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

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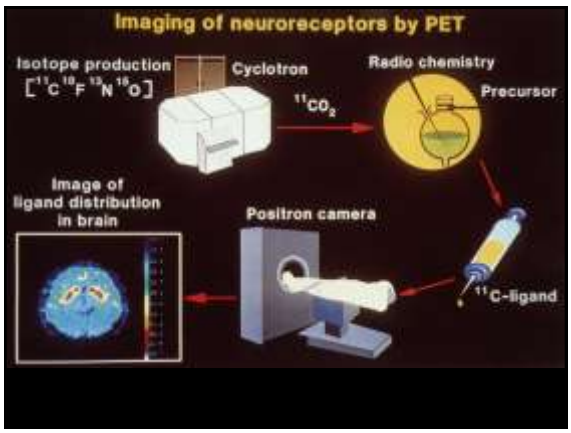
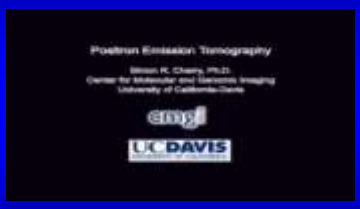
Outline of Talk

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: block distribution to periphery and increase distribution to brain
5. Study drug metabolism: inhibit defluorination



Positron Emission Tomography



PET vs. MRI

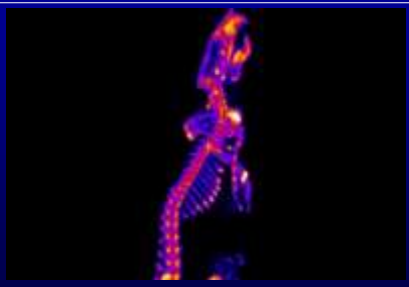
	PET	MRI
Spatial Resolution	2 – 6 mm	<< 1 mm
Sensitivity	10^{-12} M	10^{-4} M
Temporal Resolution	minutes	<1 sec

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}F bone uptake rat

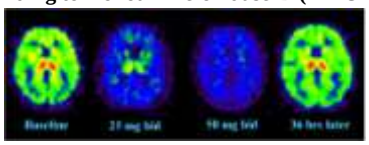


Developed By: Mike Green & Jurgen Seidel

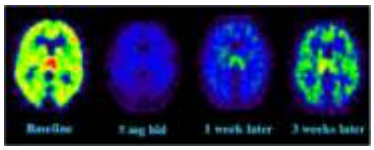
PET: Tool in Therapeutic Drug Development

- 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

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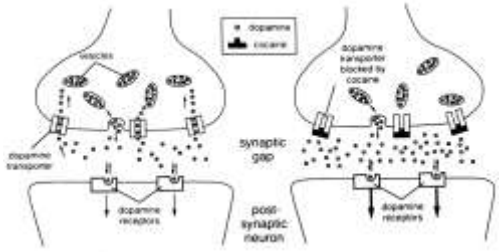
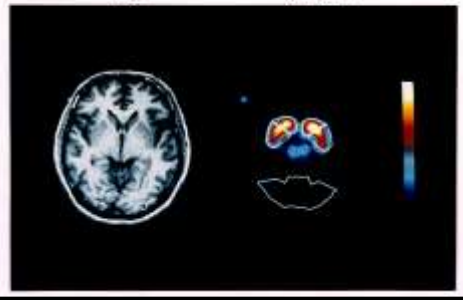
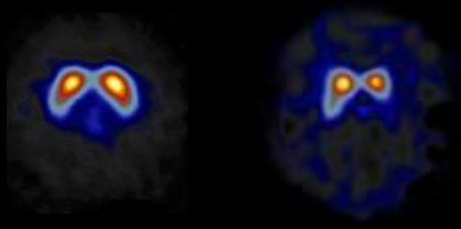
Dopamine Transporter: Located on DA Terminals Removes DA from Synapse



