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Title: Role of 5-HT receptor mechanisms in sub-chronic PCP-induced reversal learning deficits in the rat.

Samantha L. McLean¹, Marie L. Woolley², Dave Thomas², Joanna C. Neill¹

¹Bradford School of Pharmacy, University of Bradford, Bradford, West Yorkshire, BD7 1DP, UK

²GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW, UK

Prof Jo Neill
Bradford School of Pharmacy
The University of Bradford
Bradford
West Yorkshire
BD7 1DP
UK
Tel: 01274 234677
Fax: 01274 234660
E-mail: j.c.neill@bradford.ac.uk

Abstract

Rationale: 5-HT receptor mechanisms have been suggested to mediate improvements in cognition in schizophrenia. *Aim:* To investigate the involvement of 5-HT receptor mechanisms in sub-chronic PCP-induced reversal learning deficits in female rats, a task of relevance to schizophrenia. *Methods:* Adult female hooded-Lister rats were trained to perform an operant reversal learning task and then received sub-chronic PCP (2 mg/kg) or vehicle i.p. twice daily for seven days, followed by 7-days washout. Rats then received an acute dose of the 5-HT₇ receptor antagonist SB-269970A (1.0, 3.0, 10.0 mg/kg; i.p.) or vehicle. In experiment 2, PCP-treated rats received the selective 5-HT_{2C} receptor antagonist, SB-243213A acutely (1.0, 3.0, 10.0 mg/kg; i.p.) or vehicle. In experiment 3, PCP-treated rats received the 5-HT_{1A} receptor partial agonist, buspirone (0.15625, 0.3125, 0.625 mg/kg, i.p.) in combination with the selective 5-HT_{1A} receptor antagonist WAY-100635 (0.3, 1.0 mg/kg). *Results:* In all experiments sub-chronic PCP significantly impaired reversal phase performance ($P < 0.01$ - 0.001), with no effect in the initial phase. SB-269970A at 3.0 and 10.0 mg/kg significantly improved the PCP-induced deficit ($P < 0.05$). SB-243213A also significantly attenuated the deficit at 10 mg/kg ($P < 0.05$). In experiment 3, buspirone attenuated the deficit with significant effects at 0.3125 mg/kg and 0.625 mg/kg ($P < 0.05$). WAY-100635 at 0.3 and 1.0 mg/kg produced a partial attenuation of buspirone's effect as buspirone (0.3125 mg/kg) in the presence of WAY-100635 did not significantly reverse the PCP-induced deficit. *Conclusions:* These studies implicate the role of 5-HT₇, 5-HT_{2C} and 5-HT_{1A} receptors in the improvement of cognitive dysfunction of relevance to schizophrenia.

Keywords: Reversal learning; 5-HT₇; 5-HT_{1A}; 5-HT_{2C} receptors; Phencyclidine; Rat

Introduction

Sub-chronic phencyclidine (PCP) dosage regimes used to induce cognitive impairments in rats are believed to mimic those seen in schizophrenia (Javitt and Zukin, 1991; Jentsch and Roth, 1999). In our laboratory, we have shown that PCP selectively impairs performance in reversal learning (Abdul-Monim *et al.*, 2006; 2007; McLean *et al.*, 2009), attentional set-shifting (McLean *et al.*, 2008a) and novel object recognition (Grayson *et al.*, 2007), importantly these tests are all of relevance to schizophrenia as highlighted by the MATRICS.ucla.edu initiative (Measurement and Treatment Research to Improve Cognition in Schizophrenia), and subsequently the TURNS.ucla.edu program (Treatment Units for Research on Neurocognition and Schizophrenia). Our sub-chronic PCP dosing regime causes reduced density of parvalbumin-immunoreactive neurons in hippocampal regions (Abdul-Monim *et al.*, 2007) and levels of brain-derived neurotrophic factor mRNA (BDNF) in cortical regions (Snigdha *et al.*, 2007) in rats. Reductions in GABAergic interneurons in these areas have been found in post-mortem analysis from patients with schizophrenia (Benes *et al.*, 1991; Benes and Berretta, 2001; Beasley *et al.*, 2002; Zhang and Reynolds, 2002). We have shown that atypical but not classical antipsychotics can reverse these cognitive deficits; however, in the clinic there is differing evidence for the efficacy of atypical antipsychotics in improving cognition with the CATIE study (Lieberman, 2006; Keefe *et al.*, 2007) and the UK Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS; Jones *et al.*, 2006; Lewis *et al.*, 2006) suggesting that antipsychotics actually have a limited effect. Cognitive dysfunction is a core characteristic of schizophrenia (Sullivan *et al.*, 1994; Elvevag and Goldberg, 2000; Kuperberg and Heckers, 2000), occurring in 75-85% of patients

(Reichenberg *et al.*, 2006), and is becoming increasingly important as impaired cognition has been implicated in poor long-term functional outcome (Marder and Fenton, 2004) which can often persist when other symptoms may be improved with treatment (Gold *et al.*, 1991; Heinrichs, 2005).

