Positron Emission Tomography of Translocator Protein 18 kDa (TSPO) as a Biomarker of Neuroinflammation in Dementia and in Depression

Robert B. Innis, MD, PhD
Chief, Molecular Imaging Branch
NIMH
Translocator Protein (TSPO) aka Peripheral Benzodiazepine Receptor

1. Mitochondrial protein transports cholesterol to enzyme that synthesizes pregnenolone

2. Highly expressed in macrophages, activated microglia, and reactive astrocytes

3. Putative biomarker for activation of the immune system in brain: ‘neuroinflammation’
Major Findings

Alzheimer’s Disease

1) TSPO binding increased in Alzheimer’s disease but not mild cognitive impairment

2) Increased TSPO binding correlates with disease severity (cross sectional study) and with disease progression (longitudinal study)

Major Depressive Episode

1) TSPO binding increased in unmedicated patients

2) TSPO binding not changed in medicated patients
TSPO imaging in Alzheimer’s disease

• Neuroinflammation a proposed contributor to Alzheimer’s disease pathology
  – Unclear if early or late phenomenon

• Prior TSPO PET studies have shown conflicting results in AD and mild cognitive impairment

• PBR28 an improved TSPO radioligand
  – Genotype correction expected to detect differences in TSPO density in AD, MCI, and controls
Increased TSPO in Alzheimer’s Disease: Compared to Controls and MCI

Control
Mild Cognitive Impairment
Alzheimer

Kreisl, Brain. 2013
$[^{11}C]PBR28$ binding greater in Alzheimer’s in target regions after correcting for TSPO genotype

Inf parietal cortex

- AD: $p = 0.001$
- MCI: $p = 0.009$
- HC: $p = 1.000$

Cerebellum

- AD: $p = 0.277$
- MCI: $p = 0.204$
- HC: $p = 1.000$
$[^{11}\text{C}]\text{PBR28}$ binding correlates with clinical severity across Alzheimer’s disease spectrum

$r = 0.590$

$p = 0.001$
Longitudinal $[^{11}\text{C}]$PBR28 study

- Objective: Determine if TSPO binding increases during progression of AD and normal aging

- Methods:
  - 14 patients (5 AD + 9 MCI at baseline) and 8 controls returned for follow up
  - $[^{11}\text{C}]$PBR28 data analyzed using cerebellar ratio method (60 – 90 min scan data)
  - Image data analyzed with correction for partial volume effects
Results: \([^{11}\text{C}]\text{PBR28 binding increased in patients but not controls}\)

Inferior parietal lobule

![Graph showing [\(^{11}\text{C}\)PBR28 binding (SUVR)] over years from baseline scan for patients and controls.]}
Increased $[^{11}\text{C}]$PBR28 binding correlates with increased clinical severity

Inferior parietal lobule

Change in CDR-SB (standardized)

Change in $[^{11}\text{C}]$PBR28 binding (standardized)

$R = 0.717$

$P = 0.004$
Conclusions from Alzheimer’s disease study

- Cross-sectional study: Neuroinflammation occurs after conversion of MCI to AD and worsens with disease progression.
  
  Biomarker of disease severity

- Longitudinal study: $^{11}$C]PBR28 increases in AD but not in controls and correlates with disease progression.
  
  Biomarker of disease progression
TSPO Imaging in Major Depressive Episode

Erica Richards, MD, PhD
Paolo Zanotti Fregonara, MD, PhD*
Masahiro Fujita, MD, PhD
Wayne Drevets, MD†
Giacomo Salvadore, MD†
Robert Innis, MD, PhD
Carlos Zarate, Jr., MD

National Institute of Mental Health, Bethesda, MD, USA
*Houston Methodist Hospital
†Janssen Pharm R&D, Titusville, NJ, USA
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Study Aims

- To evaluate TSPO binding in MDE patients compared to healthy volunteers without a history of depression.

- To investigate any effects of medication on TSPO binding: half of MDE patients were on antidepressants.
TSPO binding in anterior cingulate was increased in unmedicated MDE patients

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<th>$V_{T/f_p}$</th>
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<tbody>
<tr>
<td>Healthy</td>
<td>114 ± 27</td>
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<tr>
<td>Medicated MDE</td>
<td>122 ± 42</td>
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<tr>
<td>Unmedicated MDE</td>
<td>166 ± 58</td>
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Healthy vs. Unmed MDE: $p = 0.002$
Med MDE vs. Unmed MDE: $p = 0.033$
Healthy vs. Med MDE: not significant

In unmedicated patients, TSPO binding was increased by 31% compared to healthy controls and by 27% compared to medicated patients.
Major Findings

- TSPO binding showed widespread increase in unmedicated MDE patients compared to controls.
  -Replicates findings of Meyer et al. (2015)

- But medicated MDE showed normal TSPO density.
  -SSRI may modulate this PET inflammatory biomarker

- Need a longitudinal study of patients before and after treatment.
  -Two treatments: SSRI and anti-inflammatory
Summary

1. TSPO (translocator protein): marker of inflammation: activated microglia, reactive astrocytes, and macrophages

2. Alzheimer’s disease: Increased TSPO binding correlates with disease severity (cross sectional) and with disease progression (longitudinal).

3. Major Depressive Episode: Confirms finding of Meyer et al. (2015) of increased TSPO binding, but also found medication effects

4. How can PET facilitate anti-inflammatory trials in dementia and depression?
The Cyclooxygenase System

Membrane phospholipids → Phospholipase A₂ → Arachidonic acid

- Inducible COX-2
- Constitutive COX-1

NSAIDs

PGH₂

- Prostaglandins
- Prostacyclin
- Thromboxane

Prostanoids
**11C-PS13: COX-1**

Constitutive Microglia

**11C-MC1: COX-2**

Inducible Neurons + Microglia

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<th>Human Enzyme</th>
<th>IC$_{50}$ (nM)</th>
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COX-1 is primarily in microglia: human epilepsy tissue

COX-1

Microglia

Astrocytes

Merge
COX-2: neurons and microglia: human epilepsy tissue
COX-2: neurons and microglia
human epilepsy tissue
$^{11}$C]PS13: Specific binding to COX-1 in monkey brain
[\textsuperscript{11}C]PS13: specific binding to COX-1 in brain, spleen, GI tract, and kidney.
$^{11}$C-MC1: Specific / Displaceable binding to COX-2 only after inflammogen LPS
Macrophages in Rheumatoid Arthritis (RA)

- Macrophages and RA pathogenesis
  - Disease activity is associated with activated macrophages in joint lining
  - All disease-modifying drugs directly or indirectly reduce macrophage number and activity in joint tissues
  - Macrophages produce most of the key cytokines in joint tissues
- PET imaging with older TSPO ligand 11C-]-PK11195 showed increased uptake in RA synovitis that correlated with clinical activity

Laken et al.. Arthritis & Rheumatism, 2008
Using PET to Guide Treatment Trials

Patient Stratification: Precision Medicine

PET

- High inflammation
- Low inflammation

Drug Delivery to Brain: Target Engagement

No blockade | partial blockade | complete blockade
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Radiochemistry and clinical staff in labs of Pike and Innis