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Research report

Dopamine D1 receptor activation improves PCP-induced performance disruption in the 5C-CPT by reducing inappropriate responding

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HIGHLIGHTS

- Repeated PCP administration induced robust deficits in 5C-CPT performance.
- Pre-treatment with dopamine D1 receptor partial agonist, SKF 38393, partially attenuated PCP-induced deficits.
- Augmenting dopamine D1 receptors improved PCP-induced deficits by reducing inappropriate responding.

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ABSTRACT

Attentional deficits contribute significantly to the functional disability of schizophrenia patients. The 5-choice continuous performance test (5C-CPT) measures attention in mice, rats, and humans, requiring the discrimination of trial types that either require a response or the inhibition of a response. The 5C-CPT, one version of human continuous performance tests (CPT), enables attentional testing in rodents in a manner consistent with humans. Augmenting the prefrontal cortical dopaminergic system has been proposed as a therapeutic target to attenuate the cognitive disturbances associated with schizophrenia. Using translational behavioural tasks in conjunction with inducing conditions relevant to schizophrenia pathophysiology enable the assessment of pro-attentive properties of compounds that augment dopaminergic activity. Here, using a repeated phencyclidine (PCP) treatment regimen and the 5C-CPT paradigm, we assess the pro-attentive properties of SKF 38393, a dopamine D1 receptor agonist, in rats. We show that repeated PCP treatment induces robust deficits in 5C-CPT performance indicative of impaired attention. Pre-treatment with SKF 38393 partially attenuates the PCP-induced deficits in 5C-CPT performance by reducing false alarm responding and increasing response accuracy. Impaired target detection was still evident in SKF 38393-treated rats however. Thus, augmentation of the dopamine D1 system improves PCP-induces deficits in 5C-CPT performance by selectively reducing aspects of inappropriate responding. These findings provide evidence to support the hypothesis that novel therapies targeting the dopamine D1 receptor system could improve aspects of attentional deficits in schizophrenia patients.

1. Introduction

Cognitive deficits in schizophrenia remain an unmet clinical need that contribute significantly to long-term functional and occupational impairments [1,2]. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative identified seven cognitive domains that are dysfunctional in schizophrenia patients; one of which was attention/vigilance [3,4]. Improving attention is an important therapeutic target for schizophrenia, as impairments in attention impact other cognitive domains [5,6] and are associated with higher costs of care-giving [7]. If pro-attentive therapies are to be developed, animal models that consist of inducing conditions relevant to the pathophysiology of schizophrenia and cross-species translational procedures are required [8].

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The Continuous Performance Test (CPT) is commonly used to assess attention in humans [9] and schizophrenia patients exhibit CPT deficits [10–13]. Although several variants exist, all CPTs include target and non-target trials that require either a response or the inhibition of a response, respectively [14]. As subjects must discriminate between two trial types, generating either hits, misses, correct rejections or false alarms, signal detection theory (SDT) can be used to quantify signal sensitivity and response bias. Using an animal task that generates the same response outcomes as human CPTs will be advantageous in the assessment of novel therapeutics designed to improve attention. Several attentional tasks exist in rodents. Widely used since 1983, the 5-choice serial reaction time task (5-CSRTT) [15,16] has significantly improved our understanding of the neural substrates that underlie attentional processing [16,17]. However, while assessing sustained attention, the 5-CSRTT differs from human CPTs in that it does not include non-target trials that must be correctly rejected. As a result, the 5-CSRTT was modified to include both target and non-target trials, the latter requiring the inhibition of a response. As responding in this task, termed the 5-choice continuous performance task (5C-CPT), results in hits, misses, correct rejections or false alarms, SDT analyses can be performed in a manner similar to human CPT analysis. The 5C-CPT was originally described in mice [18–20] and subsequently validated in rats by us [21–24] and others [25]. This test has also been reverse-translated for use in humans and performance involves neural activation in brain regions consistent with other CPTs [26], sleep deprivation causes similar deficits in mice and man [27], and importantly, is clinically sensitive since schizophrenia patients exhibit deficits in the human 5C-CPT [28]. Accordingly, the 5C-CPT had been proposed as a potential cross-species test of attention by the cognitive neuroscience-based NIMH-initiative Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) [29]. Using the 5C-CPT may provide a method to assess putative pro-attentive compounds with cross-species translational relevance to human testing [8].

