A novel Kv3 ion channel modulator restores cognitive function in an animal model of cognitive impairment in schizophrenia

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Introduction: Cognitive dysfunction remains a clinical unmet need in schizophrenia, along with negative symptoms. Indeed the recent schizophrenia commission report has dubbed schizophrenia the "forgotten illness" [1]. Development of improved medication is therefore of the utmost importance. this can only be achieved with the careful development and validation of animal models.The voltage gated ion channel, Kv3 is closely involved in brain circuitry thought to be affected in schizophrenia, see Large et al this meeting (abstract CG13P-0140). Kv3 channels are expressed by parvalbumin-positive (PV+) inhibitory interneurons in cortex, hippocampus, amygdala, and thalamus.There is therefore the possibility that novel Kv3 channel modulators may improve therapy of this currently inadequately treated illness, particularly for cognitive deficit and negative symptoms. The aim of this study was to explore the efficacy of a novel and selective Kv3 channel modulator, the imidazolidinedione derivative, AUT1 in our carefully validated animal model of cognitive impairment in schizophrenia, sub-chronic PCP treatment in female rats [2].

Methods: 50 adult female hooded-Lister rats trained to criterion in an operant serial reversal learning task received sub-chronic PCP (2 mg/kg) or vehicle i.p. twice daily for seven days, followed by 7 days washout. PCP-treated rats then received risperidone at 0.1 mg/kg; i.p. or AUT1 at 30-60 mg/kg p.o. and were tested in the reversal learning task 30-60 min later. A separate batch of 50 adult female hooded-Lister rats received the same sub-chronic PCP treatment regime and were tested in the novel object recognition-NOR-task following the same acute drug treatments. We use a 3 min acquisition trial, followed by a 1 min inter-trial interval and then a 3 min retention trial. Behaviour was scored by a trained experimenter blinded to treatments. Data were analysed using one-way ANOVA followed by post-hoc LSD and paired t-tests.

Results: Sub-chronic PCP produced a significant and selective deficit in the reversal phase of the reversal learning task ($P<0.001$). This reversal learning deficit was significantly attenuated by AUT1 at both doses and by risperidone ($P<0.05$-0.001) In the NOR task, vehicle treated rats showed a significant preference for the novel over the familiar object in the retention trial ($P<0.001$) an effect abolished in PCP-treated rats. AUT1 at 30 mg/kg significantly restored this recognition memory deficit ($P<0.05$) as did risperidone ($P<0.01$).

Conclusions: These data demonstrate the efficacy of this novel Kv3 channel modulator in two cognitive domains (recognition memory and problem solving) in the PCP model of cognitive deficits in schizophrenia in female rats, in a manner comparable with low dose risperidone. This suggests that modulation of Kv3 channels could be an important target for improving symptomatology of schizophrenia. Clearly further experiments are required to explore the effects of this compound in other cognitive doamins of relevance to schizophrenia eg working memory, and in tests for negative symptoms. However these results suggest that this mechanism of action may be an important target for future drug development in this area.

Reference(s)

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