The serotonergic system has been strongly implicated in the neurobiology of schizophrenia (for reviews see Meltzer, 1995; Roth *et al.*, 2004). In 1989 Meltzer defined atypical antipsychotic drugs as having higher affinity for 5-HT_{2A} receptors than for D₂ receptors. 5-HT_{2A} receptor antagonists increase dopamine release in the prefrontal cortex (PFC; Ichikawa and Meltzer, 1990). Although atypical antipsychotics such as risperidone and clozapine have high affinity for 5-HT_{2A} receptors, it is unlikely that this mechanism alone is responsible for their antipsychotic action, as both have been shown to saturate 5-HT₂ receptors at sub-therapeutic doses (Kapur *et al.*, 1999). In our laboratory we plan to identify which 5-HT receptors are important for cognition through use of selective compounds; as part of this work we have already shown that the 5-HT_{2A} antagonist, M100.907, is efficacious in improving a sub-chronic PCP-induced deficit in reversal learning (Neill *et al.*, 2008).

5-HT₇ receptors have been shown to have a role in learning and memory (Hedlund and Sutcliffe, 2004; Thomas and Hagan, 2004). Risperidone and asenapine have high 5-HT₇ receptor affinity (Shahid *et al.*, 2009) and we have demonstrated efficacy of asenapine to reverse PCP-induced deficits in our models (Neill *et al.* submitted). 5-HT_{1A} receptor agonism has been suggested to contribute to an atypical antipsychotic drug profile (Protais *et al.*, 1994). There are also interactions between 5-HT_{2A}, 5-HT_{2C} and 5-HT_{1A} receptors (Kapur and Remington, 1996; Meltzer, 1999). Antipsychotics which have been shown to be superior in improving cognition

compared to typical antipsychotics in the clinic, including risperidone, olanzapine and ziprasidone (Harvey *et al.*, 2004; Purdon *et al.*, 2000), have high affinity for the 5-HT_{2C} receptor (see Miyamoto *et al.*, 2005). Furthermore, the 5-HT_{2C} antagonist, SB 242084, has recently been shown to improve serial spatial reversal learning (Boulougouris *et al.*, 2008), supporting a role for 5-HT_{2C} receptors in cognition.

The aim of this study was to elucidate the 5-HT receptor mechanisms involved in the PCP-induced reversal learning deficit; by using selective compounds we also intend to further enhance the understanding of the mechanism of efficacy for current atypical antipsychotics. Although the 5-HT₆ receptor is a topical target for schizophrenia, this will not be addressed in this manuscript as we have previously shown that a selective 5-HT₆ receptor antagonist can successfully reverse the PCP-induced deficit in our laboratory (Neill *et al.*, 2008). Experiments were carried out using the partial 5-HT_{1A} receptor agonist, buspirone, alone and in combination with the selective 5-HT_{1A} receptor antagonist, WAY-100635. We also investigated the effect of the selective 5-HT_{2C} receptor antagonist, SB-243213A, and the 5-HT₇ receptor antagonist SB-269970A.

Materials and Methods

Subjects and housing conditions

Two cohorts of fifty female hooded-Lister rats (Harlan, UK) housed in groups of four to five were used as subjects. Animals initially weighing 200-220 g 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 light/dark cycle (lights on at 07.00 hours), training and testing was carried out between 08.30 and 16.30. Prior to operant training and testing, rats 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 ethical review process.

Apparatus

All rats were tested in one of eight operant chambers (constructed in-house). Each chamber (29×30×30 cm) consisted of Plexiglas walls and ceiling, and a metal grid floor over sawdust. A hinged Plexiglas panel (6×6 cm) provided access to a food hopper containing food pellets (45 mg Noyes pellets, Sandown Scientific, UK). Two retractable levers (4×2 cm) were positioned on either side of the food hopper. A light emitting diode (LED) was positioned centrally above each lever and a house light was located in the ceiling of each chamber. The chambers were placed individually within ventilated sound-attenuating hardboard boxes (69×38×42 cm) containing a Perspex window to allow viewing. A small fan was built into each chamber to mask external noise. Each animal was tested in the same operant chamber throughout the study. All boxes were controlled by Med-PC software (Version 2.0 for DOS or Med-PC for Windows, Med Associates, Inc. Lafayette, Indiana). Programmes were written using Medstate notation.

