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Research report

Effects of asenapine, olanzapine, and risperidone on psychotomimetic-induced reversal-learning deficits in the rat

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ABSTRACT

Background: Asenapine is a new pharmacological agent for the acute treatment of schizophrenia and bipolar disorder. It has relatively higher affinity for serotonergic and α_2-adrenergic than dopaminergic D_2 receptors. We evaluated the effects of asenapine, risperidone, and olanzapine on acute and subchronic psychotomimetic-induced disruption of cued reversal learning in rats.
Methods: After operant training, rats were treated acutely with D-amphetamine (0.75 mg/kg intraperitoneally [i.p.]) or phencyclidine (PCP; 1.5 mg/kg i.p.) or subchronically with PCP (2 mg/kg i.p. for 7 days). We assessed the effects of acute coadministration of asenapine, risperidone, or olanzapine on acute D-amphetamine- and PCP-induced deficits and the effects of long-term coadministration of these agents (for 28 additional days) on the deficits induced by subchronic PCP.
Results: Deficits in reversal learning induced by acute D-amphetamine were attenuated by risperidone (0.2 mg/kg i.p.). Acute PCP-induced impairment of reversal learning was attenuated by acute asenapine (0.025 mg/kg subcutaneously [s.c.]), risperidone (0.2 mg/kg i.p.), and olanzapine (1.0 mg/kg i.p.). Subchronic PCP administration induced an enduring deficit that was attenuated by acute asenapine (0.075 mg/kg s.c.) and by olanzapine (1.5 mg/kg i.p.). Asenapine (0.075 mg/kg s.c.), risperidone (0.2 mg/kg i.p.), and olanzapine (1.0 mg/kg i.p.) all showed sustained efficacy with chronic (29 days) treatment to improve subchronic PCP-induced impairments.
Conclusion: These data suggest that asenapine may have beneficial effects in the treatment of cognitive symptoms in schizophrenia. However, this remains to be validated by further clinical evaluation.

1. Introduction

Cognitive dysfunction is a core component of schizophrenia [19]. Deficits affecting attention, perception, executive function, and memory may even be present in schizophrenics experiencing their first psychotic episode [34]. These cognitive deficits have significant bearing on patient recovery, functional capacity, and societal reintegration [4,8,9].

Given the negative impact of cognitive dysfunction on long-term patient function and quality of life, the lack of reliably effective treatment is considered to be a key unmet clinical need [16]. However, the clinical literature has generally reported no consistent, substantial improvement in cognition with the current pharmacotherapies for schizophrenia [20,42]. In one long-term naturalistic study, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, some antipsychotics produced small but statistically significant improvements in cognition [32]. In further recognition of the need to address cognitive dysfunction in patients with schizophrenia and to encourage the development of cognition-enhancing drugs for schizophrenia, the National Institute of Mental Health, in collaboration with the University of California at Los Angeles and the US Food and Drug Administration, initiated the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) programs.

Preclinical studies have routinely demonstrated that second-generation antipsychotics (SGAs) enhance cognitive function in animal models that assess reversal learning, working and nonspatial memory, and selective attention [1–3,11,18,24,25,35,39,56,57]. In a rodent operant reversal-learning paradigm based on tasks developed by Smith et al. [49] and Jones et al. [30], deficits in reversal learning produced by phencyclidine (PCP) were attenuated by the SGAs clozapine, ziprasidone, and olanzapine, but not by the first-generation antipsychotics haloperidol or chlorpromazine [2,3,25]. Similarly, deficits in novel object recognition and attentional set shifting induced by 7 days of treatment with PCP

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are reversed by clozapine and risperidone but not by haloperidol [18,39]. Importantly, doses of SGAs that attenuate the effects of PCP do not generally have an effect on reversal learning in non-impaired rats, and we have recently demonstrated lack of impairment in control rats treated with clozapine and risperidone at doses that improve PCP-induced deficits, including the doses of risperidone shown to be effective in the present study McLean personal communication.

