AUT00206 restores cognitive function in an animal model in 2 tasks in the presence of antipsychotic drugs.

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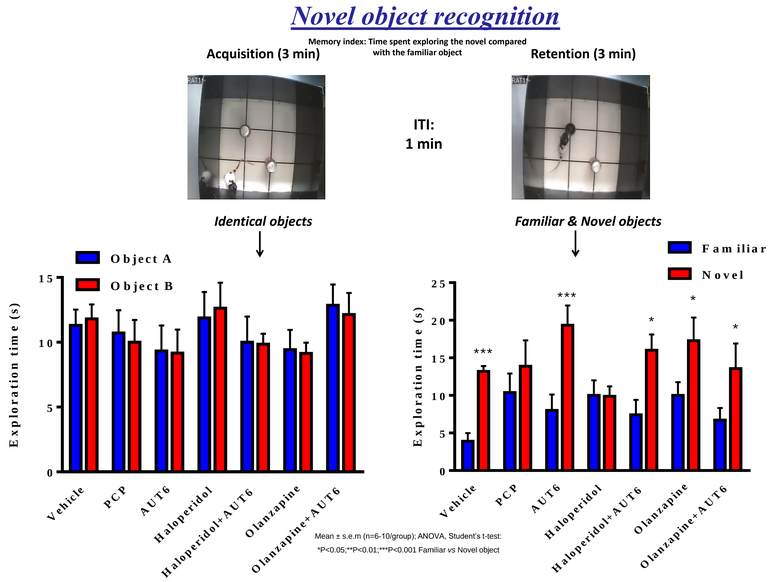
Abstract

Background: Although antipsychotic drugs alleviate positive symptoms of schizophrenia, cognitive deficit and negative symptoms remain an unmet clinical need (Keefe et al. Arch Gen Psychiatry 2007; 64: 633-647). Accumulating evidence supports glutamatergic dysfunction in the pathophysiology of schizophrenia, leading to disinhibition of cortical circuitry, dysregulation of gamma oscillations and reductions in the calcium binding protein parvalbumin (PV), located in fast spiking GABAergic interneurons (Tse et al. Biol Psychiatry 2015; 77: 929–939, for review). The voltage gated potassium channel Kv3.1 is predominantly localized to PV-positive inhibitory interneurons and has been shown to be reduced in un-medicated schizophrenia patients (Yanagi et al. Mol Psychiatry 2014; 19: 573-579). We have extensively demonstrated efficacy of a novel molecule targeting these Kv3.1 channels, AUT00206 to restore sub-chronic PCP (scPCP) induced cognitive and social behaviour deficits, in addition to restoration of PV in cortex and hippocampus (Neill et al., Poster M153, this meeting, 2015). Although scPCP is a well validated model for chronic schizophrenia and of particular relevance to this project as it produces robust cognitive and PV deficits (Neill et al. Pharmacol & Ther. 2010; 128(3): 419-432) in order to fully mimic the clinical condition, the animal model must include chronic antipsychotic treatment prior to, and concomitant with, treatment with any novel drug. Here we test the efficacy of AUT00206 to restore cognitive function in two tests for different domains affected in schizophrenia in scPCP treated rats that also received sub-chronic treatment with the dopamine antagonist drug for schizophrenia, haloperidol or the dopamine/serotonin antagonist drug, olanzapine at doses providing >70% dopamine D2 receptor occupancy (Kapur et al. JPET 2003; 305: 625-631).

Methods

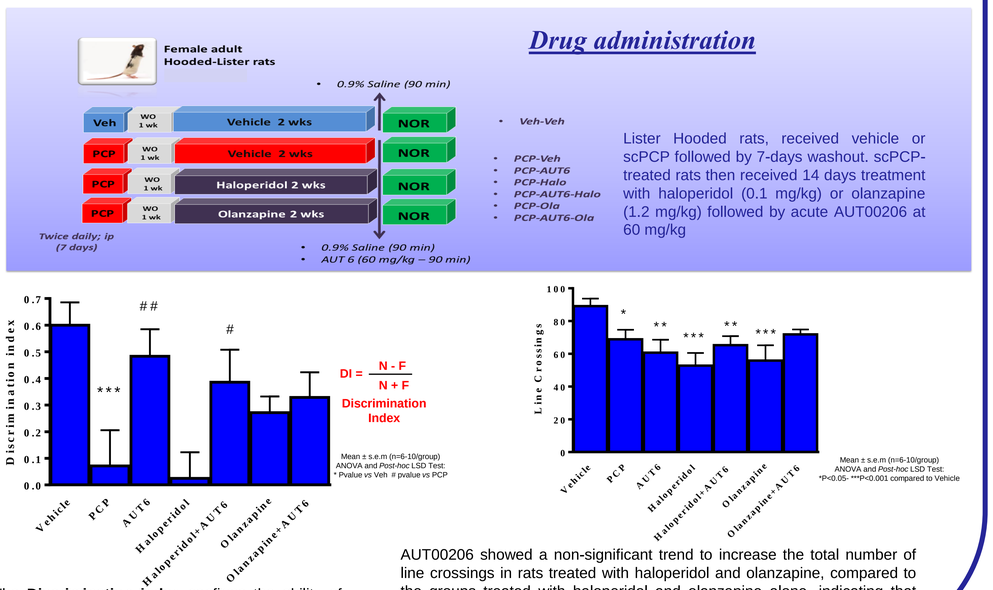
Fifty adult female Lister Hooded rats, received vehicle or scPCP (2 mg/kg) i.p. twice daily for 7 days, followed by 7-days washout. scPCP-treated rats then received 14 days treatment with the first generation antipsychotic-FGA, haloperidol (0.1 mg/kg, i.p. once daily) or the second generation antipsychotic-SGA, olanzapine (1.2 mg/kg, i.p. once per day) followed by acute AUT00206 at 60 mg/kg, given orally (for novel object recognition-NOR testing, visual recognition memory). A separate cohort of 40 female Lister Hooded rats received 21 days' treatment with haloperidol plus AUT00206 at 60 mg/kg orally once per day for 14 days from day 8 onwards and were then tested in the attentional set shifting task-ASST, for executive function. AUT00206 was also tested alone in these tests in scPCP-treated rats. We chose a dose of 60 mg/kg given via the oral route, which was previously shown to be most effective in our scPCP model and is predicted to be a clinically relevant dose (see Hutchison et al. this meeting).

