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D_1-like receptor activation improves PCP-induced cognitive deficits in animal models: Implications for mechanisms of improved cognitive function in schizophrenia

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Abstract

Phencyclidine (PCP) produces cognitive deficits of relevance to schizophrenia in animal models. The aim was to investigate the efficacy of the D_1-like receptor agonist, SKF-38393, to improve PCP-induced deficits in the novel object recognition (NOR) and operant reversal learning (RL) tasks. Rats received either sub-chronic PCP (2 mg/kg) or vehicle for 7 days, followed by a 7-day washout. Rats were either tested in NOR or the RL tasks. In NOR, vehicle rats successfully discriminated between novel and familiar objects, an effect abolished in PCP-treated rats. SKF-38393 (6 mg/kg) significantly ameliorated the PCP-induced deficit ($P<0.01$) an effect significantly antagonised by SCH-23390 (0.05 mg/kg), a D_1-like receptor antagonist ($P<0.01$). In the RL task sub-chronic PCP significantly reduced performance in the reversal phase ($P<0.001$); SKF-38393 (6.0 mg/kg) improved this PCP-induced deficit, an effect antagonised by SCH-23390 ($P<0.05$). These results suggest a role for D_1-like receptors in improvement of cognitive function in paradigms of relevance to schizophrenia.

1. Introduction

Cognitive dysfunction in schizophrenia is becoming an increasingly important therapeutic target as one reason for the residual disability of schizophrenia appears to be the long-standing cognitive deficits of the disorder (Green and Nuechterlein, 2004). The MATRICS initiative (Measurement and Treatment Research to Improve Cognition in Schizophrenia) aims to facilitate the development of better treatments targeted at cognition (Marder and Fenton, 2004). It has been often reported that atypical antipsychotics have some beneficial effect on cognitive deficits (Hagger et al., 1993; Buchanan et al., 1994; Rossi et al., 1997; Meltzer and McGurk, 1999; Harvey et al., 2004). However, the effect is small (Lieberman, 2006; Keefe et al., 2007) and hence there remains a great unmet need for novel antipsychotics to improve cognitive function.

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There is mounting evidence for the role of dopamine dysregulation in the prefrontal cortex (PFC) in schizophrenia (for review see Goldman-Rakic et al., 2004). It has been suggested that the negative symptoms and cognitive deficits seen in schizophrenia may arise from a dopaminergic deficit in the prefrontal cortex i.e. hypofrontality (Davis et al., 1991), whereas the positive symptoms are related to hyperactivity of sub-cortical dopaminergic neurons (Grace, 1991). In keeping with this, inhibitors of catechol-O-methyltransferase (COMT), the primary enzyme responsible for metabolic degradation of dopamine specifically in the medial prefrontal cortex (mPFC), have been shown to improve cortical processing in both humans (Apud et al., 2007) and rats (Tunbridge et al., 2006).

Spano et al. (1978) proposed the existence of two populations of dopamine receptors after it was shown that dopamine both stimulated and inhibited adenylate cyclase (AC) activity (Brown and Makman, 1972; Kebabian et al., 1972). D_1 and D_5 receptors belong to the D_1-like family in that they stimulate adenylate cyclase (AC), whereas D_2, D_3 and D_4 receptors inhibit AC. D_1-like receptors are predominantly found in the PFC, while D_2-like receptors are expressed in sub-cortical regions (see Guillin et al., 2007), although D_4 receptors are present in the PFC and hippocampus (Lahti et al., 1998). In keeping with the dopaminergic hypothesis of schizophrenia current antipsychotics attenuate positive symptoms by blocking sub-cortical D_2 receptors (Seeman et al., 1975; Creese et al., 1976) but these drugs have, at best, only limited efficacy at treating cognitive deficits.

Mounting evidence suggests that the D_1 receptor in the mPFC may be important in regulating cognitive function in schizophrenic patients. Okubo et al. (1997) reported a down-regulation of D_1 binding in the PFC of treatment-free/-naïve schizophrenic patients. Another study has demonstrated an association between genetic risk for schizophrenia and alterations in cortical D_1 receptor binding (Hirvonen et al., 2006). It has also been shown that D_1 receptors are more abundant than D_2 receptors in the PFC of non-human primates (Lidow et al., 1991), and this D_1 receptor subfamily has been implicated in working memory functions of the PFC (Arnsten et al., 1994, Sawaguchi and Goldman-Rakic, 1991), one aspect of cognition impaired in schizophrenia. Thus, it is possible that stimulation of the D_1 receptor may represent a potential strategy for treating cognitive deficits associated with schizophrenia. Indeed, D_1 agonists have been highlighted as a molecular target for cognitive enhancement in schizophrenia (see Gray and Roth, 2007).