Cognitive deficits induced by drugs affecting glutamatergic function—in particular, N-methyl-D-aspartate (NMDA) receptor antagonists such as PCP and ketamine—mimic cognitive dysfunction in schizophrenia [7,27,33]. These findings support the NMDA hypothesis of schizophrenia, which proposes that cognitive deficits in schizophrenics may be partially attributed to NMDA receptor hypofunction [44]. Therefore, inducing cognitive deficits with subchronic PCP treatment may be useful for assessing the treatment of cognitive dysfunction in schizophrenia [26,29].

Asenapine is a novel psychopharmacologic agent recently approved for the treatment of schizophrenia and bipolar disorder. It has been shown to be effective and well tolerated in the treatment of schizophrenia [45] and mania in bipolar disorder patients [38]. It shows nanomolar level binding and antagonist activity at cloned human serotonin (5-HT: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_5, 5-HT_6, 5-HT_7,), dopamine (D_1, D_2, D_3, D_4), α-adrenergic (α_{1A}, α_{2A}, α_{2B}, α_{2C}), and histamine (H_1, H_2) receptors but minimal affinity for muscarinic receptors [47,48]. In particular, asenapine has higher affinity for some serotonergic (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_6, 5-HT_7), adrenergic (α_{2B}), and dopamine receptors (D_3) when compared with dopamine D_2 receptors [48].

In this report, we assess the effects of asenapine on reversal-learning deficits induced by acute PCP or D-amphetamine, or subchronic PCP. Because modulation of dopaminergic and glutamatergic activity may be mediated through antagonism of 5-HT receptors, it was hypothesized that asenapine would exhibit beneficial effects in these models of psychotomimetic-induced cognitive deficits. The effects of olanzapine and risperidone monotherapy were independently examined to provide comparators for asenapine. Both have shown efficacy to reverse PCP-induced impairments in this and other models [1,18,39,42]; however, neither has previously been tested against D-amphetamine-induced cognitive deficits.

2. Materials and methods

2.1. Animals

Adult female Lister hooded rats ($n = 100$ in all 3 studies combined) obtained from Harlan, UK, were used in these studies. Female rats were used because they show robust cognitive deficits induced by PCP in several other paradigms and perform better in certain cognitive tasks compared with male rats [51,52]. Stage of the estrous cycle does not affect the ability of rats to perform in novel object recognition or reversal-learning tasks [41,51].

Rats were housed in groups (4–5 per cage) and maintained under standard laboratory conditions (temperature, 21 ± 2 °C; humidity, 40–50%). A 12-h light/dark cycle (lights on at 7:00 AM) was maintained. All procedures were performed during the light phase. All rats were reduced to approximately 85% of their free-feeding body weight (225–250 g) before each study and maintained at this weight by restricting food access to 12 g/day of standard laboratory chow (Special Diet Services, Essex, UK). Free access to water was provided. All experiments were conducted in accordance with the Animals (Scientific Procedures) Act, UK, of 1986 and approved by the University of Bradford ethical review process.

2.2. Drugs

Asenapine, olanzapine, and risperidone were supplied by Schering-Plough Corporation (Newhouse, Lanarkshire, UK). Asenapine was dissolved in 0.9% saline and administered subcutaneously (s.c.). Asenapine was given s.c. in an attempt to provide a surrogate for the sublingual route used in clinical studies [45], as well as for consistency with other preclinical studies that have assessed the effects of asenapine [15,23,54,55]. Olanzapine and risperidone were dissolved in a small volume of acetic acid, adjusted to their final concentration with 0.9% saline, pH-adjusted to 5.5–6.0 with 0.1 M NaOH, and administered intraperitoneally (i.p.). PCP hydrochloride and D-amphetamine sulfate (Sigma–Aldrich, Irvine, Scotland, UK) were dissolved in 0.9% saline and administered as an i.p. injection. All doses are base equivalent weight and were administered in a volume of 1 mL/kg.

