



# Disruption of social cognition in the sub-chronic PCP rat model of schizophrenia: Possible involvement of the endocannabinoid system

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Received 24 August 2015; received in revised form 13 November 2015; accepted 4 December 2015

## KEYWORDS

Endocannabinoid;  
Odor discrimination;  
Phencyclidine;  
Social cognition

## Abstract

Previous studies have shown that social withdrawal in the phencyclidine (PCP) rat model of schizophrenia results from deficient endocannabinoid-induced activation of CB<sub>1</sub> receptors. To understand the underlying cognitive mechanisms of the social deficit in PCP-treated rats, we examined the impact of pharmacological manipulation of the endocannabinoid system on sociability (i.e. social approach) and social novelty preference (which relies on social recognition).

Control rats showed a clear preference for a “social” cage (i.e. unfamiliar stimulus rat placed under a wire mesh cage) versus an “empty” cage, and spent more time exploring a “novel” cage (i.e. new stimulus rat) versus a “familiar” cage. In contrast, rats receiving PCP (5 mg/kg, b.i.d. for 7 days, followed by a 7 day-washout period) showed intact sociability, but lacked social novelty preference. This PCP-induced deficit was due to increased activity at CB<sub>1</sub> receptors as it was reversed by systemic administration of the CB<sub>1</sub> antagonist AM251 (1 mg/kg). In agreement with this hypothesis, the cannabinoid agonist CP55,940 (0.003–0.03 mg/kg) dose-dependently suppressed social novelty preference in control animals without affecting sociability.

Taken together, these data suggest that PCP-treated rats have a deficit in social cognition, possibly induced by increased stimulation of CB<sub>1</sub> receptors. This deficit, however, is distinct from the social withdrawal previously observed in these animals, as the latter is due to deficient, rather than increased, CB<sub>1</sub> stimulation.

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## 1. Introduction

Social withdrawal, a hallmark of several psychiatric disorders, is a behavioral construct that can be assessed in humans and animals (Wilson and Koenig, 2014). Chronic administration of the N-methyl-D-aspartate (NMDA) glutamate receptor antagonist phencyclidine (PCP) in rodents has been widely used to model schizophrenia (Enomoto et al., 2007) and negative symptoms, as it mimics the complex clinical and pathological features of the disease (Jentsch and Roth, 1999). In particular, PCP-treated rats represent the best pharmacological model of social withdrawal (for schizophrenia) in term of construct, face and predictive validity (Gururajan et al., 2010). Nevertheless, the ability of PCP to model schizophrenia varies greatly depending on the treatment regimen, and only withdrawal from repeated PCP administration, rather than acute exposure, produces behavioral, neurochemical and brain circuit alterations matching those observed in schizophrenia (Dawson et al., 2014b; Jentsch and Roth, 1999). Moreover, NMDA antagonists (e.g. PCP, MK801 and ketamine) cannot be used interchangeably when modeling schizophrenia (Dawson et al., 2014a), as only PCP has been shown to produce behavioral deficits reminiscent of positive/negative symptoms, and the characteristic cognitive deficits observed in the disease (Seillier and Giuffrida, 2009).

Social dysfunction plays a central role in schizophrenia (Billeke and Aboitiz, 2013), and negative symptoms seem to intersect with alterations in social cognition and emotional processing in particular (Ochsner, 2008). Indeed, social withdrawal is mainly associated with *asociality*, a domain of negative symptoms that results from indifference or lack of desire to have social contacts, as well as with impaired *social cognition*, a domain of cognitive deficits referring to the mental operations underlying social interactions (e.g., ability and capacity to perceive the intentions and dispositions of others) (Hoernagel and Hofer, 2014). Thus, a comprehensive understanding of social withdrawal requires the study of the altered psychological processes underlying this behavioral deficit.

