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

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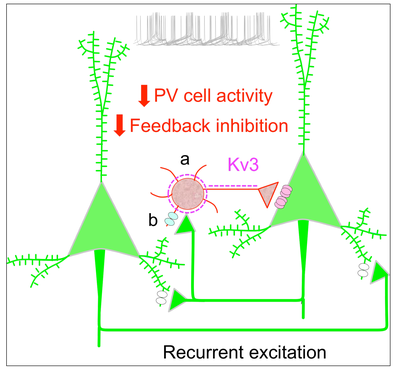
Innovate UK Technology Strategy Board

BACKGROUND AND RATIONALE

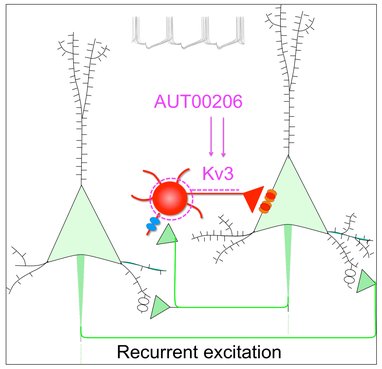
Cortical disinhibition in schizophrenia

- Loss of recurrent GABA inhibition of glutamate neurones
- Loss of parvalbumin (PV) containing fast-spiking GABA interneurones (a)
- Due to impaired NMDA-mediated glutamate drive of PV neurones? (b)
- Mimicked by ketamine block of NMDA associated ion-channels

Cortical disinhibition in psychosis



Restoration of inhibition by Kv3 activation

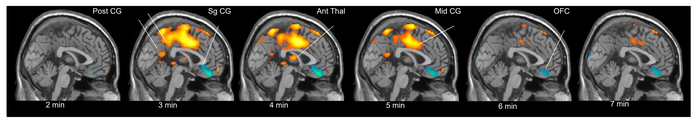


Restoration of inhibition by AUT00206?

- AUT00206 is a Kv3.1/3.2 potassium channel positive allosteric modulator
- Kv3.1/3.2 channels specifically located on PV GABA interneurones
- Kv3 channels contribute to repolarisation of action potentials thus permitting fast firing and precise GABA release
- Reversed cognitive deficits in chronic PCP rat model
- Could AUT00206 reverse cortical disinhibition induced by ketamine?

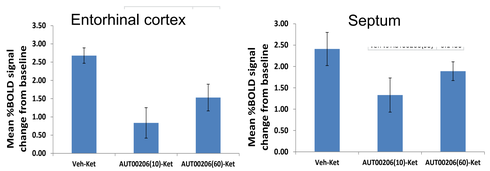
Ketamine pharmaco MRI (phMRI) elicits disinhibition

- Intravenous ketamine elicits increased blood oxygen level dependent (BOLD) signal detected using functional magnetic resonance imaging
- Elicits correlated dissociation and mild psychosis –like symptoms
- Reflects cortical disinhibition - reversed by lamotrigine (Deakin 2008)



Reversal of ketamine phMRI in the rat by AUT00206

- AUT00206 10mg/kg more effective than 60mg/kg

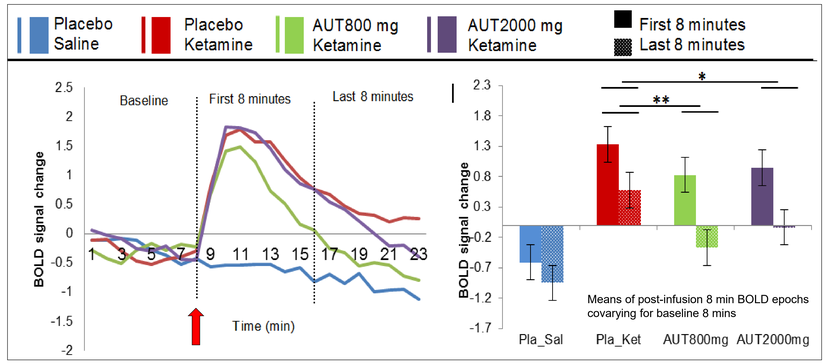


Attenuation of ketamine in 41 of 44 regions after 10mg/kg AUT 00206

RESULTS

Dorsal Anterior Cingulate Cortex (dACC)

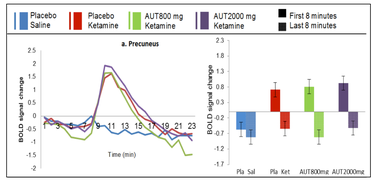
- Both doses of AUT00206 attenuated ketamine BOLD responses
- 800mg AUT00206 effective in first and second 8 minute post-infusion epochs
- 2000mg AUT00206 effective only in second 8 minute epochs

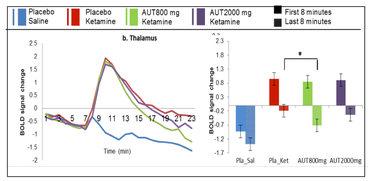


* Treatment x time interaction AUT2000 mg vs placebo on ketamine p=0.04
**Treatment x time interaction AUT800 mg vs placebo on ketamine p=0.003

