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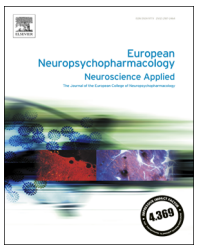

Effects of cariprazine, a novel antipsychotic, on cognitive deficit and negative symptoms in a rodent model of schizophrenia symptomatology

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Abstract
Negative symptoms and cognitive impairment associated with schizophrenia are strongly associated with poor functional outcome and reduced quality of life and remain an unmet clinical need. Cariprazine is a dopamine D_3/D_2 receptor partial agonist with preferential binding to D_3 receptors, recently approved by the FDA for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder. The aim of this study is to evaluate effects of cariprazine in an animal model of cognitive deficit and negative symptoms of schizophrenia. Following sub-chronic PCP administration (2 mg/kg, IP for 7 days followed by 7 days drug-free), female Lister Hooded rats were administered cariprazine (0.05, 0.1, or 0.25 mg/kg, PO) or risperidone (0.16 or 0.1 mg/kg, IP) before testing in novel object recognition (NOR), reversal learning (RL), and social interaction (SI) paradigms. As we have consistently demonstrated, sub-chronic PCP significantly impaired behavior in these tests. Deficits were significantly improved by cariprazine, in a dose dependent manner in the operant RL test with efficacy at lower doses in the NOR and SI tests. Locomotor activity was reduced at the highest doses of 0.1 mg/kg and 0.25 mg/kg in NOR and SI. Risperidone also reversed the PCP-induced deficit in all tests. In conclusion, cariprazine was effective to overcome PCP-induced deficits in cognition and social behavior in a thoroughly validated rat model in tests representing specific symptom domains in

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schizophrenia patients. These findings support very recent results showing efficacy of cariprazine in the treatment of negative symptoms in schizophrenia patients.

1. Introduction

Schizophrenia is thought to comprise 3 main symptom clusters: positive symptoms (e.g., delusions, disorganized speech, paranoia), negative symptoms (with expressive deficit and avolition domains, including blunted affect and social withdrawal, respectively), and deficits in cognition (e.g., executive function, working memory, and attention) (Kalkstein et al., 2010; Millan et al., 2014). While antipsychotics are generally effective in managing positive symptoms, treatment of negative symptoms and cognitive impairment remains a clinical challenge. Effective management of neurocognitive deficits and negative symptoms is a critical component of successful schizophrenia treatment, as these domains are strongly associated with poor quality of life in schizophrenia patients (Savilla et al., 2008; Tsapakis et al., 2015). Recent clinical trials have investigated a number of adjunctive therapies for managing cognitive and negative symptoms in patients with schizophrenia. Unfortunately, these therapies have been largely unsuccessful (Citrome, 2014), which underscores the importance of developing new antipsychotic treatments that can effectively treat all 3 schizophrenia symptom domains.

Cariprazine is a potent dopamine D_3 and D_2 receptor partial agonist with preferential binding to D_3 receptors that recently received approval by the FDA for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder. Cariprazine has been shown to be well tolerated and effective in 3 recent Phase III trials in patients with an acute exacerbation of schizophrenia (Durgam et al., 2014, 2015; Kane et al., 2015) and demonstrated enhanced efficacy for negative symptoms, compared with other antipsychotics, in patients with high negative symptom scores (Debelle et al., 2015). The D_3 receptor is thought to play a role in mood and cognition (Gross and Drescher, 2012) and cariprazine was developed based on the hypothesis that high affinity at D_3 and D_2 receptors may provide benefits in the treatment of affective and cognitive deficits associated with schizophrenia and bipolar disorder (Gyertyán et al., 2008; Kiss et al., 2008). In vitro studies have demonstrated that the affinity of cariprazine for the D_3 receptor is almost an order of magnitude greater than for the D_2 receptor (Kiss et al., 2010). In vivo, cariprazine demonstrates high occupancy of both D_3 and D_2 receptors at antipsychotic effective doses in rats (Gyertyán et al., 2011) and clinically active dose ranges in patients with schizophrenia (Slifstein et al., 2013). This pharmacological profile differs from other atypical antipsychotics such as aripiprazole, clozapine, olanzapine, and risperidone, which have varying levels of in vitro affinity for D_3 receptors, but failed to show D_3 receptor occupancy at clinically relevant doses (Caravaggio et al., 2014; Graff-Guerrero et al., 2009; Mizrahi et al., 2011).

In animal studies, cariprazine shows potent antipsychotic-like activity in amphetamine-induced hyperactivity, apomorphine-induced climbing, and in conditioned avoidance models (Gyertyán et al., 2011), demonstrating putative efficacy against positive symptoms of schizophrenia. Cariprazine also shows antidepressant-like activity in chronic stress-induced models of anhedonia (Duman et al., 2012; Papp et al., 2014); this anti-anhedonic activity was at least partially mediated by the D_3 receptor (Duman et al., 2012). These data suggest a role for the D_3 receptor in reward processing, which is thought to be disrupted in schizophrenia and is part of the negative symptom domains.

The disruption of glutamatergic function has been hypothesized to play a major role in the pathophysiology of schizophrenia (Olney et al., 1999). Consistent with this theory, NMDA receptor antagonists such as phencyclidine (PCP) have demonstrated the ability to induce psychopathology similar to the symptoms of schizophrenia in healthy individuals (Luby et al., 1959) and to exacerbate the symptoms in patients with schizophrenia (Malhotra et al., 1997). As a result, PCP-based models have been increasingly used as a method of modeling schizophrenia symptoms in animals. Unlike many other schizophrenia models, PCP-based models are capable of inducing cognitive impairment and deficits in social interaction in addition to aspects of positive symptoms (Meltzer et al., 2013; Neill et al., 2010, 2014; Sams-Dodd, 1996). These features provide a particularly relevant model of schizophrenia that can be used to test the efficacy of new antipsychotic compounds across multiple schizophrenia symptom domains.

Both acute and sub-chronic PCP administration can effectively produce deficits across all 3 major symptom clusters of schizophrenia in rodent models. Indeed, results from the acute model provide a clear indication of procognitive effects of cariprazine and importantly showed a D_3 receptor mechanism. Cariprazine demonstrated antipsychotic-like activity in hypermotility tests (Gyertyán et al., 2011) and D_3-dependent reversal of acute PCP-induced deficits in social recognition memory, spatial working memory, and attentional set shifting (Zimnisky et al., 2013).

Repeated PCP administration may provide a more enduring model of the symptoms of schizophrenia and represent the chronic condition (Jentsch and Roth, 1999; Morris et al., 2005; Neill et al., 2010). Previous work in our laboratory and elsewhere has consistently demonstrated that a sub-chronic PCP treatment regimen (2 mg/kg; twice daily for 7 days) produces robust and persistent deficits in behaviors in female rats that correspond with the various domains of cognition affected in the illness (attention, executive function, recognition memory) and reduced social behavior, an aspect of negative symptoms (Neill et al., 2010, 2014). These deficits are robust, enduring, and reliably attenuated by several atypical antipsychotic agents, but not by first