Changes of $[^{11}C]$DASB binding in human brain after citalopram infusion

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Introduction

Quantification of brain PET studies is commonly based on two assumptions with respect to a reference region
(1) devoid of specific binding,
(2) free and nonspecific binding of the radioligand uniform across the entire brain.

In studies of radioligand binding to the serotonin transporter (SERT), several reports suggested that these assumptions may not be met

- Szabo Z et al. (JNM 43 (2002), 678-92): changes of \([^{11}C](+)^{\text{McN5652}} \) and \([^{11}C]\text{DASB}\) binding in cerebellum after MDMA lesion or paroxetine treatment observed in baboons,
- Ikoma Y et al. (JCBFM 22 (2002), 490-501): dual injection paradigm using \([^{11}C](+)^{\text{McN5652}}\) and \([^{11}C](-)\text{McN5652}\) to estimate regionally variable free and nonspecifically bound,
- Kish SJ et al. (Nucl Med Biol 32 (2005), 123-8): SERT concentration in cerebellar cortex and white matter approximately 20% of cerebral cortex or 5% of striatum,
- Parsey RV et al. (Biol Psychiatry 59 (2006), 821-8): in \([^{11}C]\text{DASB}\) scans, 33% reduction of the VD in cerebellar grey matter after daily oral sertraline treatment.
Four healthy male volunteers underwent two PET scans.

In a randomised design, either 5 ml saline or 10 mg citalopram, a selective serotonin re-uptake inhibitor (SSRI), in the same amount of saline were infused intravenously over 30 minutes.

Then approximately 550 MBq of \[^{11}C\]DASB were injected as a smooth bolus.

90 min dynamic 3D data were acquired in list mode on the ECAT EXACT3D tomograph (Siemens/CTI).

The arterial plasma input function was derived from continuous on-line whole blood monitoring and 10 discrete blood samples, in 8 of which the fraction of unmetabolised parent compound was determined.

Regions of interest (ROI) were defined on the co-registered MRI with the help of a probabilistic brain atlas template.

Tissue time-activity curves (TACs) were generated from sampling the grey matter voxels of those ROIs.

Regional estimates of total volumes of distribution VD were obtained from compartmental modelling, from Logan graphical analysis of reversible binding and from spectral analysis.

Binding potential estimates were calculated indirectly

\[
BP_2 = \frac{VD_{ROI}}{VD_{Cerebellum}} - 1.
\]

Occupancy was expressed as percentage reduction of binding potential

\[
Occ = (1 - \frac{BP_{Blocked\ scan}}{BP_{Baseline\ scan}}) \times 100\%.
\]
Results: Input Function

\[
\text{plasma-over-whole blood (POB) ratio} = \frac{\text{activity concentration in plasma}}{\text{activity concentration in whole blood}}
\]

Observation:
In the initial phase of the blocked scans, the POB ratio was significantly higher than in the baseline scans.

Discussion:
SERT binding sites on the platelets blocked by citalopram?

At later times:
• most of the activity due to radiolabelled metabolites rather than \([^{11}\text{C}]\text{DASB}\),
• lower concentration of citalopram than at the beginning.
Results: Input Function

Fraction of radioactivity due to unmetabolised parent $[^{11}C]DASB$ in plasma

Observations consistent in all four subjects:

1. In the early phase (before 5 min), citalopram administration caused an increase of the parent fraction.

2. In a middle phase (between 10 and 45 min), the parent fraction was decreased after citalopram administration.

Citalopram administration lead only to subtle systematic changes.
The blockade of peripheral SERT binding sites by citalopram led to a substantial increase of [11C]DASB availability in plasma.
Results: Tissue Response

Summed images from 9 to 90 min p.i. (oblique slices)

[Images of brain scans showing activity concentration in kBq cm⁻³ over scan time in minutes]
Results: Parameter Estimates

Compartmental models:
- Two-tissue, four rate constants: difficulties with convergence, negative $k_4$ and sometimes also $k_5$ estimates
- One-tissue, two rate constants: always converges to a solution. However, the quality of the fit, particularly in the regions with lower uptake, is not good (high residual sum of squares).