Operant training sessions

Following habituation to the operant chambers, rats were trained to respond for food on a fixed ratio 1 (FR1) schedule of reinforcement with both levers active, as previously described in detail (Abdul-Monim *et al.*, 2003; 2006). When responding

stabilised, rats were trained to press either the left or right lever for food delivery according to a visual cue (LED on or off). The position of the LED to the active lever did not change within the session. The experimental session was terminated following a total of 128 lever presses, which took approximately 30 minutes. Rats were trained once daily and this was repeated until rats had reached criterion, i.e. 90% correct responding for three consecutive days, this took approximately 6 weeks of training, 5 days per week.

Reversal-learning task

The day before each reversal task session, a full 30-min operant training session (as described above) was conducted in order to ensure stable responding, i.e. 90% correct responding. The reversal-learning session involved animals being first exposed to a 5-min period during which the active lever was the same as on the previous operant training day. During this period, responses on both correct and incorrect levers were recorded. This part of the session was termed the initial phase. This was followed by a 2-min time-out period, which was signalled by the house light being turned off. In the subsequent 5-min period, the active lever was reversed. Responses made on the correct and incorrect levers were again recorded. This second period was termed the reversal phase. Animals undertook several of these reversal-learning sessions before beginning the drug studies in order to ensure that they attained a stable level of performance, i.e. 90% correct responding and at least 25 lever presses in total, in both the initial and reversal phases of the task. This process took approximately 6 weeks of training, 5 days per week. In both training phases all rats achieved training criterion within 5 days of each other.

Experimental design—drug studies

Eight to 10 trained rats were used per group in the drug studies. Rats were tested on a cycle of 4 days (previously described by Idris *et al.*, 2005, see table 1). On day 1, each animal had a 30-min operant training session. The following day animals received the appropriate drug(s) and undertook a reversal-learning test session. On day 3 and day 4, each animal underwent a further operant training session and reversal test session, respectively, in order to ensure that responding was regained after the drug treatment. In the current experiments normal responding was restored following each drug treatment, if performance was not fully restored, the cycle shown in table 1 would be repeated with no drug treatments until baseline performance in the reversal test was restored.

A total of four drug experiments were carried out using two cohorts of 50 rats. The first cohort was only used for the first drug experiment (SB-269970A). The second cohort took part in the other three experiments. The experiment with buspirone and WAY-100635 was carried out over 2 experiments; subsequently the data were pooled giving 20 rats in the vehicle and PCP groups. The drug treatment given to each rat (and within each home cage) over the course of these experiments was randomised. Every effort was made to keep the number of drug and vehicle treatments equivalent among animals and to randomise the order of treatments. The order of procedures and drug treatments are shown as weeks post training in table 2.

Drugs

The doses of buspirone were selected based on previous dose-response experiments carried out in this reversal learning task (McLean *et al.*, 2008b). WAY-100635 has selective 5-HT_{1A} receptor antagonist activity at the doses used in this study (Prinssen

et al., 1999). The doses of SB-269970A were selected based on pharmacokinetic analysis (Hagan *et al.*, 2000), doses of SB-243213A (5-methyl-1-[[2-[92-methyl-3-pyridyl]oxy]-5-pyridyl]carbamoyl]-6-trifluoromethylindone hydrochloride) were selected based on effects observed in a study by Wood *et al.*, (2001).

For both cohorts the study design involved five groups ($n = 10$ per group initially); following stable performance in the reversal learning task, rats were given either 2.0 mg/kg PCP ($n = 40$) or vehicle (0.9% saline; $n = 10$) by the intraperitoneal (i.p.) route twice daily for seven days. Dosing with sub-chronic PCP or vehicle was followed by a washout period of a further seven days. PCP hydrochloride (Sigma, UK) was dissolved in 0.9% saline. This dosage regime has proved to be very successful in our laboratory in producing robust reversal learning (Abdul-Monim *et al.*, 2006; 2007; McLean *et al.*, 2009) object recognition (Grayson *et al.*, 2007) and attentional set-shifting deficits (McLean *et al.*, 2008a), and social behaviour deficits (Snigdha and Neill, 2008a; 2008b). In these experiments we have used female rats and we have previously shown that the stage of oestrous cycle does not affect reversal learning performance (McLean *et al.*, 2009). We have also found females to be better at novel object recognition compared with males (Sutcliffe *et al.*, 2007), and we have demonstrated that female rats are more sensitive to our PCP dosage regime in attentional set-shifting (McLean *et al.*, 2007).

