HT$_{2A}$ and dopamine D$_2$ receptor antagonism reproduces atypical antipsychotic drug effects on phencyclidine-impaired novel object recognition in rats

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HIGHLIGHTS

- Novel object recognition (NOR) in rats models cognitive impairment in schizophrenia (CIS).
- Subchronic (sc)phencyclidine (PCP) produces NOR deficit, a model of CIS, in rats.
- Atypical, but not typical, antipsychotic drugs (AAPDs), restore or prevent the scPCP NOR deficit.
- Combined 5-HT1A agonism, 5-HT2A and D2 antagonism rescues and prevents the scPCP NOR deficit.
- The combination of these three actions may enable the efficacy of most AAPDs to improve CIS.

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ABSTRACT

Subchronic administration of an N-methyl-D-aspartate receptor (NMDAR) antagonist, e.g. phencyclidine (PCP), produces prolonged impairment of novel object recognition (NOR), suggesting they constitute a hypoglutamate-based model of cognitive impairment in schizophrenia (CIS). Acute administration of atypical, e.g. lurasidone, but not typical antipsychotic drugs (APDs), e.g. haloperidol, are able to restore NOR following PCP (acute reversal model). Furthermore, atypical APDs, when co-administered with PCP, have been shown to prevent development of NOR deficits (prevention model). Most atypical, but not typical APDs, are more potent 5-HT$_{2A}$ receptor inverse agonists than dopamine (DA) D$_2$ antagonists, and have been shown to enhance cortical and hippocampal efflux and to be direct or indirect 5-HT$_{1A}$ agonists in vivo. To further clarify the importance of these actions to the restoration of NOR by atypical APDs, sub-effective or non-effective doses of combinations of the 5-HT$_{1A}$ partial agonist (tandospirone), the 5-HT$_{2A}$ inverse agonist (pimavanserin), or the D$_2$ antagonist (haloperidol), as well as the combination of all three agents, were studied in the acute reversal and prevention PCP models of CIS. Only the combination of all three agents restored NOR and prevented the development of PCP-induced deficit. Thus, this triple combination of 5-HT$_{1A}$ agonism, 5-HT$_{2A}$ antagonism/inverse agonism, and D$_2$ antagonism is able to mimic the ability of atypical APDs to prevent or ameliorate the PCP-induced NOR deficit, possibly by stimulating signaling cascades from D$_1$ and 5-HT$_{1A}$ receptor stimulation, modulated by D$_2$ and 5-HT$_{2A}$ receptor antagonism.

1. Introduction

Deficits of variable severity in multiple domains of cognition, including declarative memory, in schizophrenia, represent a major unmet treatment [1–3]. Animal models of cognitive impairment in schizophrenia (CIS) have been widely used to study the pathophysiology of CIS and developing treatments to prevent or ameliorate CIS. It has been suggested that atypical antipsychotic drugs (APDs) are more effective than typical APDs to attenuate some of the

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cognitive deficits in schizophrenia [1,4–8]. An influential report to the contrary [9] has been challenged because of a failure of that study to take into account the deleterious effect of tardive dyskinesia (TD) on the ability of atypical APDs to improve CIS and non-inclusion of TD patients in the group treated with the typical APD, perphenazine [10]. Some individuals with schizophrenia have large, clinically significant improvements in some domains of cognition e.g. declarative memory, semantic memory, speed of processing and attention, following switching from typical to atypical APDs [7,11,12] inconsistent with the proposal that most of the reported improvement in cognition with APDs are due to practice effects [13]. Understanding the basis for APDs to produce limited improvement in CIS is important, as it could factiliate the discovery and development of even more effective treatments [1,14].

Atypical APDs have diverse pharmacologic profiles which differentiate them from each other and from typical APDs. The majority of the atypical APDs are more potent 5-HT_{2A} inverse agonists than dopamine (DA) D_2 antagonists [15]. Inverse agonists block constitutive activity as well as agonist-stimulated 5-HT_{2A} receptor stimulation. All of the atypical APDs which have high affinity for 5-HT_{2A} receptors relative to D_2 receptors are inverse agonists at 5-HT_{2A} receptors (see Meltzer and Huang [15]). The prototype of this class of atypical APDs is clozapine, which is particularly effective in treating positive symptoms in treatment resistant schizophrenia [16] and was the first atypical APD shown to improve some domains of CIS [6]. Other atypical APDs of this type include asenapine, iloperidone, lurasidone, olanzapine, quetiapine, risperidone, sertindole, and ziprasidone [17]. Clozapine, lurasidone, quetiapine, and ziprasidone are also direct acting 5-HT_{1A} partial agonists [15,18,19]. As will be discussed, other atypical APDs act as indirect 5-HT_{1A} agonists, as the diverse actions they exert, such as increasing cortical and hippocampal DA and acetylcholine (ACh) release as well as various behavioral effects, are blocked by 5-HT_{1A} selective antagonists [15,18,20–23]. This indirect 5-HT_{1A} agonism can result from the release of 5-HT, or possibly be secondary to diminished 5-HT_{2A} receptor stimulation [24].