SPECT Imaging of Dopamine Transporter in Caudate and Putamen of Human Brain



^{123}I-β-CIT Dopamine Transporter SPECT: Decreased in Parkinson's Disease



Healthy **Parkinson Stage 1**

PET: Tool in Therapeutic Drug Development

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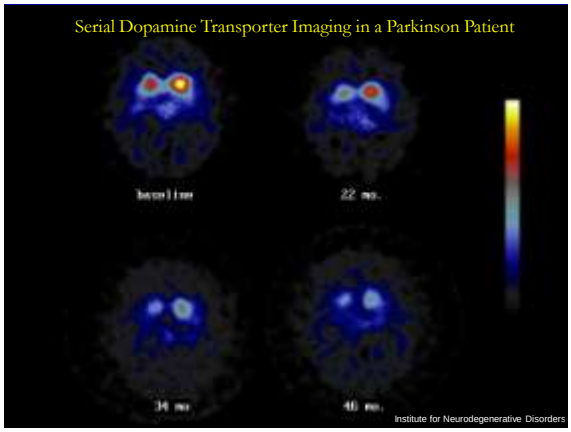

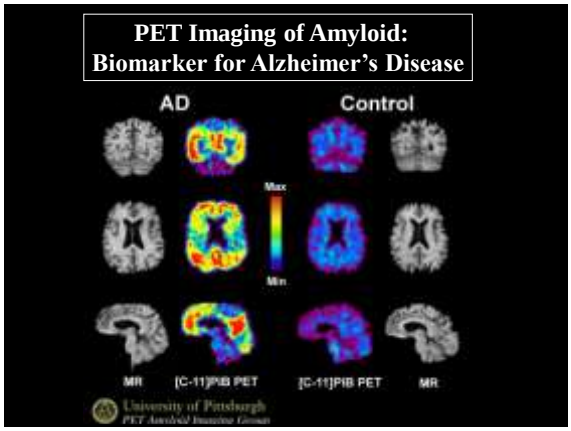

PET: Tool in Therapeutic Drug Development

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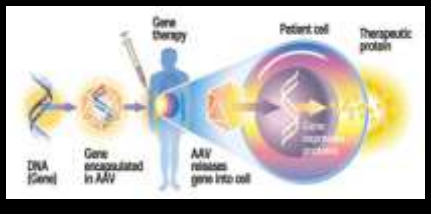
Gene Therapy Using Viral Vectors

Viral vectors deliver gene that synthesizes dopamine (DA)

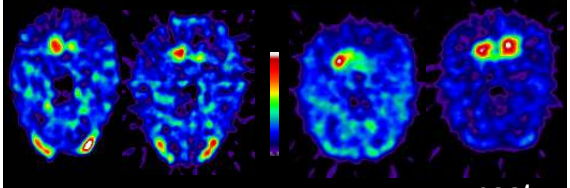
Infuse virus into striatum (target cells)

Target cells express the DA gene



PET Dopamine Imaging in Hemi-Parkinson Monkey:

Monitors gene for DA synthesis in right striatum



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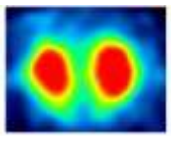
Control Gene: Lac-Z

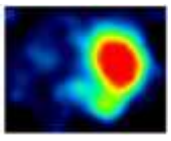
DA Synthesis Gene: AADC

PET Imaging to Monitor Embryonic Stem Cell Treatment of "Parkinson Disease" in Rats

Normal



Unilateral Lesion



Embryonic Stem Cells

PET & MRI

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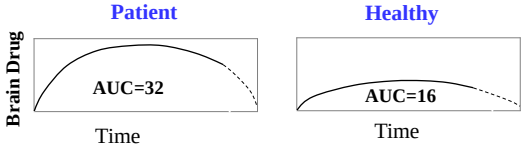
Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine



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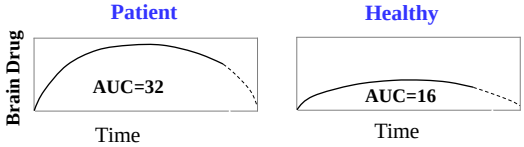