SB-269970A (supplied by GSK, Harlow, UK) was prepared in distilled water and given in a volume of 1 ml/kg via the i.p. route, and was administered 45min before testing. Buspirone hydrochloride (Sigma, UK) and WAY-100635 (Sigma, UK) were dissolved in 0.9% saline and given in 1 ml/kg volume via the i.p. route; buspirone was administered 30 min prior to testing and WAY-100635 was administered 30 min prior to buspirone. In the experiment with WAY-100635 alone,

doses of 0.3 and 1.0 mg/kg were administered 30 min prior to testing. SB-243213A (supplied by GSK, Harlow, UK) was dissolved in vehicle containing cyclodextrin (8% by weight) plus 25mM citric acid, and was administered 30 min prior to testing via the i.p. route in a volume of 2 ml/kg.

Data and statistical analysis

Data for percentage correct responding was calculated using the number of presses on the correct lever divided by the total number of presses multiplied by 100. The percent correct data was then arcsine transformed and analysed by a one-way ANOVA followed by *post-hoc* Dunnett's t-test comparing drug treatment to the PCP-treated group. The total number of lever presses was calculated by adding the correct and incorrect presses together within the 5-min test session, this was used to assess whether drugs had caused any sedation or motor impairments.

Results

Experiment 1 – Effect of SB-269970A

There was no significant effect on total lever pressing in the initial or reversal phases, suggesting that neither locomotor capacity nor motivation were affected (fig 1a). For percent correct responding, a paired t-test showed a significant reduction in responding in the reversal phase compared to the initial phase in the PCP-treated group ($P < 0.001$). A one-way ANOVA in the reversal phase showed a significant effect of treatment ($F_{4,43} = 5.94$, $P < 0.01$). Post-hoc analysis revealed that SB-269970A at 3 mg/kg and 10 mg/kg significantly ($P < 0.01$) improved the PCP-induced deficit (fig 1b).

Experiment 2 – Effect of SB-243213A

There was no significant effect on total lever pressing in the initial or reversal phases, suggesting that neither locomotor capacity nor motivation were affected (fig 2a). For percent correct responding, a paired t-test showed a significant reduction in correct responding in the reversal phase compared to the initial phase in the PCP-treated group ($P<0.001$), 1.0 mg/kg treated group ($P<0.01$) and 3.0 mg/kg treated group ($P<0.001$). A one-way ANOVA in the reversal phase showed a significant effect of treatment ($F_{4,49} = 7.27$, $P<0.001$). Post-hoc analysis revealed that SB-243213A at 10 mg/kg significantly ($P<0.05$) improved the PCP-induced deficit (fig 2b).

Experiment 3 – Effect of buspirone and WAY-100635

There was no significant effect on total lever pressing in the initial or reversal phases following any acute drug treatment (fig 3a). For percent correct responding, a paired t-test showed a significant reduction in correct responding in the reversal phase compared to the initial phase in the PCP-treated group ($P<0.001$), and in the PCP animals treated acutely with buspirone at 0.15625 mg/kg ($P<0.05$). A one-way ANOVA in the reversal phase showed a significant effect of treatment ($F_{6,75} = 5.77$, $P<0.001$). Post-hoc analysis revealed that PCP rats treated with buspirone at 0.3125 and 0.625 mg/kg had significantly improved reversal learning compared to the PCP alone group ($P<0.01$; fig 3b). The lower dose of 0.156 had no effect as indicated by significant reduction in responding compared with the initial phase. Pre-treatment with WAY-100635 (0.3 and 1.0 mg/kg) partially antagonised the effect of buspirone (0.3125 mg/kg) such that buspirone in the presence of WAY-100635 (0.3 and 1.0 mg/kg) did not significantly reverse the PCP-induced deficit ($P=0.208$ and $P=0.082$ respectively). However, there was no significant difference between buspirone alone

(0.3125 mg/kg) and buspirone (0.3125 mg/kg) in the presence of WAY-100635 at 0.3 mg/kg ($P=0.451$) and 1.0 mg/kg ($P=0.712$).