Phencyclidine (PCP) is a non-competitive NMDA receptor antagonist, which has been shown to produce enduring cognitive deficits similar to those observed in schizophrenia (Javitt and Zukin, 1991) particularly when administered sub-chronically rather than acutely (Jentsch and Roth, 1999). Repeated and intermittent administrations of PCP have been shown to reduce dopamine turnover in the PFC of rats and monkeys (Jentsch et al., 1997a,b); moreover, the use of a sub-chronic PCP regimen has been suggested to provide a superior pharmacological model of the hypodopaminergic state seen in schizophrenia (see Jentsch and Roth, 1999). Sub-chronic PCP also causes reduced density of parvalbumin-immunoreactive neurons (Abdul-Monim et al., 2007) and brain-derived neurotrophic factor (BDNF) levels in cortical regions (Snigdha et al., 2007a) in rats. Indeed, the sub-chronic PCP dosage regime has been well-validated in our laboratory producing enduring cognitive deficits which can be reversed by atypical but not classical antipsychotics in NOR (Grayson et al., 2007), reversal learning (Abdul-Monim et al., 2006, 2007) and attentional set-shifting (McLean et al., 2008) tasks. Sub-chronic PCP also produces social behaviour deficits in our laboratory which are improved by atypical but not by classical antipsychotics (Snigdha and Neill, 2008a,b). Using this model we have observed cognitive deficits in NOR lasting up to 5 months following the last dose of PCP (Grayson et al. unpublished observations). As many atypical antipsychotics have affinity for a multitude of receptors, much research is now focusing on identifying specific receptor subtypes as potential novel targets and on the development of selective compounds (Gray and Roth, 2007) for the treatment of cognitive dysfunction in schizophrenia.

The core aim of this study was to utilise the selective D_1-like receptor agents SKF-38393 and SCH-23390 to elucidate the role of D_1-like receptors in cognition using two rodent tests validated in our laboratory, the NOR test and the operant reversal learning task, which are both tests highlighted by the MATRICS initiative as being relevant translational models for studying visual learning and memory and reasoning and problem solving respectively (see Hagan and Jones, 2005). It is expected that SKF-38393 will ameliorate the sub-chronic PCP-induced deficit, and that the antagonist SCH-23390 will block these effects. Both ligands shall be referred to as D_1-like throughout as SKF-38393 and SCH-23390 have been reported to have similar Ki values at D_1 and D_5 receptors; SKF-38393 having reported Ki values of 26 nM and 80 nM at D_1 and D_5 receptors respectively (Neumeyer et al., 2003; Qandil et al., 2003), whilst SCH-23390 has reported Ki values of 0.37 nM and 0.47 nM for D_1 and D_5 receptors respectively (Lawler et al., 1999).

We also sought to determine if the stage of oestrous cycle had any effect on reversal learning ability since an interaction between gonadal steroids, in particular oestrogen, and cognitive function has previously been reported (see Cahill, 2006 for review). However, we have previously shown no effect of oestrous cycle on novel object recognition (Sutcliffe et al., 2007). It is important for each task to determine whether the oestrous cycle has an effect, therefore this was assessed here in reversal learning.

2. Experimental procedures

2.1. Subjects and housing conditions

Two cohorts of fifty female hooded-Lister rats, 100 in total (Harlan, UK) housed in groups of four or five were used as subjects, rats weighed between 200 and 250 g. Animals were maintained under standard laboratory conditions at a temperature of 21 °C (±2 °C) and humidity of 40–50%. They were maintained on a 12-h/12-h light/dark cycle (lights on at 0700 h) and experimental procedures were performed during the light phase. Cohort 1 were allowed free access to food, while cohort 2 prior to operant training and testing, were gradually food deprived to approximately 90% of free-feeding body weight; reduced body weight was maintained by restricting the amount of food (standard laboratory chow, Special Diet Services, Essex, UK) given to each rat per day (12 g/day). The availability of water was not restricted. Experiments were conducted in accordance with the Animals Scientific Procedures Act, UK, 1986, and approved by the University of Bradford ethics review process.