2.3. Protocols

2.3.1. Operant training

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 described in detail previously [2]. Rats were trained to press either the left or right lever for food delivery according to a visual cue (LED on or off). The experimental session was terminated following a total of 128 lever presses, which took approximately 30 min. Rats were trained once-daily for 5 days, and this was repeated until rats had reached criterion (i.e., 90% correct responding for 3 consecutive days).

The day before each reversal-learning session, a full 30-min operant training session (as described above) was conducted 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 training day. During this period, responses on both correct and incorrect levers were recorded. This part of the session was the initial phase. This was followed by a 2-min time-out period, which was signalled by the house light being turned off. The 2-min time-out period acts as a cue that the rule is about to change. 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 the reversal phase. Animals undertook several of these reversal-learning sessions before beginning the drug studies 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).

2.3.2. Studies 1a and 1b: effects of acute intervention on deficits induced by acute D-amphetamine or PCP

Rats were tested on a cycle of 4 days. 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 session. On day 3 and day 4, each animal underwent a further operant training session and reversal-learning session, respectively, to ensure that normal responding was regained following drug treatment. If responding was not normalized, the 4-day cycle was repeated. The order of treatment exposure was determined randomly for each rat. This cycle of testing has previously been described in detail [25]. For drug treatments we used 9–10 rats per treatment. The PCP (1.5 mg/kg) and D-amphetamine (0.75 mg/kg) doses used were chosen based on previous studies [2,25]. Both were administered 30 min before testing. Based on preliminary tests with asenapine (0.003–0.1 mg/kg s.c.) that assessed effects on spontaneous locomotor activity, doses of asenapine (0.025, 0.05, and 0.075 mg/kg s.c.) were chosen that were expected to have minimal effects on motor function. The asenapine doses and s.c. route used in these studies were also based on studies demonstrating D_2 receptor occupancy in rat brain [47] and demonstrating antipsychotic-like activity in established neurochemical and behavioral paradigms [15,23,55]. Asenapine was administered 40 min before testing and 10 min before PCP or D-amphetamine. The risperidone (0.05, 0.1, and 0.2 mg/kg i.p.) and olanzapine (0.5, 1.0, and 1.5 mg/kg i.p.) doses were also based on previous studies from this laboratory [3,18,39] and do not exceed the range that is suggested to be clinically relevant, based on dopamine D_2 receptor occupancy in rat brain [31]. Olanzapine and risperidone were given 45 min before testing and 15 min before PCP or D-amphetamine.

2.3.3. Study 2: effects of acute intervention on deficits induced by subchronic PCP

After completion of reversal-learning training as described above, another group of rats was treated twice-daily for 7 days with PCP 2 mg/kg ($n = 40$) or 0.9% saline at 1 mL/kg ($n = 10$). The PCP dose was chosen based on previous work in our laboratory demonstrating robust and enduring cognitive and social behavior deficits [1,3,18,39,50]. During PCP treatment and the subsequent 7-day drug-free period, reversal-learning sessions were discontinued to prevent the development of an association between PCP treatment and the reinforcement contingencies of the reversal-learning task and to ensure that PCP-induced deficits were enduring and not related to acute PCP withdrawal. Treatment with asenapine, risperidone, olanzapine, and respective vehicles was performed according to the same 5-day cycle and procedures described for study 1. Overall, it took 3–4 weeks to complete this study.

2.3.4. Study 3: effects of chronic intervention on deficits induced by subchronic PCP

After completing study 2, the same rats then continued to be treated for 28 days with twice-daily asenapine 0.075 mg/kg, once-daily risperidone 0.2 mg/kg, once-daily olanzapine 1.5 mg/kg, or vehicle. Because it took 3–4 weeks to complete study 2, chronic treatment during study 3 was initiated approximately 4–5 weeks after subchronic PCP treatment had ended.

In vehicle- and asenapine-treated rats, injections were administered at 8:00 AM and 4:00 PM. In risperidone- and olanzapine-treated rats, drug injections were administered at 8:00 AM, and an additional vehicle injection was administered at