Positron Emission Tomography: Tool to Facilitate Drug Development and to Study Pharmacokinetics

Robert B. Innis, MD, PhD
Molecular Imaging Branch
National Institute Mental Health

October 8, 2009
Outline of Talk

1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling of plasma concentration and tissue uptake can measure receptor density
4. Study drug distribution: “peripheral” benzodiazepine receptor
5. Study drug metabolism: inhibit defluorination
Imaging of neuroreceptors by PET

Isotope production: 
\[
\left[ _{\text{11}}^{\text{C}} \text{, } _{\text{18}}^{\text{F}} \text{, } _{\text{13}}^{\text{N}} \text{, } _{\text{15}}^{\text{O}} \right]
\]

\[ ^{11}\text{CO}_2 \]

Radio chemistry
Precursor

Image of ligand distribution in brain

Positron camera

\[ ^{11}\text{C-}\text{ligand} \]
Positron Emission Tomography

Positron Emission Tomography
Simon R. Cherry, Ph.D.
Center for Molecular and Genomic Imaging
University of California-Davis

ucdavis

university of California
## PET vs. MRI

<table>
<thead>
<tr>
<th></th>
<th>PET</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spatial Resolution</strong></td>
<td>2 – 6 mm</td>
<td>&lt;&lt; 1 mm</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>$10^{-12}$ M</td>
<td>$10^{-4}$ M</td>
</tr>
<tr>
<td><strong>Temporal Resolution</strong></td>
<td>minutes</td>
<td>&lt;1 sec</td>
</tr>
</tbody>
</table>

Radionuclide ($^{11}$C): high sensitivity
Ligand (raclopride): high selectivity
Radioligand [$^{11}$C]raclopride: high sensitivity & selectivity
**Radioligand = Drug + Radioactivity**

1. **Drug administered at tracer doses**
   a) No pharm effects
   b) Labels <1% receptors
   c) Labeled subset reflects entire population

2. **Radioligand disposed like all drugs**
   a) Metabolism & distribution

3. **Radiation exposure**
NIH Rodent PET Camera

\(^{18}\text{F} \) bone uptake rat

Developed By: Mike Green & Jurgen Seidel
PET: Tool in Therapeutic Drug Development

• Determine dose and dosing interval

• Identify homogeneous group

• Biomarker for drug efficacy

• Monitor gene or stem cell therapy
Lazabemide blocks $[^{11}C]deprenyl$ binding to monoamine-oxidase-B (MAO-B)

Selegilene is more potent and longer acting than lazabemide
PET: Tool in Therapeutic Drug Development

- Determine dose and dosing interval
- Identify homogeneous group
- Biomarker for drug efficacy
- Monitor gene or stem cell therapy
Dopamine Transporter: Located on DA Terminals
Removes DA from Synapse
SPECT Imaging of Dopamine Transporter in Caudate and Putamen of Human Brain
123I-β-CIT Dopamine Transporter SPECT: Decreased in Parkinson’s Disease

Healthy

Parkinson Stage 1
PET: Tool in Therapeutic Drug Development

• Determine dose and dosing interval
• Identify homogeneous group
• Biomarker for drug efficacy
• Monitor gene or stem cell therapy
Serial Dopamine Transporter Imaging in a Parkinson Patient

baseline

22 mo.

34 mo.

46 mo.

Institute for Neurodegenerative Disorders
PET Imaging of Amyloid: Biomarker for Alzheimer’s Disease

AD

Control

Max

Min

University of Pittsburgh
PET Amyloid Imaging Group
PET: Tool in Therapeutic Drug Development

- Determine dose and dosing interval
- Identify homogeneous group
- Biomarker for drug efficacy
- Monitor gene or stem cell therapy
Gene Therapy Using Viral Vectors

Viral vectors deliver gene that synthesizes dopamine (DA)
Infuse virus into striatum (target cells)

Target cells express the DA gene
PET Dopamine Imaging in Hemi-Parkinson Monkey: Monitors gene for DA synthesis in right striatum

Control Gene: Lac-Z

DA Synthesis Gene: AADC
PET Imaging to Monitor Embryonic Stem Cell Treatment of “Parkinson Disease” in Rats

Normal
Embryonic Stem Cells

Unilateral Lesion
PET & MRI
Outline of Talk

1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling: plasma concentration and tissue uptake
4. Study drug distribution: “peripheral” benzodiazepine receptor
5. Study drug metabolism: inhibit defluorination
Brain Uptake of $[^{18}\text{F}]{\text{Fluoxetine}}$: Measures Density of Serotonin Transporters & Affinity of Fluoxetine