	Patient	Healthy
Inject Activity	20 mCi	10 mCi

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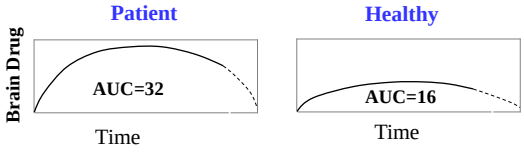
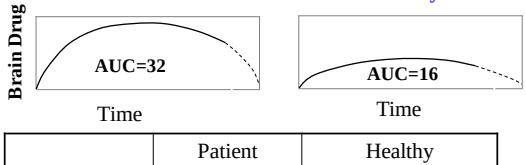


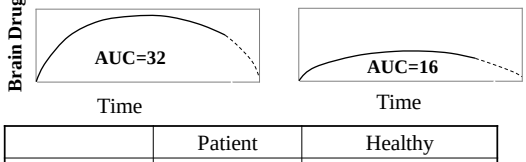
	Patient	Healthy
Inject Activity	20 mCi	20 mCi

Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine



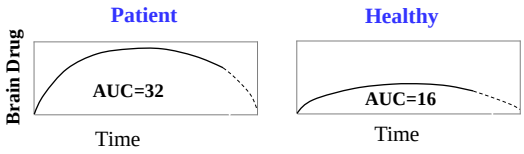
	Patient	Healthy
Inject Activity	20 mCi	20 mCi
Weight	50 kg	100 kg

Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine



	Patient	Healthy
Inject Activity	20 mCi	20 mCi
Weight	100 kg	100 kg

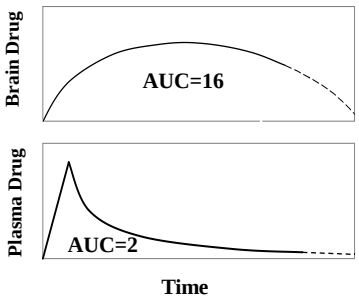
Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters



	Patient	Healthy
Inject Activity	40 mCi	20 mCi
Weight	100 kg	100 kg
Liver disease	Yes	No

Binding Potential (BP): Receptor Density * Affinity

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



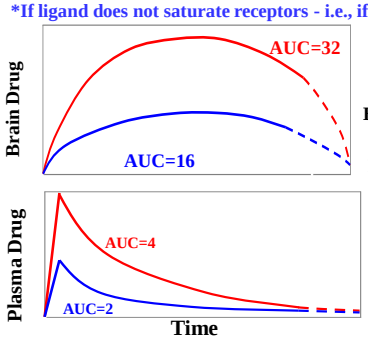
$$BP = \frac{\text{Area Brain Curve}}{\text{Area Plasma Curve}}$$

$$BP = \frac{16}{2} = 8$$

Binding Potential: Independent of Injected Dose*

Double Plasma Input =>Double Brain Response

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

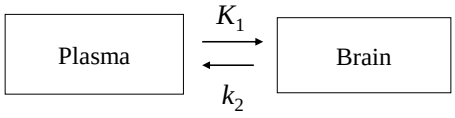


BP 1st Time = $\frac{16}{2} = 8$

BP 2nd Time = $\frac{32}{4} = 8$

BP can be calculated from the Area Under Curve (math integral) as well as rate constants (math differential).

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

Binding Potential

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

B_{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 X affinity
- "Drug Exposure" to tissue is AUC of:
  plasma concentration *vs.* time
- "Response" (uptake) of tissue is AUC of:
  tissue concentration *vs.* time

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

- 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.**

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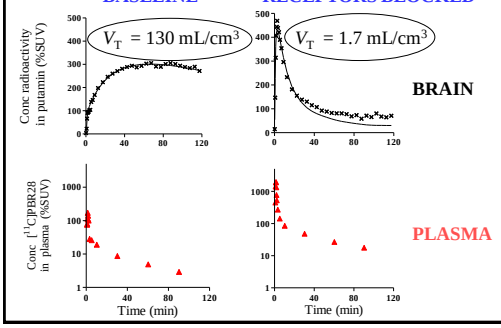
Translocator Protein (18 kDa)
a.k.a. "peripheral benzodiazepine receptor"