This issue may be addressed by employing multiple testing paradigms capable of capturing several aspects of social behavior (e.g. social approach, social cognition, etc.) (O'Tuathaigh et al., 2010b). Social behavior in rodent models of schizophrenia is typically assessed by measuring social interactions between two freely moving animals (Wilson and Koenig, 2014). Using this paradigm, we recently demonstrated that PCP-induced social withdrawal results from lack of cannabinoid CB<sub>1</sub> receptor stimulation (Seillier et al., 2013). However, to quote Millan and Bales (2013), a “challenge with this basic version of the task is that both animals are freely moving, making it difficult to disentangle factors such as social motivation, emotional status, attention and motor drive, etc. Further, and of particular importance for translational research in schizophrenia, the unmodified procedure does not specifically address the issue of social cognition”. Therefore, in line with the CNTRICS initiative for improving animal models of cognitive impairments in schizophrenia (Millan and Bales, 2013), we developed a behavioral test adapted from “the mice three-chamber social approach task” (Nadler et al., 2004) that allows the evaluation of two fundamental aspects of social

behavior: sociability and social novelty preference. Sociability - defined as the motivation to spend more time with a social stimulus - is assessed by comparing the time spent by an animal interacting with a conspecific versus a non-social object. Social novelty preference - defined as the propensity to spend more time with an unfamiliar animal - relies on the ability to remember a conspecific and discriminate between familiar versus novel individuals (social recognition).

In this study, we aimed to: 1) explore the cognitive processes underlying social withdrawal in the sub-chronic PCP rat model of schizophrenia, and 2) assess whether these putatively altered processes shared the same pharmacology observed in PCP-induced social withdrawal as assessed by the classical dyadic social interaction test (Seillier et al., 2013). In contrast to the experimental protocol used for the three-chamber task, our rats were tested in an open arena virtually divided into quadrants. Nevertheless, as in the case of the original paradigm, the “stimulus” rat was placed under a wire mesh cage (unable to move freely), allowing the experimental rat to initiate and terminate any interaction (free choice).

## 2. Experimental procedures

### 2.1. Animals

One hundred and eight male Wistar rats (200–225 g; Charles River Laboratories, Wilmington, MA) were housed in pairs at  $22 \pm 1^\circ\text{C}$ , under a 12 h light-dark cycle with food and water available ad libitum. All animals were habituated to the housing conditions for one week prior to the behavioral tests. All experiments were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee of the University of Texas Health Science Center at San Antonio.

### 2.2. Social approach and social novelty preference task

This task was directly adapted from the three-chamber social approach task developed by Crawley et al. (Nadler et al., 2004), using an open arena (100 cm  $\times$  100 cm  $\times$  40 cm) made of black acrylic. The arena was located in a dimly lit room (5 lx at the arena center), and was virtually divided into quadrants (Figure 1A). A holding cage adjacent to the arena was used to host the animals during the inter-trial intervals (2 min). During the procedure, a blinded experimenter stayed motionless next to the corner in which the experimental rat was introduced in the arena, and manually scored the time spent by the test rat exploring the “mesh cages” (see below). The procedure, which was videotaped for further analysis, consisted of three phases:

**Habituation.** The experimental rat was placed in one corner of the empty arena and free exploration was allowed for 30 min. The first 5 min of open field behavior were examined by an experimenter blind to the study by off-line analysis of the videotape (a  $7 \times 7$  grid image was superimposed on the monitor; Figure 1A left panel). The primary measures were the number of entries (E), time spent (T), number of rears (R) and number of squares crossed (S) in the center ( $3 \times 3$  zone;  $E_{ce}$ ,  $T_{ce}$ ,  $R_{ce}$  and  $S_{ce}$ , respectively) or in the periphery (rest of the arena;  $E_{pe}$ ,  $T_{pe}$ ,  $R_{pe}$  and  $S_{pe}$ , respectively).

**Sociability.** A wire mesh cage (white epoxy-coated aluminum round basket; 25.5 diameter, 22.9 cmH), designated as “empty” cage, was placed at one corner of the arena (6 cm from the walls), and an unfamiliar “stimulus” rat was placed under a second

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