Experiment 4 – Effect of WAY-100635 alone

There was no significant effect on total lever pressing in the initial or reversal phases following treatment with WAY-100635 (fig 4a). For percent correct responding, a paired t-test showed a significant reduction in performance of the reversal phase compared with the initial phase in the PCP-group ($P<0.001$), and both WAY-1000635 treated groups ($P<0.05$, fig 4b). A one-way ANOVA in the reversal phase showed a significant effect of treatment interaction ($F_{3,33} = 4.57$, $P<0.01$). Post-hoc analysis revealed WAY-100635 at 0.3 and 1.0 mg/kg did not significantly improve correct responding compared to PCP alone in the reversal phase ($P=0.54$ and $P=0.42$ respectively).

Discussion

The current experiments utilised an operant reversal learning paradigm to examine the effects of selective 5-HT receptor compounds in order to establish which specific receptors were involved in cognitive enhancement for identification of novel targets and to provide improved understanding of the receptor mechanisms involved in existing antipsychotic therapies. The principal findings show that the 5-HT₇ receptor antagonist, SB-269970A, the 5-HT_{2C} receptor antagonist SB-243213A and the 5-HT_{1A} receptor partial agonist buspirone attenuated the sub-chronic PCP-induced deficit in the reversal phase of the task.

Reversal learning task and PCP-induced disruption

Successful reversal learning ability relies on the intact function of the prefrontal cortex. It has been shown more specifically that lesions of the orbital prefrontal cortex impair reversal learning ability (McAlonan and Brown, 2003; Tait and Brown, 2007). The prefrontal cortex is believed to be important for effective functioning in tests such as the WCST and impaired performance is seen in patients with schizophrenia (Haut *et al.*, 1996; Pantelis *et al.*, 1999). It has been shown that 5-HT receptor antagonists could have antipsychotic efficacy via increasing release of dopamine in the PFC (Ichikawa and Meltzer, 1990; Di Matteo *et al.*, 2001). PCP has been shown to affect dopamine levels within the PFC and nucleus accumbens and reduced dopamine within the PFC is thought to mediate both negative and cognitive symptoms of schizophrenia (Jentsch and Roth 1999); thus, activity at 5-HT receptors may indirectly improve PCP-induced deficits via modulation of dopamine release in the PFC. In a recent novel object recognition study we have shown that sub-chronic PCP impairs the ability of rats to recognise the familiar object in retention (and hence discriminate between the novel and familiar object) and also abolishes prefrontal dopamine release which is increased in control rats selectively in the retention trial (Snigdha *et al.*, 2008c). Moreover, we have recently shown that the dopamine D₁ receptor agonist, SKF-38393, improves sub-chronic PCP-induced deficits in reversal learning and novel object recognition (McLean *et al.*, 2009). These findings strongly support a role for prefrontal dopamine working through a D₁ receptor mechanism to improve cognition of relevance to schizophrenia.

The present results show that vehicle-treated rats can be trained to an equivalent level of accuracy in both the initial and reversal phases of the task. Following treatment with sub-chronic PCP, rats demonstrated a robust and replicable impairment which is selective for the reversal phase. We have shown this effect

several times now (Abdul-Monim *et al.*, 2006; 2007; Neill *et al.*, submitted; McLean *et al.*, 2009) and this effect is also observed following acute treatment with PCP and d-amphetamine (Abdul-Monim *et al.*, 2003; Idris *et al.*, 2005).

Effect of SB-269970A

SB-269970A is a selective 5-HT₇ receptor antagonist (Varnäs *et al.*, 2004). 5-HT₇ receptors are located in the thalamus, hypothalamus and amygdala in addition to limbic and cortical regions (Thomas *et al.*, 2002; Varnäs *et al.*, 2004). Activity at 5-HT₇ receptors has been suggested to have a strong role in cognitive dysfunction (Hedlund and Sutcliffe, 2004; Thomas and Hagan, 2004). The 5-HT₇ receptor is a potential target of relevance to schizophrenia as many atypical antipsychotics such as risperidone and ziprasidone have affinity for this receptor (Roth *et al.*, 1994; Siegfried *et al.*, 2005), and some e.g. clozapine have significant inverse agonist activity (Mahe *et al.*, 2004). The results of experiment 1 with SB-269970A showed that 3.0 and 10.0 mg/kg of SB-269970A significantly ameliorated the PCP-induced deficit. There were no effects on the initial phase of the task or on total lever pressing.