Glutamatergic dysfunction is a prominent hypothesis of schizophrenia pathogenesis [30,31]. Indeed, blockade of the *N*-methyl-D-aspartate (NMDA) glutamate receptor generates a schizophrenia-like state in humans [32,33] and exacerbates symptoms in stabilized patients [34,35]. Consequently, NMDA receptor antagonists (e.g., phencyclidine [PCP] or ketamine) are widely used in preclinical research when investigating various aspects of schizophrenia [36]. Repeated or sub-chronic administration of NMDA receptor antagonists to experimental animals induces cognitive impairments, aspects of negative symptoms and neuropathological changes observed in schizophrenia patients [37–40]. Disruption in attentional performance is evident after NMDA receptor antagonism. Repeated [41] or chronic intermittent PCP-treatment [42] impaired 5-CSRTT performance. Furthermore, 5-CSRTT deficits induced by repeated PCP-treatment were attenuated by clozapine [41], but not quetiapine [43] treatment. Repeated PCP treatment also replicates some of the neuropathological alterations observed in schizophrenia [44]. In addition, after a one week washout period, sub-chronic PCP treatment induces 5C-CPT deficits when task difficulty is increased [24] reminiscent to 5C-CPT deficits exhibited by schizophrenia patients [28]. PCP treatment may, therefore, reflect a relevant inducing condition to test pro-cognitive agents to treat the attentional disruption observed in schizophrenia.

Dopamine transmission, mediated through the dopamine D1 receptor subtype, has been proposed as a promising target for the development of pro-cognitive agents in schizophrenia [45–47]. Indeed, decreased prefrontal dopamine D1 receptor binding [48] and a reduced capacity for cortical dopamine release [49] has been observed in schizophrenia patients. Thus, augmenting the cortical dopaminergic system may alleviate some of the symptoms associated with schizophrenia. Dopamine D1 receptor activation has been shown to improve attention/vigilance in a baseline-dependent manner [21,50]. Other dopamine-related treatments also improve attention in a baseline-dependent manner, such as methylphenidate and atomoxetine [23], and dopamine releasing agents such as nicotine [19] further demonstrating the involvement of dopamine in attentional processing. Dopamine D1 receptor activation attenuates reversal learning and novel object recognition (NOR) deficits induced by sub-chronic PCP administration [51,52]. In addition, asenapine, a newly licensed antipsychotic, recruits D1 receptor mechanisms to reverse sub-chronic PCP induced deficits in the NOR test [53]. Finally, results from a recent preliminary proof-of-principle study in a small number of unmedicated patients suggest that dopamine D1 receptor activation may improve schizophrenia-spectrum working memory deficits in humans [54]. Collectively, these findings highlight the importance of the dopamine D1 receptor system as a potential target to ameliorate cognitive dysfunction associated with schizophrenia. As a result, our aim here was to determine whether dopamine D1 receptor activation can overcome attention deficits induced by repeated PCP in the translational 5C-CPT in female rats.

2. Methods

2.1. Subjects

Female hooded-Lister rats ($n = 23$; Charles River; approx 220 ± 10 g at the start of the experiment) were housed on a 12 h reversed light cycle (lights on at 7:00 pm) in a temperature (21 ± 2 °C) and humidity (55 ± 5%) controlled environment. Female rats were used as they have consistently demonstrated reliable performance in our laboratory in a variety of cognitive tests [40] at all stages of the oestrus cycle [52,55]. Furthermore, we have thoroughly validated the 5C-CPT in our laboratory using female rats and demonstrated impaired performance following sub-chronic PCP and effects of D1 receptor agonism in "normal" rats [20–23]. All experimentation was conducted in the animal's natural dark-cycle under red lighting. Animals had free access to food (Special Diet Services, UK) and water until one week prior to the beginning of training, when food restriction reduced their weight to 90% of their free-feeding body weight (approximately 14 g rat chow/rat/day). Food restriction continued throughout training and testing, however water was available *ad libitium* in the home cage. All experiments were conducted in accordance with the UK Animals (Scientific Procedures) 1986 Act and local University ethical guidelines.

2.2. Drugs

Phencyclidine hydrochloride (PCP, Sigma–Aldrich, UK) was dissolved in 0.9% sterile saline, SKF 38393 (Sigma–Aldrich, UK) was dissolved in distilled H_2O. Drugs were administered in a volume of 1 ml/kg via the intraperitoneal (i.p.) route, where drug dose is expressed as free-base. PCP was administered at 2.5 mg/kg (i.p.). The D1 receptor agonist SKF 38393 was used at one dose only of 6 mg/kg, chosen as we have found it to be the most effective dose in our previous 5C-CPT experiments [21]. In addition, 6 mg/kg SKF 38393 has been investigated in other domains of cognition [56], and demonstrates efficacy to attenuate PCP-induced cognitive impairments in other tests [51,52].

2.3. Apparatus

The test apparatus consists of eight 25 cm × 25 cm aluminium chambers, each enclosed within a sound attenuating box [21,24].