ABSTRACT

President’s invitee

Several cohorts of adult female Lester Hooded (LH) rats received PCP (2 mg/kg, sub-chronic-scPCP) or saline i.p. for 7 days, followed by 7 days washout. Rats were then tested for cognitive (Fig. 2a) and social (Fig. 1) behaviour deficits following AUT00206, a novel small molecule, selective modulator of Kv3.1 and Kv3.2 channels, at 10-60 mg/kg i.p or po or vehicle. AUT00206 was given acutely 30-60 min prior to testing or once daily for 21 days. Effects of AUT00206 on PV interneurons and Kv3.1 channel expression were examined using immunohistochemistry on brain free-floating sections (Fig. 2b). Prefrontal cortical slices of the prefrontal and infralimbic regions were prepared from one cohort of vehicle + scPCP treated rats and efficacy of AUT00206 at 10 µM to modulate kainate-induced fast (20-80 Hz) network oscillations in vitro was examined (Fig. 3a). Effects of AUT00206 on gamma oscillations in human temporal neocortex slices were also investigated (Fig. 3b). Male Sprague-Dawley rats were pre-treated with AUT00206 at 10 or 60 mg/kg or vehicle (ip) and imaged in a 7T magnet with pharmacological challenge fMRI (phMRI) before and after in-magnet administration of 30 mg/kg ketamine sc (Fig. 4).

RESULTS

Conclusions

- AUT00206 improves cognitive and social behaviour deficits in an animal model for schizophrenia
- Cognitive restoration was sustained over 21 days’ treatment and accomplished by reversal of the PV interneuron deficit
- AUT00206 reversed BOLD activation induced by ketamine
- AUT00206 enhanced gamma oscillations in cortical slices from scPCP treated rats, from humans and from a patient
- The modulation of Kv3 channels on PV neurons by AUT00206 could be an important novel approach for improving symptoms and function in schizophrenia patients

CL and GA are employee of Autifony Therapeutics Limited. The authors declare that no other competing interests exist.