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Research report

Comparison of phencyclidine-induced spatial learning and memory deficits and reversal by sertindole and risperidone between Lister Hooded and Wistar rats

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HIGHLIGHTS

- Lister Hooded rats showed a better spatial memory than Wistar rats.
- PCP induced navigation deficits at lower doses in Lister Hooded than in Wistar rats.
- Sertindole reversed PCP-induced deficits in Lister Hooded but not in Wistar rats.
- Spatial learning and memory deficits are better modeled by PCP in Lister Hooded rats.

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ABSTRACT

Visual learning and memory are one of the key cognitive domains disturbed in schizophrenia. Glutamate NMDA receptors play a crucial role in spatial learning and memory and NMDA receptor antagonists, such as phencyclidine (PCP), impair spatial learning and memory. Pigmented rat strains have superior vision than albino rat strains and are therefore commonly used in visually-demanding cognitive tests. However, all previous water maze experiments using acutely administered PCP to induce schizophrenia-like cognitive deficits have been conducted with albino Wistar rats. This study was designed to assess whether pigmented Lister Hooded (LH) rats would be more suitable in modeling acute PCP-induced deficits in Morris water maze (MWM) task than Wistar rats. We also evaluated whether the efficacy of atypical antipsychotics in reversing PCP-induced spatial navigation deficits was dependent on the rat strain. First, we compared the PCP dose-response in the range of 1.3–2.0 mg/kg (s.c.) at causing deficits in MWM performance. Then, the efficacies of sertindole 1.6 mg/kg (s.c.) and risperidone 0.04 mg/kg (s.c.) in reversing PCP-induced spatial navigation deficits were investigated. Drug-naïve LH rats showed a better spatial memory than Wistar rats. Furthermore, PCP induced deficits in spatial navigation at lower doses in LH than in Wistar rats. In addition, PCP-induced deficits were partly reversed by sertindole in LH but not in Wistar rats. Our results suggest that the deficits in spatial learning and memory that resemble memory deficits found in schizophrenia patients are better modeled by PCP in LH rats than Wistar rats.
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1. Introduction

Schizophrenia is a multifactorial chronic neuropsychiatric disease. Its symptoms are commonly categorized into three classes: positive (hallucinations, delusions, conceptual disorganization), negative (emotional flattening, social withdrawal, anhedonia, avolition) and cognitive (impaired executive function, working memory and attention). Cognitive dysfunction constitutes a prominent and disabling part of the disease [26]. In fact, it is now recognized that several domains of cognition are affected in schizophrenia patients as concluded by the Measurement

Abbreviations: ANOVA-RM, repeated measures analysis of variance; LH, Lister Hooded rat; NMDA, *N*-methyl-D-aspartate; PCP, phencyclidine.

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and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative [40]. Currently available drug treatments of schizophrenia have little or no impact in alleviating the cognitive symptoms; this is a significant unmet medical need [7,33]. The lack of efficacious treatments for cognitive deficits may be due to complex and still poorly understood effects of schizophrenia on cognitive domains as well as difficulties in modeling cognitive dysfunction during nonclinical drug development.

The etiology and neurobiological mechanisms of schizophrenia have remained elusive even though it is more than 50 years since the discovery of the first antipsychotic drug, chlorpromazine. However, it is generally accepted that both genetic and environmental factors play a role in the etiology of schizophrenia, and brain dopaminergic and glutamatergic systems are affected (e.g., [29,37,47]. Hypofunction of *N*-methyl-D-aspartate (NMDA) receptor-mediated neurotransmission has been hypothesized to associate with the pathogenesis of schizophrenia [24,41]. NMDA receptor antagonists, such as phencyclidine (PCP) and ketamine, have been shown to induce not only the positive symptoms, but also the cognitive deficits and negative symptoms associated with schizophrenia in healthy individuals and to exacerbate these symptoms in schizophrenia patients [8,22,27,30]. Because of their apparent face validity, NMDA receptor antagonists have become an important tool for modeling schizophrenia in nonclinical studies in rodents [24,25,36,39].

Visual learning and memory are one of the key cognitive domains disturbed in schizophrenia [40]. NMDA receptors play a crucial role in spatial learning and memory, i.e., blockade of NMDA receptors impairs spatial learning and memory [31]. The Morris water maze [35] is one of the most commonly used behavioral tests for assessing spatial learning and memory in rodents. Previous studies have shown while acute PCP can indeed impair spatial navigation in rats [11,42,55,56], subchronic PCP treatment followed by a 1 week washout period has no effect on water maze task acquisition and retention [23]. Acute administration of NMDA antagonists may induce non-specific behavioral changes such as ataxia or hyperlocomotion at higher doses and thus interfere with the assessment of their specific effects on cognition [12,17,49]. However, a 3-day pre-treatment with PCP prior to water maze task acquisition was able to attenuate the undesired sensorimotor side-effects encountered after acute PCP treatment [42].

