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Increased impulsivity and disrupted attention induced by repeated phencyclidine are not attenuated by chronic quetiapine treatment

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ABSTRACT

Atypical antipsychotic medications differ in how effectively they attenuate cognitive and other deficits in schizophrenia. The present study aimed to explore whether quetiapine, an atypical antipsychotic medication, would reverse disruptions of performance in the 5-choice serial reaction time task (5-CSRTT), a test of attention and impulsivity, induced by repeated administration of the psychotomimetic phencyclidine (PCP). In confirmation of previous findings, repeated PCP administration (2 mg/kg, s.c., 30 min before behavioral testing, for 2 consecutive days, followed by a 2-week PCP-free period and then 5 consecutive days of PCP treatment) increased premature responding (impulsivity), decreased accuracy (attention), and increased response latencies (processing speed) and timeout responding (impulsivity/cognitive inflexibility). Chronic quetiapine (5 or 10 mg/kg/day, s.c.) did not attenuate these PCP-induced disruptions in performance, while at the highest dose used, quetiapine disrupted 5-CSRTT performance in the absence of PCP treatment and tended to exacerbate the PCP-induced increase in premature responding. Considering that clozapine, another atypical antipsychotic, was shown previously to reverse PCP-induced deficits in the same task [Amitai N, Semenova S, Markou A. Cognitive-disruptive effects of the psychotomimetic phencyclidine and attenuation by atypical antipsychotic medications in rats. Psychopharmacology (Berl) 2007;193:521–37], the present findings demonstrate differences between clozapine and quetiapine in their effectiveness on schizophrenia-like cognitive deficits and impulsivity that may be attributable to their different receptor affinity profiles.

1. Introduction

Schizophrenia is a devastating mental disorder that affects 1% of the population (Regier et al., 1993). The symptoms of schizophrenia include impulsivity and severe cognitive deficits that affect a wide range of cognitive modalities. Increased impulsivity in schizophrenia patients is reflected in disinhibition of inappropriate responding in cognitive tests, such as increased errors of commission in Go/No Go tasks (Kiehl et al., 2000; Weisbrod et al., 2000; Wykes et al., 2000; Badcock et al., 2002; Chan et al., 2006). Among cognitive deficits, attentional impairments are prominent (Nuechterlein and Dawson, 1984; Laurent et al., 1999). Additional aspects of cognition that are characteristically disrupted in schizophrenia patients include speed of processing (Nelson et al., 1990), cognitive flexibility (Goldberg et al., 1988; Morice, 1990), and memory (Tamlyn et al., 1992; Kuperberg and Heckers, 2000). Cognitive dysfunction in schizophrenia is highly correlated with functional impairment and is a major predictor of long-term disability (McGurk and Meltzer, 2000; Sharma and Antonova, 2003; Green et al., 2004). Typical neuroleptic medications do not ameliorate cognitive schizophrenia deficits, and in some cases have been found to worsen them (Bilder et al., 1992; Mortimer, 1997). Some studies have found enhancement of cognition in schizophrenia with the newer atypical antipsychotics (Meltzer and McGurk, 1999; Bilder et al., 2002; Bender et al., 2005), but improvement remains only partial and falls well short of restoring normal functioning (Sharma and Antonova, 2003; Keefe et al., 2004).

Interestingly, various atypical antipsychotic medications differ in their effects on impulsivity and cognition in schizophrenia. Specifically, differential effects on different cognitive modalities have been observed. For example, clozapine has been reported to improve attentional function but to have less or no effect on working memory (Sharma and Mockler, 1998; Meltzer and McGurk, 1999). The clinical record is still incomplete and confusing, however. For example, some studies indicate effectiveness of quetiapine at improving attention, but not cognitive flexibility (Velligan et al., 2002), while other studies have found enhancement of cognitive flexibility with quetiapine (Kivircik Akdede et al., 2005; Kopala et al., 2006). Similarly, some studies report amelioration of impulsivity in schizophrenia with clozapine (Spivak et al., 1997; Dursun et al., 2000), while other studies find clozapine to be ineffective (Strous et al., 2006). Olanzapine, but not risperidone, may also improve impulsivity in schizophrenia