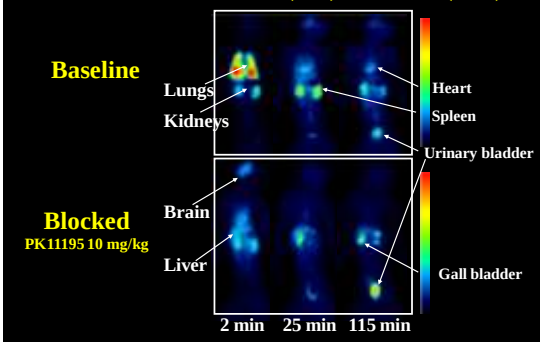
1. Mitochondrial protein highly expressed in macrophages and activated microglia
2. Exists in periphery and brain
3. Multiple potential functions: steroid synthesis, nucleotide transport
4. Distinct from typical benzodiazepine $GABA_A$ receptor in brain
5. Marker for cellular inflammation

Receptor Blockade [^{11}C]PBR28 in Monkey Brain: more radioligand in plasma and brain

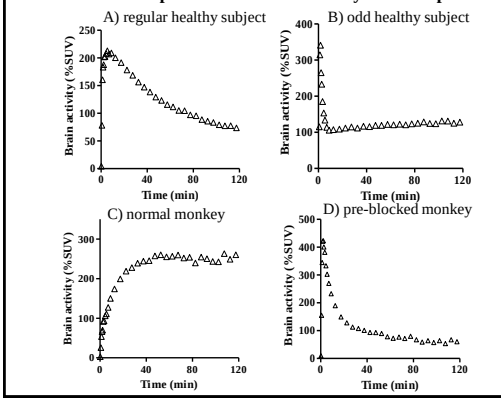


MONKEY WHOLE BODY SCANS [^{11}C]PBR28

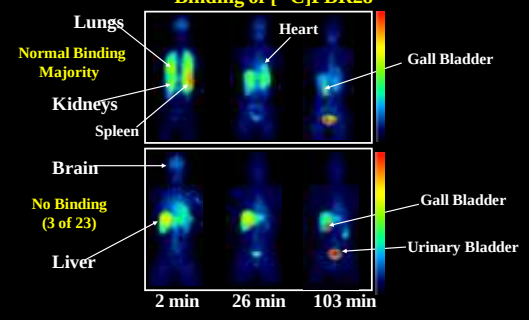
Receptor blockade displaces from lung & kidney
Drives more to metabolism (liver) and exretion (urine)



Human with low uptake is similar to monkey with receptor blockade

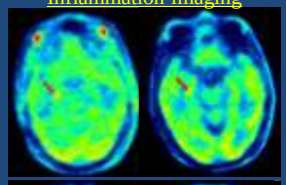
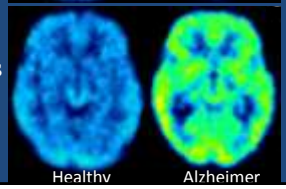


Some HEALTHY Subjects May have No Receptor Binding of [^{11}C]PBR28



Nonbinders showed a trend of higher plasma [^{11}C]PBR28

Focal and Global Increase of Inflammation

Disease	Inflammation imaging	
Epilepsy		Focal increase in epileptogenic focus
Alzheimer's disease		Global increase of inflammation

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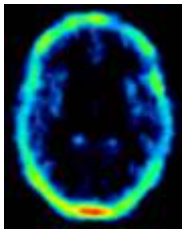
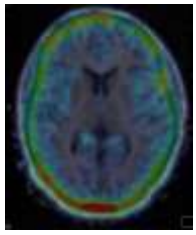
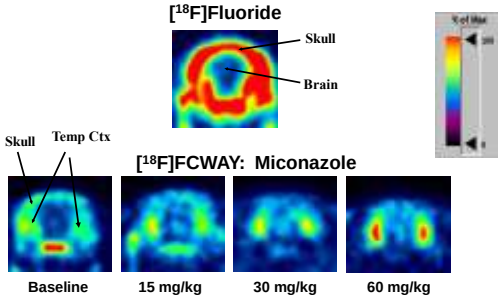
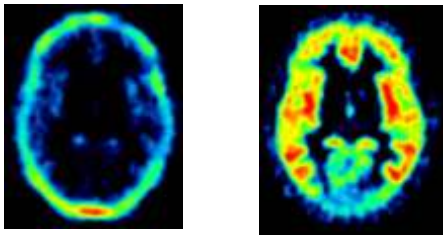
[^{18}F]FCWAY: Defluorination Bone uptake: human skull at 2 h