- **Patient**: AUC=32
- **Healthy**: AUC=16
**Brain Uptake of $[^{18}F]$Fluoxetine:**
Measures Density of Serotonin Transporters & Affinity of Fluoxetine

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inject Activity</td>
<td>20 mCi</td>
<td>10 mCi</td>
</tr>
</tbody>
</table>

AUC=32

AUC=16
**Brain Uptake of [¹⁸F]Fluoxetine:**
Measures Density of Serotonin Transporters &
Affinity of Fluoxetine

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>Inject Activity</td>
<td>20 mCi</td>
<td>20 mCi</td>
</tr>
</tbody>
</table>
### Brain Uptake of $[^{18}F]$Fluoxetine:
Measures Density of Serotonin Transporters & Affinity of Fluoxetine

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>Brain Drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inject Activity</td>
<td>20 mCi</td>
<td>20 mCi</td>
</tr>
<tr>
<td>Weight</td>
<td>50 kg</td>
<td>100 kg</td>
</tr>
</tbody>
</table>
Brain Uptake of $[^{18}\text{F}]$Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inject Activity</td>
<td>20 mCi</td>
<td>20 mCi</td>
</tr>
<tr>
<td>Weight</td>
<td>100 kg</td>
<td>100 kg</td>
</tr>
</tbody>
</table>
Brain Uptake of $[^{18}\text{F}]$Fluoxetine: Measures Density of Serotonin Transporters

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inject Activity</td>
<td>40 mCi</td>
<td>20 mCi</td>
</tr>
<tr>
<td>Weight</td>
<td>100 kg</td>
<td>100 kg</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Binding Potential (BP): Receptor Density * Affinity

BP equals uptake in brain relative to how much drug is delivered via arterial plasma.

\[
BP = \frac{\text{Area Brain Curve}}{\text{Area Plasma Curve}}
\]

BP = \frac{16}{2} = 8
**Binding Potential: Independent of Injected Dose**

**Double Plasma Input \( \Rightarrow \) Double Brain Response**

*If ligand does not saturate receptors - i.e., if tracer doses used*

\[
\text{BP 1st Time} = \frac{16}{2} = 8 \\
\text{BP 2nd Time} = \frac{32}{4} = 8
\]
From curves of plasma and brain radioactivity over time, estimate rate constants of entry and removal to/from tissue.

\[ BP = \frac{K_1}{k_2} \]
Tissue uptake is proportional to density of receptors and the affinity of the drug

\[ BP = \frac{B_{\text{max}}}{K_D} = B_{\text{max}} \times \frac{1}{K_D} = B_{\text{max}} \times \text{affinity} \]

\( B_{\text{max}} \) = receptor density
\( K_D \) = dissociation binding constant
\( \frac{1}{K_D} \) = binding affinity drug
SUMMARY PET KINETICS

- Organ uptake is proportional to receptor density and affinity of drug
- Binding Potential (BP) = density \( \times \) affinity
- “Drug Exposure” to tissue is AUC of:
  - plasma concentration vs. time
- “Response” (uptake) of tissue is AUC of:
  - tissue concentration vs. time

\[
BP = \frac{\text{Response}}{\text{Exposure}} = \frac{AUC_{\text{tissue}}}{AUC_{\text{plasma}}}
\]

- BP also equals ratio of rate constants of entry and removal to/from tissue

\[
BP = \frac{K_1}{k_2}
\]
Major Point of PET Pharmacokinetics
(in words)

- Plasma pharmacokinetics provides a limited view of what’s happening to drug in plasma.
- PET provides a limited view of what’s happening to drug in tissue.
- Concurrent measurement of drug in plasma and of drug in tissue allows quantitation of the target of drug action – i.e., receptor.
Outline of Talk

1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling: plasma concentration and tissue uptake
4. Study drug distribution: “peripheral” benzodiazepine receptor
5. Study drug metabolism: inhibit defluorination
Translocator Protein (18 kDa)
a.k.a. “peripheral benzodiazepine receptor”

1. Mitochondrial protein highly expressed in macrophages and activated microglia
2. Exists in periphery and brain
3. Multiple potential functions: steroid synthesis, nucleotide transport
4. Distinct from typical benzodiazepine $\mathrm{GABA_A}$ receptor in brain
5. Marker for cellular inflammation
Receptor Blockade $[^{11}\text{C}]$PBR28 in Monkey Brain: more radioligand in plasma and brain