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(Strous et al., 2006). Quetiapine has been found to beneficially affect impulsivity in borderline personality disorder, antisocial personality disorder, and bipolar disorder with co-occurring disruptive behavior disorders (Barzman et al., 2006; Hilger et al., 2003; Walker et al., 2003; Villeneuve and Lemelin, 2005), but little is known about its effects on impulsivity in schizophrenia.

Given the limitations and unavoidable confounds of clinical studies in humans, translational animal models of schizophrenia-like cognitive deficits may offer a more controllable means of exploring the differential effects of different atypical antipsychotic medications on cognition. Because the differences in effectiveness are likely related to the different receptor profiles of these medications, such studies are apt to generate new insight into the roles of various receptors and neurotransmitter systems in impulsivity and cognitive dysfunction in schizophrenia and its possible amelioration. This information then could guide the development of novel, more effective treatments for these schizophrenia symptoms.

In previous studies, we established a model of cognitive deficits and increased impulsivity in schizophrenia using repeated administration of phencyclidine (PCP) as the inducing condition that disrupts performance in the 5-choice serial reaction time test (5-CSRTT) as the dependent variable (Amitai et al., 2007). PCP is a dissociative anesthetic that acts as a noncompetitive antagonist at *N*-methyl-D-aspartate (NMDA) glutamate receptors. PCP intoxication produces a psychosis-like state in healthy humans that comprises both positive and negative symptoms of schizophrenia (Luby et al., 1959; Bakker and Amini, 1961; Allen and Young, 1978; Castellani et al., 1982; Javitt, 1987; Steinpreis, 1996). As a result, the effects of PCP on various behaviors have found wide recognition as models of different aspects of schizophrenia (Javitt, 1987; Sams-Dodd, 1996; Steinpreis, 1996; Jentsch and Roth, 1999). Most relevant to the topic of the present study is the fact that PCP exposure disrupts cognition in both humans (Rosenbaum et al., 1959; Yesavage and Freeman, 1979; Pearlson, 1981; Pradhan, 1984) and animals (Handelmann et al., 1987; Stefani and Moghaddam, 2005; Rodefer et al., 2005, 2008; Idris et al., 2003, 2005; Abdul-Monim et al., 2003, 2006, 2007; Depoortère et al., 2007; Didriksen et al., 2007) and increases impulsive responding in experimental animal models (Balster and Baird, 1979; Sanger and Jackson, 1989; Compton et al., 2001; Jentsch and Anzivino, 2004; Amitai et al., 2007), indicating the usefulness of PCP in inducing impulsivity and cognitive dysfunction with relevance to schizophrenia.

The 5-CSRTT was developed originally as a test of attentional performance (for review, Robbins, 2002). In addition, this task allows assessment of disinhibition of inappropriate responding and has become recognized as a means to gauge impulsivity (Puumala et al., 1996; Puumala and Sirviö, 1998; Evenden, 1999; Talpos et al., 2006). Furthermore, the 5-CSRTT provides measures of processing speed and cognitive flexibility (Robbins, 2002). Repeated administration of PCP increases impulsivity and disrupts cognitive performance in the 5-CSRTT. The profile of deficits induced by PCP in the 5-CSRTT includes a profound increase in impulsive-type responding in PCP-treated animals. Repeated PCP administration also disrupts attentional performance in the task and decreases processing speed and cognitive flexibility (Amitai et al., 2007). Chronic clozapine treatment has been shown to significantly attenuate the increased impulsivity induced by repeated PCP. Moreover, it partially ameliorates the PCP-induced attentional disruption, but does not alter the effects of repeated PCP on processing speed and cognitive flexibility (Amitai et al., 2007).