SB-269970 (at 3.0 and 10.0 mg/kg) has been previously shown to reverse cognitive impairments induced by scopolamine and dizocilpine (Meneses, 2004). In a recent study by Galici and co-workers (2008) SB-269970 (10 and 30 mg/kg) significantly antagonised both amphetamine and ketamine-induced hyperactivity in mice; in addition to this, the effect on amphetamine-induced hyperactivity was not observed in 5-HT₇ knock-out mice, suggesting that SB-269970 has good selectivity for the 5-HT₇ receptor. However, SB-269970 did not block ketamine-induced deficits in PPI (Galici *et al.*, 2008). PCP-induced deficits in PPI were reversed by SB-258741, an analogue of SB-269970 (Pouzet *et al.*, 2002). Conversely, in a more recent study it

was shown that SB-269970 at 10 mg/kg did not reverse PCP-induced deficits in PPI (Semenova *et al.*, 2008). Therefore, there are conflicting results surrounding the effect of SB-269970 against PCP-induced deficits in PPI; however, we have demonstrated that SB-269970 at 3 and 10 mg/kg significantly reverses our sub-chronic PCP-induced deficits in a reversal learning task of relevance to schizophrenia thus strengthening the argument for its importance in therapy of cognition in schizophrenia. It has been hypothesised that 5-HT₇ receptor antagonists may reverse PCP-induced deficits via the prevention of 5-HT and/or glutamate release (Semenova *et al.*, 2008). However, more research is needed to elucidate the cognitive-enhancing mechanisms of 5-HT₇ receptor antagonists.

Effect of SB-243213A

SB-243213A is a selective 5-HT_{2C} receptor antagonist (Bromidge *et al.*, 2000). 5-HT_{2C} receptors are located in a variety of brain regions including the neocortex, amygdala, hippocampus, nucleus accumbens, substantia nigra and the ventral tegmental area (Pompeiano *et al.*, 1994; Abramowski *et al.*, 1995; Eberle-Wang *et al.*, 1997). Antagonism at 5-HT_{2C} receptors by various atypical antipsychotics (e.g. clozapine, risperidone, sertindole and ziprasidone; Roth *et al.*, 2003) may play a role in their beneficial effects and their improved adverse effects profile (Meltzer, 1995; 1999). However, antagonism at the 5-HT_{2C} receptor can increase food intake and body weight in rats (Bonhaus *et al.*, 1997), thus this may not be an advantageous strategy for treatment in patients as weight gain is a major adverse effect and could affect compliance (see Allison *et al.*, 1999 for meta-analysis).

SB-243213A is active in preclinical models of anxiety and has an improved anxiolytic profile compared with benzodiazepines (Wood *et al.*, 2001; Blackburn *et*

al., 2002). SB-243213A may also have antidepressant-like activity as it increased deep slow wave sleep quantity with similar effect to paroxetine (Smith *et al.*, 2002). There is limited data concerning the efficacy of SB-243213A in tests of cognition. The current data show that SB-243213A at 10.0 mg/kg selectively and significantly improved the PCP-induced deficit in the reversal phase of the task i.e. there were no effects on the initial phase or on total lever pressing. This is supported by recent data showing improvements in spatial reversal learning by the 5-HT_{2C} antagonist, SB242084 (Boulougouris *et al.*, 2008), suggesting that the facilitatory effects of 5-HT_{2C} antagonists could be mediated by the orbitofrontal cortex (OFC) as this task (Boulougouris *et al.*, 2007) and reversal learning within the attentional set shifting task (McAlonan and Brown, 2003) have been shown to be dependent on the OFC. The mechanism of the observed cognitive enhancement may be via increasing dopamine in the PFC. 5-HT_{2C} receptor activation has been suggested to reduce dopamine release in the nucleus accumbens and prefrontal cortex (Di Matteo *et al.*, 2001). The 5-HT_{2C} antagonist, SB242084, enhances dopamine release in the nucleus accumbens (Di Matteo *et al.*, 1999) and cortex (Gobert *et al.*, 2000).

Effect of buspirone and WAY-100635

In the current study, the efficacy of buspirone to improve the PCP-induced reversal learning deficit was antagonised partially by the 5-HT_{1A} antagonist, WAY-100635. There is evidence that 5-HT_{1A} receptor density is abnormally high in the frontal cortices of patients with schizophrenia (Burnet *et al.*, 1997) and a subsequent PET study has shown an increase in cortical 5-HT_{1A} receptor binding in schizophrenia (Tauscher *et al.*, 2002). Post-mortem studies have also indicated abnormalities in 5-

HT_{1A} receptor-mediated transmission in the frontal cortex of patients with schizophrenia (Sumiyoshi *et al.*, 1996).