Miconazole Inhibits Defluorination & Bone Uptake



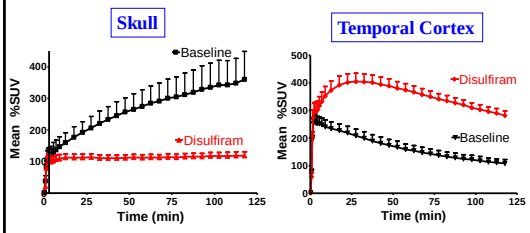
Disulfiram: Decreases Skull Activity & Increases Brain Uptake



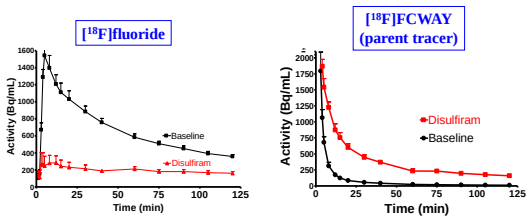
Baseline **Disulfiram**

Images at 2 h in same subject. Disulfiram 500 mg PO prior night

Disulfiram: Decreases skull uptake of fluoride & Increases brain uptake of [^{18}F]FCWAY



Disulfiram: Decreases plasma fluoride & Increases plasma radiotracer [^{18}F]FCWAY



Summary

1. PET has high sensitivity and specificity
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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.

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**

CRITICAL PATH to New Medical Products
FDA, March 2004

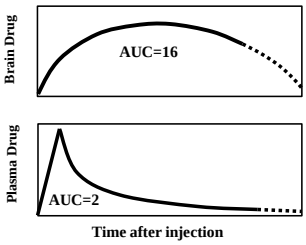
"There is currently an urgent need for additional **public-private collaborative work** on applying technologies such as … new imaging technologies.

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."

Quantification of receptor density

Distribution volume

Uptake in brain relative to how much drug is delivered via arterial plasma



$$V_T = \frac{\text{Area Brain Curve}}{\text{Area Plasma Curve}}$$

$$V_T = \frac{16}{2} = 8$$

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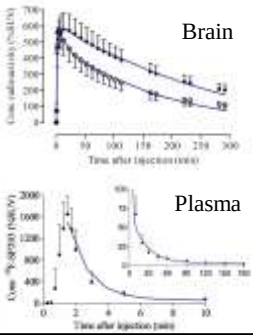
^{18}F-SP203 in Human: Quantification went well



Regions	V_T (mL∗cm^{-3})
Temporal cortex	25.8 ± 2.4
Cerebellum	14.2 ± 1.6

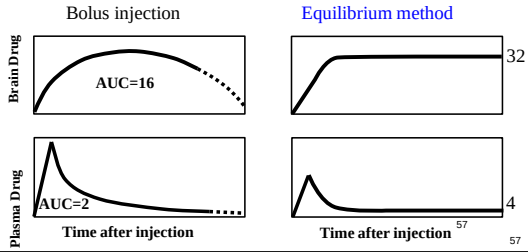
Brown et al. 2008

Quantification of receptor density

Equilibrium method

Distribution volume

Concentration ratio of tissue to plasma under equilibrium



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Advantages of equilibrium method

- Determine VT directly from concentration ratio of tissue to plasma under equilibrium
- Less invasive
- Rapid equilibrium can be achieved with bolus and constant infusion

Rapid equilibrium with bolus plus constant infusion

From pharmacokinetic course 2009 by R.E. Carson

Radioactivity became stable in plasma and brain with bolus plus constant infusion