# Effects of Clozapine, Aripiprazole and Bitopertin in Rats Social Withdrawal Assessed in an Automatic Social Interaction Test

S. Deiana, H. Rosenbrock and R. Arban

Department of CNS Diseases Research, Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany.
serena.deiana@boehringer-ingelheim.com

## Introduction and aims

Deficient N-methyl-D-aspartate (NMDA) signaling is hypothesized to underlie cognitive and negative symptoms associated with schizophrenia which to date are poorly responsive to currently available antipsychotics.

In healthy volunteers, the NMDA receptor antagonists phencyclidine (PCP) and ketamine induce psychotomimetic effects mirroring positive, negative and cognitive symptoms of schizophrenia [1, 2]. Moreover, these NMDAR antagonists can exacerbate positive and negative symptoms of schizophrenics [3-5]. Social withdrawal is one of the negative symptoms of schizophrenia and it can be mimicked in animals via PCP administration [6,7].

In the present set of experiments, we aimed at implementing an automatic three-chamber social interaction test in rats. Social withdrawal was induced by PCP treatment [7] and possible reversal by the antipsychotics clozapine, aripiprazole and the GlyT1-inhibitor Bitopertin [8, 9] was evaluated. The development of a robust pre-clinical model that closely mimics social interaction deficits typical of schizophrenia would contribute to the discovery of efficacious therapies aimed at alleviating such symptom.

## Methods

Male Wistar rats (Janvier Labs; 8-9 weeks old, n=6-13) received either PCP (0.5-3 mg/kg, sc) or saline for three consecutive days; on the third day, rats were injected with PCP, and either vehicle or Clozapine (2.5 - 10mg/kg, po, 1hr prior to test), Aripiprazole (1, 3 mg/kg, ip, 30 min. prior to test) or Bitopertin (0.3, 1, 3 mg/kg, po, 1hr prior to test). On the same day, rats were tested in the social interaction test, similarly to the three-chamber model described by Moy and co-workers [10] in mice. Rats were habituated for 10 minutes to a rectangular arena consisting of three chambers divided by two transparent walls provided with a 10 cm squared passing door. In the left and the right chambers an empty, transparent, holed cubiculum was positioned. Immediately after the habituation session, a juvenile co-gender Wistar rat (3-4 weeks old) was positioned in one of the empty cubicles in a fully counterbalanced fashion. The transparent cubicles permitted visual, olfactory, auditory, and some tactile contact between the stranger and the test rat. The animal's behavior was recorded with a video-camera connected to a PC, such that a video tracking software (Anymaze, Stoelting) extrapolated x,y coordinates to compute the animal's position. Locomotor activity and time spent in the 6 cm vicinity area from each of the two cubicles were measured. This 6 cm area was defined via software to determine direct social contacts based on the optimal distance for the tested rat to sniff at a stranger. During the first validation experiment, social interaction time was also manually scored for comparison with software-produced data.

## Results

Manually-scored social interaction time was comparable to the times computed by the tracking software. Control rats showed a strong preference for the inhabited cubiculum versus the empty one. PCP induced a robust and dose-dependent reduction of social interaction duration, with doses superior to 2mg/kg inducing motor incoordination and increased activity. Clozapine did not reverse PCP (1mg/kg)-induced social withdrawal, with the high dose inducing sedation. Bitopertin revealed inefficacious at reversing PCP-effects. By contrast, Aripiprazole induced a dose-dependent amelioration of the social withdrawal induced by PCP.

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## Conclusions

These findings proved that social withdrawal induced by NMDA signaling disruption can be modeled in rats using the three chambers procedure. Pharmacological results are in line with previous findings [7] in rats tested in a dyadic open field social interaction set up, showing that the two models (dyadic versus unilateral) of social interaction test are pharmacologically equally sensitive. Finally, in line with some small studies conducted in humans [11, 12] the social withdrawal was ameliorated by antipsychotic treatment, suggesting that this model may serve as a tool for testing novel drug candidates for the treatment of negative symptoms of schizophrenia.

*All experimental procedures were approved by the Ethics Committee and the Regierungspräsidium Tübingen and adhered to the guidelines of the committee for Research and Ethical Issues OASP 1983.*

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