Buspirone is a 5-HT_{1A} receptor partial agonist with weak D₂ receptor antagonist properties compared to typical antipsychotic drugs, with K_i values of 20nM and 240nM respectively (Hamik *et al.*, 1990). WAY-100635 may not have fully antagonised the effects of buspirone as it is rapidly converted to its metabolite 1-(2-pyrimidinyl)-piperazine (1-PP; Caccia *et al.*, 1986), a potent α_2 -adrenoceptor antagonist, which is able to stimulate cortical dopamine release (Gobert *et al.*, 1999). The effect of buspirone cannot be due to D₂ blockade as haloperidol is ineffective in reversing the PCP-induced deficit (Abdul-Monim *et al.*, 2006).

It is important to highlight that WAY-100635 administered alone at both 0.3 and 1.0 mg/kg did not improve the PCP-induced deficit. This is in agreement with a study in mice using a novel object recognition task whereby WAY-100635 at 1.0 mg/kg did not produce any improvement in the PCP-induced cognitive deficit (Hagiwara *et al.*, 2008). However, there are conflicting results surrounding the effects of WAY-100635 and other 5-HT_{1A} receptor antagonists; Wedzony *et al.* (2000) reported that WAY-100135 attenuated the deficit induced by MK-801 in tests of working memory and selective attention in rats. In addition, WAY-100635 has been shown to prevent learning deficits induced by blockade of AMPA receptors (Schiapparelli *et al.*, 2006). An explanation for the conflicting effects of WAY-100635 and WAY-100135 could be due to the acute administration of MK-801 (an NMDA receptor antagonist) and NBQX (an AMPA receptor antagonist) in comparison to our sub-chronic PCP administration, and also, the aforementioned studies were performed in male Wistar rats compared to our female hooded-Lister rats.

The antipsychotics clozapine, quetiapine, and ziprasidone have partial agonist properties at 5-HT_{1A} receptors, like buspirone (Newman-Tancredi *et al.*, 1998; Ichikawa *et al.*, 2001). There are conflicting preclinical results with 5-HT_{1A} compounds with selective agonists, partial agonists, and antagonists all being highlighted as potential molecular targets for cognitive enhancement in schizophrenia (see Gray and Roth, 2007). As previously mentioned there is a high concentration of 5-HT_{1A} receptors on cortical and hippocampal pyramidal neurons (Azmitia *et al.*, 1996). There is also a population of 5-HT_{1A} receptors on raphe neurons, where 5-HT_{1A} receptors function as somatodendritic autoreceptors providing inhibitory feedback control of 5-HT release (Barnes and Sharp, 1999). It is thought that this is where the action of 5-HT_{1A} antagonists is seen to improve cognition, while the beneficial effects on cognition in animal studies of 5-HT_{1A} partial agonists are thought to be mediated via an action at pyramidal neurons (Roth *et al.*, 2003; Schechter *et al.*, 2002). In schizophrenic patients, the 5-HT_{1A} agonist, tandospirone, has been shown to improve executive function and verbal memory when added on to ongoing typical antipsychotic treatment (Sumiyoshi *et al.*, 2001).

Our results from the present study are supported by another investigation from our laboratory in a social interaction test (Snigdha and Neill, 2008a). It was demonstrated that co-administration of WAY-100635 with aripiprazole, a partial 5-HT_{1A} agonist (Shapiro *et al.*, 2003), successfully prevented the beneficial effects of aripiprazole in a social interaction model of negative symptoms. It was suggested that 5-HT_{1A} receptor activation selectively augments cortical dopamine levels which results in improvement in the social behaviour deficits. This suggestion is in agreement with a previous report by Ichikawa and colleagues (2001) suggesting that 5-HT_{1A} induced dopamine release in the mPFC may be the potential basis for the

mechanism of action of at least some of the atypical antipsychotics. Our previous results showing impaired cortical dopamine release in PCP treated rats supports this hypothesis.

Conclusions

Sub-chronic PCP induces a robust reversal learning deficit, which is selective for the reversal phase of the reversal learning task; this is of great relevance for cognition in schizophrenia and this paradigm is listed by TURNS as a relevant task. SB-269970A, SB-243213A and buspirone attenuated the PCP-induced deficit, with WAY-100635 partially antagonising the effect of buspirone. We have also demonstrated that when administered alone WAY-100635 did not improve the PCP-induced cognitive deficit. The current studies suggest possible mechanisms of action of antipsychotics and particularly implicate the role of 5-HT₇, 5-HT_{2C} and 5-HT_{1A} receptors in the improvement of cognitive dysfunction of relevance to schizophrenia.

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Tables and Figures

Table 1 The experimental design for each drug study.

