Title: Two novel KV3 ion channel modulators alleviate cognitive dysfunction and social behaviour deficits of relevance to schizophrenia in an animal model

Marianne Leger[1], Mike Harte[1], Ben Grayson[1], Sam Marsh[1], Charles Large[2], Jo Neill[1]

[1] Manchester Pharmacy School, University of Manchester, Manchester, M13 9PT, UK
[2] Autifony Therapeutics Ltd, Imperial College Incubator, Bessemer Building, Imperial College London, SW7 2AZ, UK

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Background: Cognitive dysfunction and negative symptoms remain a major clinical unmet need in schizophrenia [1]. Development of improved medication is therefore of great importance. Cognitive dysfunction has been linked to dysfunction in corticolimbic circuitry with attention focused on parvalbumin (PV)-positive GABAergic interneurons. The voltage gated ion channel Kv3.1 is a key component of PV interneurons, allowing them to fire at high frequency in order to synchronise local neuronal activity. Evidence linking Kv3 channels with schizophrenia [2] suggests that positive modulation of the channels may help to normalise the function of PV interneurons and thus may have the potential to improve symptoms of schizophrenia. Our aim was to explore the efficacy of two novel and selective Kv3 channel modulators, AUT6 and AUT9, in our carefully validated animal model of cognitive and social behaviour deficits in schizophrenia, sub-chronic PCP treatment in rats [3]. The working hypothesis is that acute treatment with Kv3 channel modulators will attenuate the selective deficits induced by sub-chronic PCP, in a manner comparable to risperidone, as measured in the novel object recognition (NOR) and social interaction (SI) tests.
Methods: 240 adult female hooded-Lister rats received sub-chronic phencyclidine, n=160 (PCP) (2 mg/kg) or vehicle, n=80 i.p. twice daily for 7 days, followed by 7 days washout. PCP-treated rats then received risperidone at 0.1 mg/kg, i.p.; AUT6 at 10-60 mg/kg, i.p. or AUT9 at 10-60 mg/kg, i.p. and were tested 30 min later, either in NOR or in SI. Data were analysed using a one-way ANOVA followed by post-hoc LSD t-test and paired or unpaired t-tests.
Results: In the NOR task, vehicle treated rats showed a significant preference for the novel over the familiar object during the retention trial ($P<0.001$), an effect that was abolished in PCP-treated rats ($P>0.05$). AUT6 ($P<0.05$-0.001) and AUT9 ($P<0.05$-0.001) at all doses significantly restored recognition memory in the task, as did risperidone ($P<0.05$-0.01). In SI, sub-chronic treatment with PCP induced a significant reduction in sniffing behaviour ($P<0.01$) and a significant increase in avoidance behaviour ($P<0.001$) compared to the vehicle group. In this test, the positive control risperidone significantly attenuated both PCP-induced deficits ($P<0.05$ and $P<0.001$, respectively). AUT6 significantly attenuated the reduction in sniffing behaviour ($P<0.001$ at 30 mg/kg and $P<0.01$ at 60 mg/kg) as well as the increase in avoidance behaviour ($P<0.001$ at all doses tested) induced by PCP. Similarly, AUT9 significantly restored the PCP-induced reduction in sniffing behaviour ($P<0.01$ at 10 mg/kg; $P<0.05$ at 30 mg/kg and 60 mg/kg) and in avoidance behaviour ($P<0.001$ at all three doses).
Discussion: These data demonstrate the efficacy of two novel Kv3 channel modulators in two symptom domains (visual recognition memory for cognition and social behaviour for an aspect of negative symptoms) in the PCP model. Efficacy was comparable to low dose risperidone. These data suggest that modulation of Kv3 channels could be an important novel approach to the treatment of schizophrenia and that Kv3 channel modulation could improve several symptom domains in schizophrenia.

1. The Schizophrenia Commission (2012) The abandoned illness: a report from the Schizophrenia Commission. London: Rethink Mental Illness.
2. Yanagi, M, Joho, RH, Southcott, SA, Shukla, AA, Ghose, S, Tamminga, CA. (2013) Kv3.1-containing K channels are reduced in untreated schizophrenia and normalized with antipsychotic drugs. Molecular Psychiatry, doi: 10.1038/mp.2013.49
3. Neill, JC, Barnes, S, Cook, S, Grayson, B, Idris, NF, McLean, SL, Snigdha S, Rajagopal, L, Harte, MK. (2010) Animal models of cognitive dysfunction and negative symptoms of schizophrenia: focus on NMDAR receptor antagoni,m. Pharmacology and Therapeutics, 128(3), 419-432.