**BASELINE**

- $V_T = 130 \text{ mL/cm}^3$
- Concentration of radioactivity in putamin (%SUV)

**RECEPTORS BLOCKED**

- $V_T = 1.7 \text{ mL/cm}^3$
- Concentration of radioactivity in plasma (%SUV)

**BRAIN**

**PLASMA**
MONKEY WHOLE BODY SCANS \([^{11}C]PBR28\)
Receptor blockade displaces from lung & kidney
Drives more to metabolism (liver) and excretion (urine)

Baseline
Lungs
Kidneys

Blocked
PK11195 10 mg/kg
Brain
Liver

Heart
Spleen
Urinary bladder
Gall bladder

2 min 25 min 115 min
Human with low uptake is similar to monkey with receptor blockade

A) regular healthy subject

B) odd healthy subject

C) normal monkey

D) pre-blocked monkey
Some HEALTHY Subjects May have No Receptor Binding of $[^{11}\text{C}]\text{PBR28}$

Nonbinders showed a trend of higher plasma $[^{11}\text{C}]\text{PBR28}$
INFLAMMATION IMAGING
On-going Studies

Neurocysticercosis
Multiple sclerosis
HIV with cognitive impairment
Alzheimer’s disease
Atherosclerosis
Outline of Talk

1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling: plasma concentration and tissue uptake
4. Study drug distribution: “peripheral” benzodiazepine receptor
5. Study drug metabolism: inhibit defluorination
$[^{18}F]FCWAY$: Defluorination
Bone uptake: human skull at 2 h
Miconazole Inhibits Defluorination & Bone Uptake

\[ {^{18}\text{F}}\text{Fluoride} \]

- Skull
- Brain

\[ {^{18}\text{F}}\text{FCWAY: Miconazole} \]

Baseline 15 mg/kg 30 mg/kg 60 mg/kg

% of Max

100

0
Disulfiram: Decreases Skull Activity & Increases Brain Uptake

Baseline
Images at 2 h in same subject. Disulfiram 500 mg PO prior night
Disulfiram: Decreases skull uptake of fluoride & Increases brain uptake of $[^{18}\text{F}]{\text{FCWAY}}$
Disulfiram: Decreases plasma fluoride & Increases plasma radiotracer $[^{18}\text{F}]$FCWAY

- $[^{18}\text{F}]$fluoride
- $[^{18}\text{F}]$FCWAY (parent tracer)
Summary of Talk

1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling: plasma concentration and tissue uptake
4. Study drug distribution: “peripheral” benzodiazepine receptor
5. Study drug metabolism: inhibit defluorination
FDA Critical Path Initiative

- Approvals for new drugs declining
- R&D funding by industry and NIH is increasing
- Problem: tools are inadequate for efficient evaluation of new drugs in the “critical path” of development
- Still using old tools like liver enzymes and hematocrit to evaluate safety and efficacy
- Need new Product Development Toolkit
“There is currently an urgent need for additional public-private collaborative work on applying technologies such as … new imaging technologies.

Opportunity: Imaging technologies, such as molecular imaging tools in neuropsychiatric diseases or as measures of drug absorption and distribution, may provide powerful insights into the distribution, binding, and other biological effects of pharmaceuticals.”
THE BIOMARKERS CONSORTIUM

The Biomarkers Consortium is a public-private biomedical research partnership of the Foundation for the National Institutes of Health, Inc. that involves a variety of public and private stakeholders including the National Institutes of Health (NIH), Food and Drug Administration (FDA), Centers for Medicare & Medicaid Services (CMS), the pharmaceutical, biotechnology, diagnostics, and medical device industries, non-profit organizations and associations, and advocacy groups (News/Events).

The Consortium will search for and validate new biological markers—biomarkers—to accelerate dramatically the competitive delivery of successful new technologies, medicines, and therapies for prevention, early detection, diagnosis, and treatment of disease. Biomarkers are molecular, biological, or physical characteristics that indicate a specific, underlying physiologic state. For example, cholesterol and blood pressure are perhaps the most well known biomarkers; these biomarkers are indicators of cardiovascular health.
Self-Assessment Quiz: True or False?

- Positron emission tomography (PET) studies involve the injection of a radioactively labeled drug that emits a particle called a positron.
- PET shows the location of radioactivity in a cross section (or tomograph) of the body.
- PET can be used to quantify the density of specific proteins in the body.
- Compartmental modeling of PET data typically uses measurements over time of 1) PET images of the target tissue and 2) concentrations of unchanged parent radioligand in plasma.