The pigmented Lister Hooded (LH) rat strain is a commonly used strain to model schizophrenia-like cognitive deficits in tasks that require good vision such as novel object recognition [45,46,50,54] and touchscreen-based cognitive tasks [1,15,23,51]. However, all previous water maze experiments using acute PCP to induce schizophrenia-like cognitive deficits have been carried out with albino Wistar rats [11,42,55,56], a rat strain with much poorer vision than their pigmented counterparts [14,28,43,44]. Therefore, we aimed to compare whether spatial learning and memory deficits induced by acute PCP effect could be better modeled in LH rats than Wistar rats in a Morris water maze task. Since the atypical antipsychotics, sertindole and risperidone, have been shown to reverse PCP-induced spatial navigation deficits in rats [11], we also aimed to compare whether the efficacy of sertindole and risperidone in reversing PCP-induced deficits is dependent on the rat strain.

2. Materials and methods

2.1. Animals

Male Wistar rats were delivered from Kuopio Laboratory Animal Centre (HsdHan:WIST; University of Eastern Finland, Kuopio, Finland, n = 218, age: 10–11 weeks, weight: 240–385 g). Male Lister Hooded (LH) rats were delivered from Harlan Laboratories (HsdOla:LH, UK and the Netherlands, n = 214, age: 10–11 weeks, weight: 230–395 g). The rats were housed in groups of two in stainless steel cages (28.5 × 48.5 × 20 cm) and maintained under controlled laboratory conditions (lights on 7.00 a.m.–7.00 p.m., room temperature 21 ± 2 °C, humidity 55 ± 15%). The rats were allowed to acclimatize to housing conditions at least 7 days before starting the behavioral tests. Food pellets (Teklad 2016S, Harlan Laboratories, the Netherlands) and water were available ad libitum. All experiments were performed in accordance with European Union guidelines (Directive 2010/63/EU and guidelines 2007/526/EC) and approved by the National Animal Experiment Board of Finland.

Table 1
Treatment groups and number of animals in experiments.

Treatments (mg/kg)	Lister Hooded (n)	Wistar (n)
PCP dose-response		
SAL	12	16
PCP 1.3	18	16
PCP 1.6	18	8
PCP 2.0	8	16
Sertindole		
SAL + VEH	30	35
PCP 2.0 + VEH	45	35
PCP 2.0 + SERT 1.6	45	35
Risperidone		
SAL + VEH	6	19
PCP 2.0 + VEH	16	19
PCP 2.0 + RISP 0.04	16	19

2.2. Drugs and treatments

Phencyclidine hydrochloride (PCP; 1-(1-phenylcyclohexyl) piperidine hydrochloride, Tocris Bioscience, Bristol, UK) was dissolved in physiological saline (0.9%) (doses refer to PCP hydrochloride). Sertindole (Sigma-Aldrich, St. Louis, MO, USA) and risperidone (Sigma-Aldrich, St. Louis, MO, USA) were dissolved in phosphate buffer solution (United States Pharmacopeia, pH 6.0) containing 2% Tween®80. Vehicle solution was 2% Tween®80 in phosphate buffer solution (pH 6.0). All compounds were administered subcutaneously in a volume of 5 ml/kg. PCP was given once daily for 8 days, starting 3 days before the first water maze test day. On the test days, PCP was administered 30 min before first daily trial. Sertindole 1.6 mg/kg and risperidone 0.04 mg/kg were administered on water maze test days 60 min before the first daily trial. The doses of PCP and antipsychotics were selected on the basis of previous rat studies [11,42,55,56]. Experiments were conducted in a blinded manner, i.e., the researcher was not aware of the treatment given to the animals. Three different set of water maze experiments were performed in LH and Wistar rats: dose-response of PCP-induced deficits in spatial navigation, reversal of PCP-induced deficits in spatial navigation by sertindole and reversal of PCP-induced deficits in spatial navigation by risperidone. The treatment groups in the experiments are presented in Table 1.

2.3. Test apparatus

A black circular pool was used in experiments with albino Wistar rats (diameter of 150 cm and height 76 cm) while a white pool (diameter of 146 cm and height 70 cm) was used with black/white LH rats to ensure optimal contrast for video tracking. The water temperature was always 19 ± 1 °C. A rectangular escape platform (10 × 10 cm) was situated 2 cm below the water surface in the north-east pool quadrant. Illumination at the water surface was approximately 50 lx. Five start positions at the perimeter of the pool were south-east, south, south-west, west and north-west. Several

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