PharmacomRI and cognitive effects of the low-trapping NMDA channel blocker AZD6765 compared with ketamine in untreated major depressive disorder

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Introduction
Subgenual cingulate (SGC) overactivity in depression is reversed by successful drug treatment
SGC activation induced by emotional faces is also diminished by antidepressants

Both drugs reduced amygdala responses to fear and sadness in the emotional faces task 24 hours post-infusion

The SGC responses correlated with improvement in MADRS scores 24 hours and 7 days post-infusion

Methods
Subjects
Sixty treatment-naïve males or females aged 18 to 45 years with major depressive disorder

Aim
To investigate effects of AZD6765 and ketamine given by steady infusion on neural activity in the SGC and its relationship with subsequent change in depressive symptoms and emotion processing using pharmaco- and functional magnetic resonance imaging (phMRI, fMRI)

Treatments
On Day 1 subjects were assigned to 1 of 3 groups and received a single 40-ml (6) infusion over 40 min of either: (a) Placebo (5% saline); (b) Ketamine 0.5 mg/kg; (c) AZD6765 100 mg (total dose)

Day 1: phMRI scanning (75 min) (i) Emotional memory; (ii) Facial expression recognition; (iii) Dot probe

Day 2: phMRI scanning (60 min) (i) Facial expression processing; (ii) Emotional counting Stroop; (iii) Emotional encoding: Resting state

Day 2: emotion processing fMRI (i) Emotional counting Stroop; (ii) Emotional encoding: Resting state

Table 1: Ketamine-evoked dissociation correlated with fMRI activations

<table>
<thead>
<tr>
<th>Brain regions</th>
<th>% Change</th>
<th>Z Score</th>
<th>p-val</th>
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<tbody>
<tr>
<td>Whole brain</td>
<td>-60-65</td>
<td>5.68</td>
<td>&lt;0.001</td>
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</table>
| Middle Temporal Cingulate Gyrus BA24 | 12 14 37 27 | 4.13 | p<0.001
| Subgenual Cingulate | 07 6 7 16 | 4.01 | p<0.001

Results
Both AZD6765 and ketamine increased SGC BOLD signal responses; no decreases were seen in any brain region

The SGC responses correlated with improvement in MADRS scores 24 hours and 7 days post-infusion

These findings contrast with earlier findings in healthy volunteers in which ketamine induced deactivation of the SGC

Neither AZD6765 nor ketamine caused SGC deactivation in patients

The results suggest that AZ6765 and ketamine both have antidepressant-like effects on emotion processing in the brain and that diminished NMDA glutamate neurotransmission in the SGC is a likely proximal mechanism

Conclusions
• Neither AZD6765 nor ketamine caused SGC deactivation in patients
• These findings contrast with earlier findings in healthy volunteers in which ketamine induced deactivation of the SGC
• Activation of the SGC was seen following both drugs and this effect was associated with improvement in depressive symptoms 24 hours and 7 days post-infusion

• The results suggest that AZ765 and ketamine both have antidepressant-like effects on emotion processing in the brain and that diminished NMDA glutamate neurotransmission in the SGC is a likely proximal mechanism

References

Disclosures
JFW Deakin, GM Goodwin, CA Harmer, CT Dourish, and SR Dawson are P1vital shareholders; DJ McCarthy and MA Smith are full-time employees of AstraZeneca.

Supported by funding from AstraZeneca Pharmaceuticals.

Presented at the 20th EANP World Congress of Neuropsychopharmacology • 8th June 2013 • Dublin, Ireland

Figure 1: Ketamine-induced placebo phMRI BOLD response in the SGC and percentage BOLD signal change over time in the SGC for ketamine and placebo.

Figure 2: AZD6765 minus placebo phMRI BOLD response in the SGC and percentage BOLD signal change over time in the SGC for AZD6765 and placebo.

Figure 3: Correlation between the % increase in BDI scores and the % increase in phMRI BOLD response in the SGC following AZD6765 and ketamine compared to placebo after 1 week post-infusion (left). The location of the correlated cluster (right).

Table 1: Ketamine-evoked dissociation correlated with fMRI activations.