Graphical analysis:
- Logan plots, $t^* = 35$ min

<table>
<thead>
<tr>
<th>ROI</th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Subject 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline VD BP2</td>
<td>Blocked VD BP2 Occ</td>
<td>Baseline VD BP2</td>
<td>Blocked VD BP2 Occ</td>
</tr>
<tr>
<td>Cerebell</td>
<td>9.2</td>
<td>9.2</td>
<td>9.9</td>
<td>9.2</td>
</tr>
<tr>
<td>Amygdala</td>
<td>15.3 ± 6.66</td>
<td>13.9 ± 7.30</td>
<td>13.2 ± 7.30</td>
<td>13.5 ± 8.50</td>
</tr>
<tr>
<td>Brainstem</td>
<td>26.9 ± 19.2</td>
<td>30.6 ± 10.03</td>
<td>30.1 ± 10.03</td>
<td>30.6 ± 10.03</td>
</tr>
<tr>
<td>Caudate</td>
<td>23.7 ± 13.5</td>
<td>23.4 ± 13.5</td>
<td>12.9 ± 6.2</td>
<td>11.7 ± 6.2</td>
</tr>
<tr>
<td>Hippocam</td>
<td>17.0 ± 10.9</td>
<td>16.9 ± 10.9</td>
<td>11.7 ± 6.2</td>
<td>11.7 ± 6.2</td>
</tr>
<tr>
<td>Putamen</td>
<td>29.1 ± 12.0</td>
<td>29.5 ± 12.0</td>
<td>15.7 ± 6.5</td>
<td>15.7 ± 6.5</td>
</tr>
<tr>
<td>Thalamus</td>
<td>28.7 ± 14.4</td>
<td>28.6 ± 14.4</td>
<td>13.9 ± 7.5</td>
<td>13.9 ± 7.5</td>
</tr>
</tbody>
</table>

Mean ± stand dev: 67 ± 4 | 58 ± 7 | 64 ± 8 | 52 ± 10

Negative bias?
Mean reduction in cerebellar VD: 19 ± 13 % ($n=4$).
Results: Parametric images

Spectral analysis using basis functions logarithmically spaced between $\beta_{\text{min}} = 0.0007$ s$^{-1}$ and $\beta_{\text{max}} = 0.1$ s$^{-1}$.

<table>
<thead>
<tr>
<th>ROI</th>
<th>Subject 1 Baseline</th>
<th>Subject 1 Blocked</th>
<th>Subject 2 Baseline</th>
<th>Subject 2 Blocked</th>
<th>Subject 3 Baseline</th>
<th>Subject 3 Blocked</th>
<th>Subject 4 Baseline</th>
<th>Subject 4 Blocked</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellum</td>
<td>11.8</td>
<td>10.9</td>
<td>13.3</td>
<td>14.3</td>
<td>11.9</td>
<td>11.7</td>
<td>11.4</td>
<td>11.7</td>
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<tr>
<td>Amygdala</td>
<td>30.4 1.58 18.4 0.71</td>
<td>32.0 1.36 16.4 0.59</td>
<td>37.3 1.18 18.5 0.61</td>
<td>48 33.8 1.88 15.0 0.60</td>
<td>58 37.4 1.18 18.5 0.60</td>
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<tr>
<td>Brainstem</td>
<td>30.3 1.57 18.1 0.68</td>
<td>31.6 1.33 16.0 0.54</td>
<td>35.0 1.04 17.3 0.51</td>
<td>51 29.5 1.51 13.8 0.66</td>
<td>57 35.0 1.30 17.3 0.51</td>
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<td>30.1 1.22 14.7 0.43</td>
<td>39.5 1.30 17.3 0.51</td>
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<tr>
<td>Hippocamp</td>
<td>21.9 0.86 14.1 0.30</td>
<td>23.6 0.74 13.8 0.33</td>
<td>32.0 0.82 16.6 0.46</td>
<td>43 21.3 0.81 11.9 0.43</td>
<td>48 31.0 0.82 16.6 0.46</td>
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<tr>
<td>Putamen</td>
<td>36.1 2.08 18.2 0.69</td>
<td>37.1 1.74 18.1 0.75</td>
<td>43.1 1.51 18.0 0.65</td>
<td>57 34.5 1.94 15.5 0.85</td>
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<tr>
<td>Thalamus</td>
<td>35.8 2.03 16.5 0.63</td>
<td>35.3 1.64 16.0 0.64</td>
<td>43.5 1.25 16.5 0.63</td>
<td>62 34.5 1.94 14.5 0.73</td>
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Mean ± stand dev: 65 ± 6 60 ± 5 52 ± 6 58 ± 8

Mean reduction in cerebellar VD: 24 ± 11 % (n= 4).
Summary and Conclusions

- Citalopram infusion led to a substantial increase of $[^{11}\text{C}]$DASB availability in plasma.
- Observed reductions in cerebellar $V_D$ are in line with previous reports.
- Occupancy estimates are fairly homogeneous across the SERT-rich regions. ROIs with low SERT density (e.g., cortical areas) could not be reliably quantified.
- Mean occupancy in 4 subjects: about 60 % with ROI-based Logan graphical analysis or 59 % with parametric maps generated by spectral analysis.
- However, occupancies expressed as reduction of indirectly calculated binding potentials are underestimations.
- Why is the reduction of the cerebellar $V_D$ in the blocked scans greater than expected from the reported SERT concentration?
- Did citalopram alter the $[^{11}\text{C}]$DASB transfer across the blood-brain barrier?
- Which is the right strategy for quantification? Must reference region approaches be avoided?
- High-affinity SERT radioligand for cortical regions???
- Can SERT imaging in the brain be improved by co-administration of a SSRI that is unable to cross the blood-brain barrier?