Day 1	Day 2	Day 3	Day 4	Day 5 +
Training session	Drug test day, reversal test session. Data shown in results section	Training session	Reversal test session, drug-free	The cycle repeated as needed

Table 2 The order of procedures and drug experiments post training.

Week	Experiment	Cohort	Procedure/treatment
1	-	1 and 2	Sub-chronic PCP treatment
2	-	1 and 2	7-day washout
3	1	1	SB-269970A (1, 3, 10 mg/kg)
4	2	2	SB-243213A (1, 3, 10 mg/kg)
5	3	2	Buspirone (0.15625, 0.3125, 0.625 mg/kg)
6	3	2	Buspirone (0.3125 mg/kg) alone and with WAY-100635 (0.3, 1 mg/kg)
7	4	2	WAY-100635 (0.3, 1 mg/kg)

Fig 1a: Effect of the 5-HT₇ receptor antagonist SB-269970A

Fig 1b

Fig 2a: Effect of the 5-HT_{2C} receptor antagonist SB-243213A

Fig 2b

Fig 3a: Effect of buspirone alone and in combination with WAY-100635

Fig 3b

Fig 4a: Effect of WAY-100635

Fig 4b

Figure Legends

Figure 1: The influence of acute treatment with SB-269970A (1.0, 3.0, 10.0 mg/kg, i.p.) on the effect of sub-chronic PCP on performance of the initial and reversal phase of the reversal learning task (n=8-10). **(a)** Data are shown as the mean total number of lever presses, correct responses are shown as clear bars and incorrect responses are shown as shaded bars. **(b)** Data are shown as mean $\pm$ s.e.m. percent correct responding. Paired t-tests showed a significant deficit in the reversal phase compared to the initial phase; ***P<0.001. Post-hoc Dunnett's t-test showed SB-269970A at 3.0 and 10.0 mg/kg significantly improved responding compared to PCP + vehicle in the reversal phase; ##P<0.01.

Figure 2: The influence of acute treatment with SB-243213A (1.0, 3.0, 10.0 mg/kg, i.p.) on the effect of sub-chronic PCP on performance of the initial and reversal phase of the reversal learning task (n=10). **(a)** Data are shown as the mean total number of lever presses, correct responses are shown as clear bars and incorrect responses are shown as shaded bars. **(b)** Data are shown as mean $\pm$ s.e.m. percent correct responding. Paired t-tests showed a significant deficit in the reversal phase compared to the initial phase; **P<0.01, ***P<0.001. Post-hoc Dunnett's t-test showed SB-243213A at 10.0 mg/kg significantly improved responding compared to PCP + vehicle in the reversal phase; #P<0.05.

Figure 3: The influence of buspirone (0.15625, 0.3125, 0.625 mg/kg, i.p.), and WAY-100635 (0.3, 1.0 mg/kg, i.p.) plus buspirone (0.3125 mg/kg, i.p.) on the effect

of sub-chronic PCP on performance of the initial and reversal phase of the reversal learning task (8-20). **(a)** Data are shown as the mean total number of lever presses, correct responses are shown as clear bars and incorrect responses are shown as shaded bars. **(b)** Data are shown as mean $\pm$ s.e.m. percent correct responding. A paired t-test showed a significant reduction in performance of the reversal phase compared with the initial phase; *** $P < 0.001$, * $P < 0.05$. Dunnett's t-test showed significant improvement in responding compared to PCP + vehicle in the reversal phase at 0.3125 mg/kg and 0.625 mg/kg; ## $P < 0.01$. Pretreatment with WAY-100635 at 0.3 and 1.0 mg/kg did not reverse the effect of 0.3125 mg/kg buspirone ($P = 0.208$ and $P = 0.082$ respectively).

Figure 4: The influence of WAY-100635 (0.3, 1.0 mg/kg, i.p.) alone on the effect of sub-chronic PCP on performance of the initial and reversal phase of the reversal learning task (n=8-10). **(a)** Data are shown as the mean total number of lever presses, correct responses are shown as clear bars and incorrect responses are shown as shaded bars. **(b)** Data are shown as mean $\pm$ s.e.m. percent correct responding. A paired t-test showed a significant reduction in performance of the reversal phase compared with the initial phase; *** $P < 0.001$, * $P < 0.05$. Dunnett's t-test showed no significant improvement in responding compared to PCP + vehicle in the reversal phase at 0.3 mg/kg and 1.0 mg/kg WAY-100635 ($P = 0.541$ and $P = 0.422$ respectively).