Investigating Dose Dependency of Ketamine Binding on the Serotonin Transporter with Positron Emission Tomography

Marie Spies¹, Gregory M James², Neyder Berroterán-Infante², Harald Iheschitz², Jakob Unterholzer³, Mathis Godbersen¹, Gregor Gryglewski³, Marius Hienert⁴, Johannes Junghwirth⁵, Verena Pichler⁵, Georg S Krantz⁵, Birgit Reiter⁵, Dietmar Winkler⁵, Markus Mitterhauser⁵,⁶, Thomas Stimpfl³, Marcus Hacker², Siegfried Kasper⁷, Rupert Lanzenberger¹

¹Department of Psychiatry and Psychotherapy, Medical University of Vienna, Austria
²Department of Biomedical Imaging and Image-guided Therapy, Division of Nuclear Medicine, Medical University of Vienna, Austria
³Department of Laboratory Medicine, Medical University of Vienna, Austria
⁴Ludwig Boltzmann Institute for Applied Diagnostics, Vienna, Austria

Introduction

- Ketamine is a rapid and effective antidepressant (1).
- Ketamine’s effects on the glutamatergic system are well known (2).
- S-HT has been implicated in ketamine’s antidepressant effects by animal studies.
  - S-HT depletion prior to ketamine administration was shown to inhibit ketamine’s antidepressant effects in rats (3).
  - Ketamine was shown using positron emission tomography (PET) to bind the serotonin transporter (SERT) in monkeys (4).
- The SERT is commonly relevant to depressive pathophysiology and antidepressant treatment (5).

Aim

- To assess ketamine’s binding of the serotonin transporter (SERT) and whether the extent of binding is associated with ketamine plasma levels.
  - This is the first study to investigate the extent of ketamine’s binding on the SERT in humans.
  - This study allows for further differentiation of the nature of S-HT’s role in ketamine’s antidepressant effects.
  - We provide relevant pharmacodynamic data that is necessary for safer and effective implementation.

Patients and Methods

Subjects: 12 healthy male subjects (mean age ± SD = 26.92 ± 3.45).
Study design: Two PET measurements (PET1, PET2) with [1C]DASB (4.7 MBq/kg) PET on a GE Advance full-ring scanner. PET1 was performed as a baseline scan, without pharmacologic intervention. Ketamine challenge was administered immediately prior to PET2. One MRI was performed for structural colocalization of PET data.
Study drug: 0.5 mg/kg bodyweight racemic ketamine administered over 40 minutes.
Ketamine plasma levels: Blood was drawn at 5, 10, 20, 30, 40, 60, and 80 min after PET start for quantification of ketamine plasma levels. Ketamine levels were determined by gas chromatography–tandem mass spectrometry in multiple reaction monitoring (MRM). The analytical method was validated according to the EMA guidelines.
Data analyses: [1C]DASB non-displaceable binding potential (B0) was quantified using a multilinear reference tissue model (MD) and PMOD 3.5.99. SERT occupancy was quantified for 3 SERT-rich regions of interest (ROI) defined using the automated anatomic labeling atlas (ROIs: caudate, putamen, thalamus). Occupancy was quantified using the formula occupancy (%) = (1 – B0PET2 / B0PET1) x 100. Spearman correlation analyses was performed in order to assess the relationship between ketamine plasma levels and SERT occupancy.

References


Table: Ketamine plasma levels

<table>
<thead>
<tr>
<th>Time point</th>
<th>Ketamine plasma level (mean ± SD)</th>
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<tbody>
<tr>
<td>05 min (n = 10)</td>
<td>197.06 ± 176.04 ng/ml</td>
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<tr>
<td>10 min (n = 10)</td>
<td>131.54 ± 65.40 ng/ml</td>
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<tr>
<td>20 min (n = 12)</td>
<td>90.71 ± 38.33 ng/ml</td>
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<tr>
<td>30 min (n = 12)</td>
<td>78.46 ± 31.44 ng/ml</td>
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<tr>
<td>40 min (n = 12)</td>
<td>69.28 ± 25.65 ng/ml</td>
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<tr>
<td>60 min (n = 11)</td>
<td>59.56 ± 17.02 ng/ml</td>
</tr>
<tr>
<td>80 min (n = 11)</td>
<td>52.46 ± 15.35 ng/ml</td>
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Figure 1: SERT Occupancy

Figure 2: Correlation between ketamine plasma levels and SERT occupancy

Conclusion

- Observed occupancy values are within test-retest variability of [1C]DASB (8).
- These findings are in contrast to those shown under SSRIs, which show 70-80% occupancy of the SERT (9). This suggests that SERT binding is unlikely to be a primary antidepressant mechanism.
- The positive correlation between ketamine plasma levels and occupancy points towards possible dose-dependent binding of the SERT by ketamine.
- Animal studies show more pronounced binding of the SERT at higher doses (4).

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