In the present study, we investigated how chronic treatment with another atypical antipsychotic, quetiapine, affects the increased impulsivity and cognitive performance impairments induced in the 5-CSRTT by repeated PCP administration. Repeated injections of PCP were used because previous studies showed that a single injection of PCP produced a general, nonspecific response suppression that partially or completely occluded specific cognitive and other deficits with relevance to schizophrenia. For example, premature responses tended to be decreased after a single injection of PCP (as did all types of responding), whereas repeated administration of PCP led to a profound increase in premature responses, revealing the increased impulsivity induced by PCP (Amitai et al., 2007). While several studies have explored cognitive function after subchronic PCP administration followed by a significant washout period, when animals are no longer under the direct influence of PCP (Jentsch et al., 1997; Jentsch and Taylor, 2001; Rodefer et al., 2005, 2008; Abdul-Monim et al., 2006, 2007), it should be noted that the schizophrenia-like state evoked by PCP in humans is present during PCP intoxication, not during PCP withdrawal or during prolonged post-PCP abstinence (Pradhan, 1984). Therefore, we assessed impulsivity and cognitive performance during acute PCP re-challenges after repeated PCP exposures. A dose of 2 mg/kg was chosen because the higher PCP doses commonly used in subchronic studies that test behavior during the drug-free state (Jentsch et al., 1997; Jentsch and Taylor, 2001; Rodefer et al., 2005, 2008) profoundly disrupt 5-CSRTT responding and overall behavior during acute PCP intoxication.

Previous investigations in our laboratory have shown that acute quetiapine, given at a range from 2.5 to 7.5 mg/kg, did not affect performance of the 5-CSRTT under baseline conditions (i.e., in the absence of PCP administration), with the exception of a slight decrease in percent correct responses at the highest dose. Attentional accuracy and impulsive responding were not altered by any dose of quetiapine used (Amitai et al., 2007). While both clozapine and quetiapine are atypical antipsychotic medications commonly used to treat schizophrenia (McEvoy et al., 1999), quetiapine's receptor profile differs from that of clozapine in several ways (see Table 1). Quetiapine exhibits a smaller ratio of serotonin 5-HT_{2A} receptor antagonism to dopamine D_2 receptor antagonism than clozapine, and also lacks the significant antagonism of serotonin 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptors expressed by clozapine (Bymaster et al., 1996; Schmidt et al., 2001). Thus, if the effects of chronic quetiapine on a model of schizophrenia-like impulsivity and cognitive deficits differ from those of clozapine, these disparities may provide clues to the importance of actions at different receptors in the effectiveness of atypical antipsychotics in decreasing impulsivity and improving cognition in schizophrenia.

2. Materials and methods

2.1. Subjects

Forty-one male Wistar rats (Charles River Laboratories, Wilmington, MA) were housed two per cage on a 12 h:12 h reversed light–dark cycle (lights off at 6:00 am). All behavioral testing was conducted during the animals' dark cycle. Rats were allowed to reach a body weight of at least 275 g before being restricted to 20 g of food per day (in addition to the food pellets earned during testing) and initiation of behavioral training. Water was available *ad libitum* at all times except during testing. Animals were treated in accordance with the guidelines of the American Association for the Accreditation of Laboratory Animal Care and the National Research Council's *Guide for Care and Use of Laboratory Animals.* All experiments were approved by the

Table 1
Receptor affinities of quetiapine and clozapine.

Receptor	Quetiapine	Clozapine
D_2	180 nM	130 nM
5-HT_{2A}	220 nM	8.9 nM
5-HT_{2A}:D_2 affinity ratio	0.82	14.6
5-HT_{2C}	1400 nM	17 nM
5-HT_6	4100 nM	11 nM
5-HT_7	1800 nM	66 nM
Histamine H_1	8.7 nM	1.8 nM

Data are presented as K_i values and based on Schmidt et al. (2001).