AUT00206 has the ability to attenuate the scPCP-induced visual recognition memory alone and in presence of antipsychotics in the Novel Object Recognition task



No significant difference in the exploration of the two identical objects in the **acquisition phase** in all the treatment groups

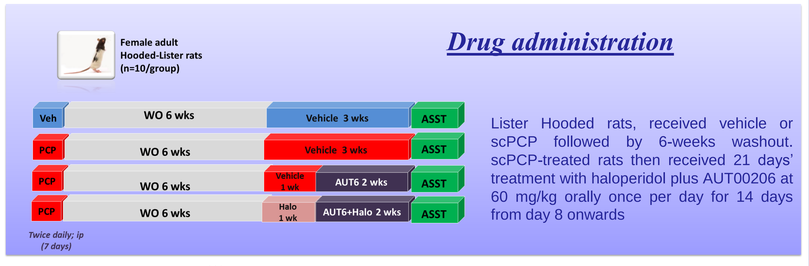
The scPCP induced deficit in the **retention phase** was restored by the acute treatment with AUT00206 alone and in combination with the APDs

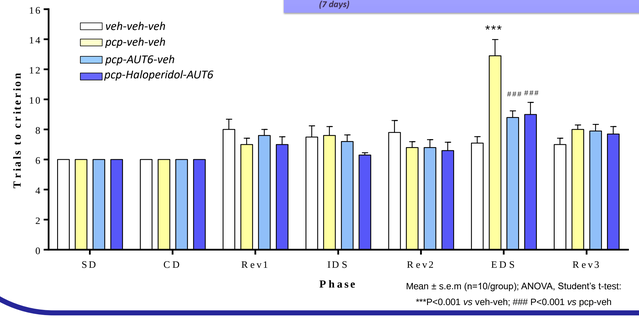


The **Discrimination index** confirms the ability of AUT00206 to improve the scPCP deficit alone and in combination with the APDs.

AUT00206 showed a non-significant trend to increase the total number of line crossings in rats treated with haloperidol and olanzapine, compared to the groups treated with haloperidol and olanzapine alone, indicating that AUT00206 does not exacerbate the reduced levels of **locomotor activity** induced by the FGA and SGA drugs tested in this study.

AUT00206 restores the scPCP-induced executive function deficit in the attentional set shifting task





The attentional set-shifting paradigm was used in this study to assess the ability of AUT00206 to restore the deficit in executive function observed in scPCP treated rats. In this study the drug dosing regimen was designed to resemble the current treatment of schizophrenia patients, following repeated treatments with antipsychotic. Haloperidol at a clinically relevant, D_2 occupying dose (>70%), was administered for 21 days in combination with chronic treatment with AUT00206 given for 14 days from day 8 onwards. Our results demonstrated that the scPCP cognitive deficit was restored by chronic treatment with AUT00206 and that the presence of haloperidol did not alter the efficacy of AUT00206 in this paradigm.

Summary and Conclusions

Studies in animals and in chronic schizophrenia patients suggest that antipsychotics can adversely affect neuronal structure and function which may further impair cognition. Our data demonstrate the efficacy of a novel Kv3.1 channel modulator in the scPCP model for schizophrenia, in the presence of antipsychotic drugs at D2 blocking doses. These results provide support for the hypothesis that modulation of Kv3.1 channels can restore cognitive function in 2 different cognitive domains affected in schizophrenia in the presence of chronic antipsychotic treatment. Work to date with this molecule has demonstrated efficacy in *in vitro* models for schizophrenia (Large et al, this meeting) and efficacy in restoring functional and pathological deficits in extensive studies in our scPCP model (Neill et al, this meeting, 2015). Phase Ia clinical evaluation of the molecule has now been successfully completed (Hutchison et al, this meeting) and Phase Ib trials are currently underway.

Disclosures

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Declaration of interests: JCN, MH, JG, BG, DC are full time employees of the University of Manchester. JCN has received expenses to attend conferences and fees for lecturing, consulting and attending advisory boards from different pharmaceutical companies. CL and GA are employees and shareholders of Autifony. CD is an employee and shareholder of P1vital Ltd.