There is extensive evidence supporting the study of the in vivo and in vitro effects of NMDAR antagonists as models for the hypoglutamatergic deficit in schizophrenia [25–27], which has been postulated to be a primary cause of CIS [14,28]. For example, non-competitive NMDAR antagonists induce schizophrenia-like cognitive impairment in healthy subjects [28,29]. Further, there is extensive post-mortem evidence for abnormalities in the dendritic morphology and spines of principal neurons at glutamate synapses in patients with schizophrenia [25,29,30], comparable to those reported after subchronic PCP treatment in rodents [31]. Analysis of the risk genes for schizophrenia also provides robust support for the hypoglutamate hypothesis [32,33].

Animal models of CIS are particularly important because of the difficulty of studying the biological basis for CIS and the mechanism of action of putative treatments for CIS in schizophrenia patients themselves. The novel object recognition (NOR) test in rodents, a non-rewarded, ethologically relevant paradigm, the basis of which is the spontaneous exploratory behavior of rodents, has been widely used to model declarative memory in humans [34,35]. It has been reported that acute, subchronic, prenatal, or perinatal treatment with an N-methyl-D-aspartate receptor (NMDAR) non-competitive antagonist, e.g. phencyclidine (PCP), dizocilpine (MK-801), or ketamine, produces acute or enduring deficits in NOR [27,36,37]. Administration of typical APDs such as haloperidol (0.03–0.3 mg/kg), perphenazine, or thioridazine prior to the acquistion trial, does not ameliorate the deficit produced by subchronic PCP treatment in rodents [38]. By contrast, single doses of all atypical APDs studied to date, including clozapine, lurasidone, olanzapine, and risperidone, administered systemically, 30–60 min prior to the acquisition trial, have been found to dose dependently reverse the subchronic PCP or MK-801-induced deficits in NOR in rats or mice [38–40].

The 5-HT_{2A} inverse agonists, M100907, 1 mg/kg, or pimavanserin (ACP103), 3 mg/kg, do not reverse the deficit in NOR produced by subchronic PCP in rats [38]. The combination of haloperidol plus pimavanserin or M100907 also is unable to reverse the deficit in NOR produced by subchronic PCP [38]. There is considerable evidence that 5-HT_{1A} receptor stimulation contributes to the ability of atypical APDs to enhance NOR in PCP-treated rats [21,41]. 5-HT_{1A} partial agonism is a characteristic feature of a number of atypical APDs, e.g. aripiprazole, clozapine, lurasidone, and ziprasidone [15,18,20–22]. The ability of clozapine to enhance electrical activity in cortical pyramidal neurons was shown to be mediated by its combined effects on 5-HT_{1A} receptors, phospholipase Cβ, and Ca^{2+}/calmdoulin-dependent protein kinase II [42].

Other atypical APDs lack intrinsic affinity for 5-HT_{1A} receptors, e.g. olanzapine and risperidone, but nevertheless, their ability to restore NOR in the PCP model of CIS is blocked by WAY100635, a selective 5-HT_{1A} antagonist [43]. Tandospirone, 0.3 mg/kg, a selective 5-HT_{1A} partial agonist at both pre- and post-synaptic 5-HT_{1A} receptors, and F15599, a selective post-synaptic 5-HT_{1A} agonist [44], alone restores NOR in subchronic PCP-treated rats [21]. The combination of sub-effective doses of tandospirone (0.2 mg/kg) and lurasidone (0.03 mg/kg) also reverses subchronic PCP-induced NOR-deficits [21]. Lurasidone (1 mg/kg), given for seven days, following the washout period of subchronic PCP, produces a prolonged (up to 3 weeks), but not indefinite, reversal of the deficit in NOR induced by subchronic PCP, but lurasidone, 0.1 mg/kg, pimavanserin, 3 mg/kg, or haloperidol 0.1–0.5 mg/kg given in this manner do not reverse the PCP-induced NOR deficit [45] Furthermore, lurasidone, 1 mg/kg or tandospirone, 5 mg/kg, but not lower doses, as co-treatment with each dose of PCP during the initial PCP treatment period, prevented the subchronic PCP-induced NOR deficit, when tested at day 22 [45]. The preventive effect of lurasidone was blocked by co-administration of the 5-HT_{1A} antagonist, WAY100635 with lurasidone, prior to each dose of PCP [45]. This result provides further evidence for the importance of 5-HT_{1A} receptor stimulation to the prevention of the NOR deficit produced by subchronic PCP [21].

The primary aim of this study was to determine whether combining several key components of the pharmacology of atypical APDs could mimic the actions of atypical APDs. To do this, we studied which combinations, if any, of the $5HT_{1A}$ agonist, tandospirone, the 5-HT_{2A} inverse agonist, pimavanserin, and the D_2 receptor antagonist, haloperidol, given to subchronic PCP-treated rats could reverse the NOR deficit, or, when co-administered with subchronic PCP, could prevent the deficit in NOR produced by subchronic PCP. As will be demonstrated, only the combination of a tandospirone, haloperidol and pimavanserin, was able to reverse or prevent the development of the subchronic PCP-induced deficit in NOR, albeit at higher doses of tandospirone to achieve prevention.

2. Materials and methods

2.1. Animals

Eighty two Long-Evans (LE) rats (8–9 weeks old, Harlan Sprague Dawley Inc, Indianapolis, IN, USA) were used in experiments 1 and 2, 49 in experiment 3. Rats were housed in groups of three or four on a 12 h light/dark cycle in separate housing areas. All experiments were conducted during the light phase. Food and water were available ad libitum. All experiments were conducted in accordance