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

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Introduction

Schizophrenia is a chronic psychiatric disorder affecting 1% of the population, with a typical onset between the ages of 15 and 35 years. Although positive symptoms of the disorder are reasonably well controlled by current medications, cognitive dysfunction and negative symptoms remain poorly treated. Development of improved treatments with efficacy across the spectrum of symptoms and a lower burden of side effects is therefore of the utmost importance.

The voltage gated ion channel Kv3, mainly located on Parvalbumin (PV) GABAergic interneurons, is closely involved in brain circuitry thought to be affected in schizophrenia. Thus, novel Kv3 channel modulators may provide an improved therapy, particularly for cognitive deficits and, perhaps, negative symptoms.

In animals, the sub-chronic administration of the NMDA receptor antagonist, Phencyclidine (PCP), has been shown to be particularly relevant to replicate the deficits in a number of cognitive domains affected in schizophrenia.

The aim was to assess the efficacy of a novel and selective Kv3 channel modulator, AUT1, to reverse the cognitive deficits in sub-chronic PCP model of schizophrenia. To better understand the neurobiological mechanisms underlying the PCP effects, the influence of PCP treatment on PV interneurons and Kv3 channels has also been investigated.

Methods

Female Hooded-Lister rats receiving:

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<tr>
<th>Twice daily (7 days; i.p.)</th>
<th>30/60 min</th>
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<tr>
<td>Vehicle</td>
<td>Washout</td>
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<tr>
<td>PCP (3mg/kg)</td>
<td>Washout</td>
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Novel object recognition (NOR, n=50)

- Initial Phase
  - NOR, RL or brain collection
  - Vehicle
- Retention Trial
  - NOR, RL or brain collection
  - Vehicle
  - AUT1 (30 or 60 mg/kg; p.o.)
  - Risperidone (0.1 mg/kg; i.p.)

Novel Object Recognition

- Representative staining of PV and Kv3.1b positive cells
- The Kv3.1b channels are localised on PV neurons (80-90%)

Immunohistochemistry

- Brain free-floating sections
  - Prefrontal cortex
  - Hippocampus
  - Kv3.1b and PV-positive cell densities

Results

- Sub-chronic PCP produced a significant deficit
- AUT1 at 30 mg/kg significantly reduced the deficit, as did risperidone

Reversal learning

- Sub-chronic PCP produced a significant deficit
- AUT1 at both doses significantly reduced the deficit, as did risperidone

Conclusions

- AUT1, a novel Kv3 channel modulator, demonstrates efficacy in two cognitive domains (recognition memory and problem solving)
- AUT1 alleviates the cognitive deficits in the PCP model in a manner comparable with low dose risperidone
- The parvalbumin cell and Kv3-positive cell densities are affected in the PCP model
- The modulation of Kv3 channels could be an important target for improving symptomatology of schizophrenia

Charles Large is an employee of Autifony Therapeutics Limited. The authors declare that no other competing interests exist.