In Vivo Imaging of Translocator Protein Expression in Low-Grade Gliomas by Positron Emission Tomography

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Introduction

Astrocytomas and oligodendrogliomas account for more than 70% of all primary neoplasms in the brain. Therapeutic management and outcome differ in these two commonest types of gliomas due to their different biological characteristics. Translocator protein (TSPO), previously termed as peripheral benzodiazepine receptor (PBR), is an 18 kDa molecule located on the outer mitochondrial membrane (Fig 1). It has been detected in gliomas and appears to be closely correlated with tumour proliferation, histological type and grade of malignancy: astrocytic type and high-grade tumours express significantly more TSPO than oligodendrogial type and low-grade ones. In the tumour, TSPO is prominently expressed in neoplastic cells instead of activated microglia, the main cells over-expressing TSPO in various other brain diseases. PET studies using TSPO-specific ligand PK11195 in glioma patients were sparse with variable results [1-9] and none of them had been conducted on oligodendroglioma patients. We are investigating the in vivo expression of TSPO in low-grade gliomas, whether PK11195 can be utilised as an imaging marker to distinguish between astrocytomas and oligodendrogliomas, and how such PET scanning can be applied in guiding biopsy.

Methods

- 8 patients (mean age 36.3, male : female = 3 : 5) with low-grade gliomas and 2 healthy volunteers (mean age 30, male : female = 2 : 3) recruited
- MRI to detect brain tumours the cerebral blood volume (CBV), followed by PET scans with the radiotracer 11-C-RK11195 (injected activity 467±7 MBq) for specific binding to the TSPO
- Reference tissue input function obtained from the grey matter of ipsilateral cerebral cortex and the supervised cluster analysis [6]: regions of interest (ROIs) drawn on the tumours with high and low PK11195 uptake, co-registered PET/MRI to guide biopsies.
- Parametric maps of binding potential (BP) calculated using the simplified reference tissue model (SRTM)[6].
- Tumour tissue assessed using H&E and immunohistochemical staining to determine the histotype and grade, cell proliferation, TSPO expression and microglial activation.

Results

Imaging

The 11-C-RK11195 uptake in most parts of the tumours was lower than that in the unaffected cortex in glioma patients. High uptake foci were found in the margin and within the generally low uptake tumour regions, from which biopsies were taken (Fig 3, 4).

Figure 1. TSPO expression in mitochondria and PK11195 binding to the TSPO (modified after [6]).

Histology

Table 1. Histology results of the 3 low-grade gliomas biopsied

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>WHO II</th>
<th>WHO III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytoma</td>
<td>25%</td>
<td>20%</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>K67</td>
<td>1.7%</td>
<td>8.8%</td>
</tr>
</tbody>
</table>

Our preliminary findings show generally lower PK11195 uptake and slightly different tracer kinetics in low-grade gliomas compared with the unaffected grey matter. The unaffected brain tissue in the patients may not be normal due to increased TSPO expression in activated microglia although such change may be suppressed in the tumour. More cases are needed to verify the imaging pattern and the correlation between PK11195 uptake and TSPO expression.

Discussion

The variable results in previous PET studies investigating TSPO expression in astrocytoma patients (Table 2) [1-3] highlight the complexity of in vivo TSPO expression in gliomas and question the generally accepted view of TSPO over-expression in activated microglia. Is it still the case in gliomas?

Table 2. Previous PK11195 PET studies in astrocytoma patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>TSPO expression</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pappata et al.</td>
<td>2009</td>
<td>astrocytoma</td>
<td>increased radiotracer uptake in the cortex and grey matter of gliomas.</td>
</tr>
<tr>
<td>Peeters et al.</td>
<td>2009</td>
<td>astrocytoma</td>
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Recent histology studies by our colleagues (AO and FR) showed significantly higher TSPO expression in astrocytomas than oligodendrogliomas (Fig 6-7), which is in keeping with our PET results and indicates that PK11195 may be used as a biomarker to distinguish them.

Conclusion

TSPO expression in low-grade gliomas may be suppressed with differences between astrocytomas and oligodendrogliomas. PK11195 PET may be useful for distinguishing these two histotypes and guiding biopsy.

Acknowledgement

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References


Figure 2. High Resolution Research Tomographic (HRRT) for PET scans

Figure 3. Co-registered MIPET images in 4 glioma patients

Figure 4. Biopsy site from high PK11195 uptake foci within the tumours.

Figure 5. Time-activity curves from PK11195 PET scans in 4 glioma patients

Figure 6. High resolution PET images of glioma patients

Figure 7. Histological images of astrocytoma and oligodendroglioma.