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)



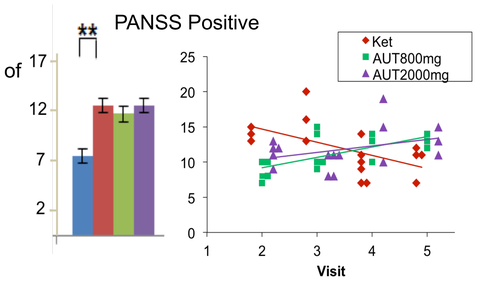


Secondary analyses

- Significant effects of AUT00206 in right DLPFC 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

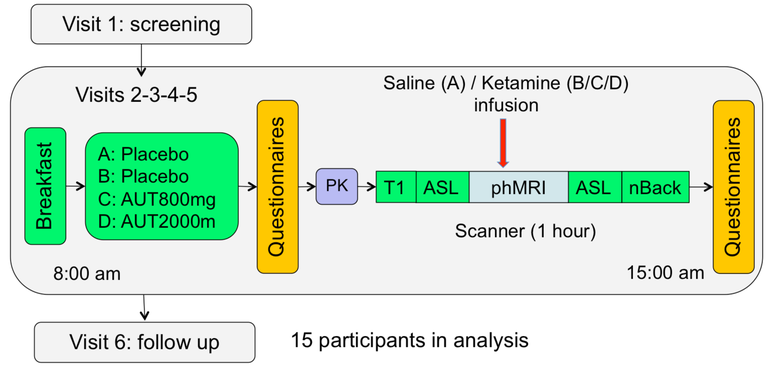
- Ketamine increased PANSS scores
- AUT00206 did not reduce the effect of ketamine
- But ketamine effects lessened with repetition
- AUT00206 did attenuate ketamine effects on first 2 exposures to ketamine



METHODS

Double-blind placebo-controlled 4-way crossover design

- pharmacoMRI effects were observed following 2 single doses (800 and 2000 mg) AUT00206 on ketamine-induced BOLD response in healthy male volunteers



15 participants in analysis

Inclusion criteria
- Males 18 to 45 years of age
- Healthy (medical history, blood & ECG QTcF screen), non-smokers, non obese
- Appropriate contraception with partners.
- Written informed consent before initiation of any study related procedures.

Exclusion criteria
- History of positive test for hepatitis B, hepatitis C, HIV-1 or HIV-2.
- Out of range screening judged relevant by responsible physician
- Known cardiovascular or cerebrovascular contraindication or hypersensitivity to the use of ketamine:
- Exceeding limits for recreational drug use, alcohol or caffeine.
- Use of other relevant medicines
- No MRI contraindications

Doses studied
- AUT00206 Dose 1: 800mg or PBO orally
- AUT00206 Dose 2: 2000mg or PBO orally
- Ketamine: bolus i.v. infusion of 0.26 mg/kg for 1 minute, followed by a maintenance infusion of 0.25 mg/kg/h for 30 minutes

Primary endpoint
- BOLD response in brain areas known to be affected by low dose ketamine, specifically dorsal anterior cingulate cortex, thalamus, and precuneus

Mixed models ANOVA
- Dependent variable: RoI 8 minute average BOLD signal; Factors: Treatment (4 treatments); Time (2 post-infusion time bins); Covariate pre-infusion time bin.
- Contrast: 1. (AUT800mg+ketamine) vs (Placebo+ketamine)
- Contrast 2. (AUT2000mg+ketamine) vs (Placebo+ketamine)

Adverse Events

AUT00206 800 mg did not add to the side effect burden of ketamine, while AUT00206 2000 mg slightly increased the reporting of dizziness and somnolence in the presence of ketamine. One participant had a severe psychological reaction to the ketamine infusion and was withdrawn from the study. A second subject (placebo) was withdrawn after his first scheduled scan having developed deranged clinical chemistry values after a bout of heavy exertion.

n (%)	Treatment			
	Placebo Saline	Placebo Ketamine	AUT00206 800 mg Ketamine	AUT00206 2000 mg Ketamine
	N=19	N=19	N=20	N=19
Any TEAE	9	14	14	18
Any treatment-related TEAE	2	13	13	18
Any TEAE related to oral capsule	0	1	1	0
Any TEAE related to IV infusion	2	13	12	16
Any TEAE related to procedure	0	8	8	13
Any AE leading to withdrawal	1	0	1	0
Any severe TEAE	1	0	2	0
Serious adverse events	0	0	0	0

Most Frequent Adverse Events	Treatment			
	Placebo Saline	Placebo Ketamine	AUT00206 800 mg Ketamine	AUT00206 2000 mg Ketamine
	N=19	N=19	N=20	N=19
Nervous system disorders				
Dizziness	0	13	10	15
Somnolence	0	6	6	9
Headache	4	3	6	4
Eye disorders				
Diplopia	0	2	2	1
Gastrointestinal disorders				
Dyspepsia	1	0	1	0
Nausea	0	0	1	1
Vomiting	0	0	1	1
Skin and subcutaneous tissue disorders				
Rash macular	0	1	0	1

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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