AUT00206, a novel Kv3 channel modulator, reduces ketamine-induced BOLD signalling in healthy male volunteers: a randomised placebo-controlled crossover trial

**BACKGROUND AND RATIONALE**

**Cortical disinhibition in schizophrenia**
- Loss of recurrent GABA inhibition of glutamate neurones
- Loss of parvalbumin (PV) containing fast-sparing GABA interneurones
- Due to impaired NMDA-mediated glutamate drive of PV neurons
- Mimicked by ketamine block of NMDA associated ion-channels

**Kv3 channels**
- contribute to repolarisation of action potentials thus permitting fast firing and precise GABA release

**Loss of parvalbumin (PV) containing fast-sparing GABA interneurones**
- Elicits correlated disinhibition and mild psychosis
- AUT00206 10mg/kg more effective than 60mg/kg

**Loss of recurrent GABA inhibition of glutamate neurones**
- AUT00206 (10)-Ket
- AUT00206 (10)-Ket
- AUT00206 (60)-Ket

**METHODS**

**Double-blind placebo-controlled 4-way crossover design**
- pharmacomRIs were observed following 2 single doses (800 and 2000 mg)
- AUT00206 on ketamine-induced BOLD response in healthy male volunteers

**RESULTS**

**Dorsal Anterior Cingulate Cortex (dACC)**
- Both doses of AUT00206 attenuated ketamine BOLD responses
- 800mg AUT00206 effective in first and second 8 minute post-infusion epochs
- 2000mg AUT00206 effective only in second 8 minute epochs

**Precuneus and Thalamus**
- AUT00206 Did not attenuate peak BOLD responses in the first 8 minute post infusion epochs in either area.
- In thalamus, 800mg AUT00206 attenuated BOLD responses in the second 8mins (*, p<0.05)

**Secondary analyses**
- Significant effects of AUT00206 in right DLPCF and L+R insula as in thalamus above,
- No significant modification of ketamine effect in 10 other regions
- No significant modification of main effect of ketamine on whole brain analysis

**Psychosis ratings**
- Ketamine increased PANSS scores
- AUT00206 did not reduce the effect of ketamine
- But ketamine effects lessened with repetition
- AUT00206 did attenuate ketamine effects on first 2 exposures to ketamine

**CONCLUSIONS**
- AUT00206 was well tolerated with no adverse safety findings
- Significant effect of AUT00206 on the primary outcome measure, with supporting data from co-primary, secondary, and exploratory measures
- Similarity between rat and human ketamine models, suggesting good translation across the species
- First conclusive evidence of the effects of AUT00206, a Kv3 channel modulator, on measures of brain function in humans.

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