Efficacy and relevance of the modulation of Kv3 channels to alleviate cognitive dysfunction in an animal model of schizophrenia symptomatology

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Background: Cognitive dysfunction remains a major clinical unmet need for patients with schizophrenia, leading to the disorder being dubbed the "forgotten illness" [1]. Development of improved medications that treat cognitive symptoms is therefore of great importance. Cognitive dysfunction had been linked to specific deficits in corticolimbic circuits that have been observed in post-mortem brains of patients with schizophrenia, with attention focused on the role parvalbumin (PV)-positive GABAergic interneurons in these circuits [2]. The potassium voltage gated ion channel (Kv3) is a key component of PV interneurons, allowing them to fire at high frequency in order to synchronise local neural activity. Evidence linking Kv3 channels with schizophrenia suggests that positive modulation of the channels may help to normalise the function of PV interneurons and thus may have the potential to treat cognitive symptoms of schizophrenia [3]. Our aim was therefore to explore the efficacy of two novel and selective Kv3.1 channel modulators, AUT6 and AUT9, in our carefully validated animal model of cognitive impairment in schizophrenia, sub-chronic PCP treatment in rats [4]. To better understand the neurobiological mechanisms underlying the PCP effects, we also examined the influence of PCP treatment on the expression of Kv3.1 channels in the prefrontal cortex (PFC) and hippocampus.
Methods: 70 adult female hooded-Lister rats were used for these studies. The first cohort (n=60) were trained to criterion in our reversal learning (RL) task and then received vehicle (n=10) or sub-chronic PCP (n=50, 2 mg/kg) i.p. twice daily for 7 days, followed by 7 days washout. PCP-treated rats received risperidone at 0.1 mg/kg, i.p.; AUT6 at 30-60 mg/kg, i.p. or AUT9 at 10-60 mg/kg, i.p. and were tested 30 min later in the RL task.
Brains of a second cohort of vehicle and PCP-treated rats (n=5 per group) were removed to determine i) the co-localisation of PV and KV3.1 channels in the PFC and hippocampus and ii) the effects of PCP on Kv3.1 channel expression in the PFC and hippocampus using immunofluorescent and immunohistochemical techniques. Data were analysed using a one-way ANOVA followed by post-hoc LSD t-test and paired or unpaired t-tests.
Results Sub-chronic PCP produced a significant and selective deficit in the reversal phase of the RL task ($P<0.001$ vs. vehicle). This deficit was significantly attenuated by AUT6 ($P<0.001$ vs. PCP) and AUT9 ($P<0.05$-0.001 vs. PCP) at all doses tested as well as by risperidone ($P<0.001$ vs. PCP).
Immunflouresecent studies demonstrated that KV3.1 channels are located on parvalbumin-containing interneurons (co-localisation of ~80%) in both the PFC and hippocampus of the rat brain. Furthermore we found a significant reduction in the number of Kv3.1-positive cells in the PFC (-60%, $P<0.05$), but no significant changes were found in the hippocampus (-20%, $P>0.05$) of PCP treated rats.
Discussion: These data demonstrate the efficacy of two novel Kv3.1 channel modulators in the PCP model of cognitive deficits of schizophrenia. Efficacy of AUT6 and AUT9 was also consistent with the observed reduction in Kv3.1 expression in the cortex of PCP-treated rats. These data suggest that modulation of Kv3 channels could be an important novel approach to the treatment of schizophrenia.

Keywords: Schizophrenia, Cognition, Kv3 channels, Animal models.

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