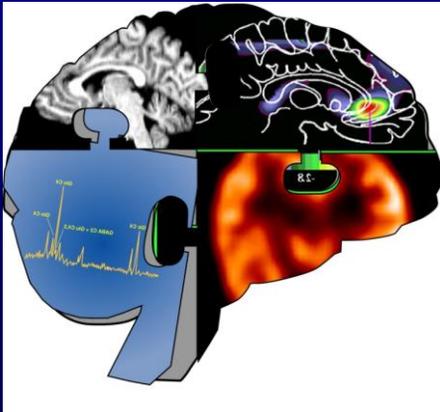


PET Imaging of P-gp: an efflux transporter at blood-brain barrier



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

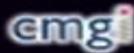
Outline of Talk

1. **Positron emission tomography (PET) has high sensitivity to measure small mass doses of radiolabeled drugs in body.**
2. **Loperamide (Imodium®) is a potent opiate that acts on receptors in gut, but P-gp blocks its entry into brain.**
3. **[¹¹C]desmethyl-loperamide (dLop) is also substrate for P-gp in mice, monkey, and man.**
4. **dLop (weak base) is ionicly trapped in acidic vesicles.**
5. **[¹¹C]dLop may measure function of P-gp in disease.**
 - * **Increased function may cause drug resistance in cancer and epilepsy.**

Positron Emission Tomography

Positron Emission Tomography

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



PET vs. MRI

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

Radionuclide (^{11}C): high sensitivity

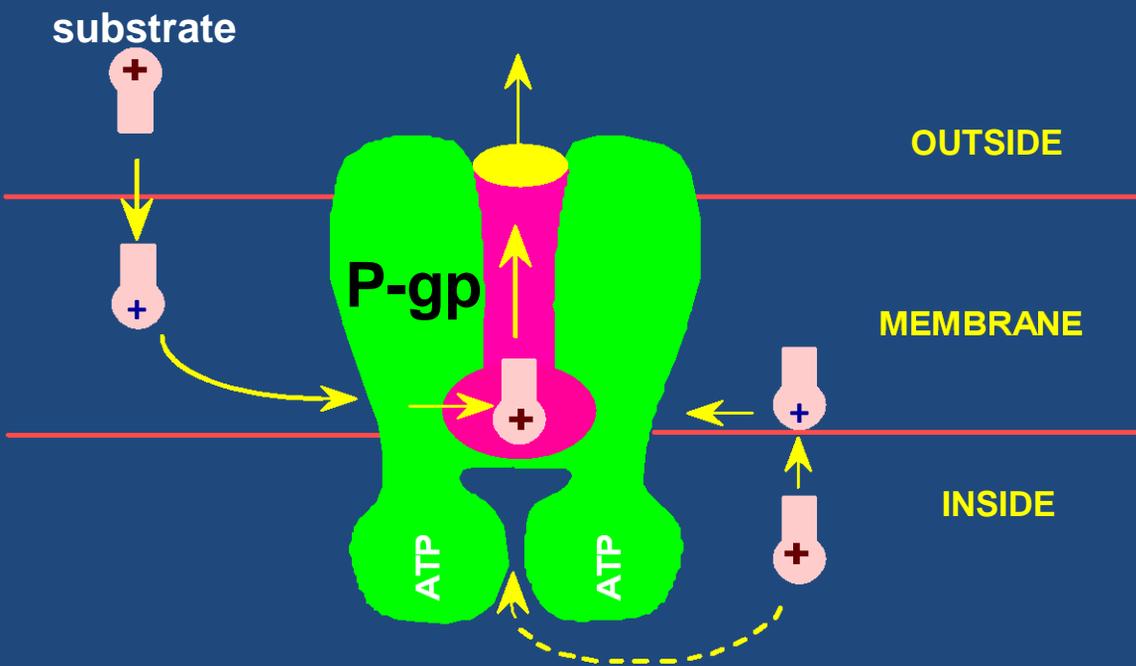
Ligand (raclopride): high selectivity

Radioligand [^{11}C]raclopride: high sensitivity
& selectivity

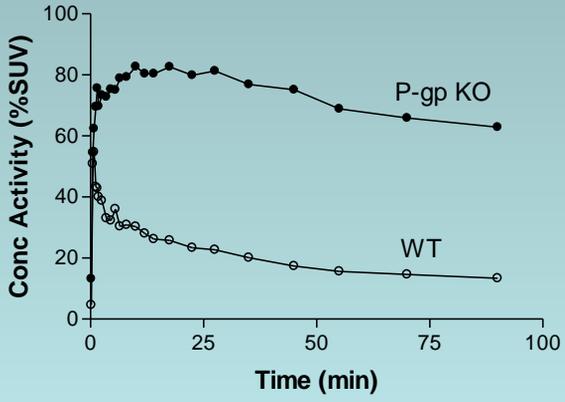
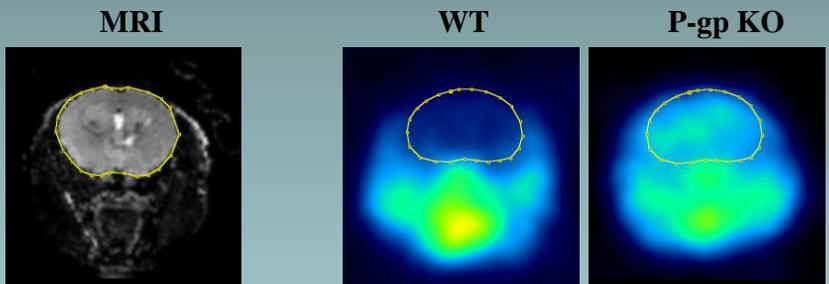
P-glycoprotein (P-gp) Efflux Transporter

1. Transports drugs out of cells in many locations – e.g., brain and testes
2. Specific component of blood-brain barrier
3. Loperamide (Imodium®) is a potent opiate that acts on gut to slow motility – but no actions in brain.
4. Over expressed in 40% of tumors resistant to chemotherapy

P-glycoprotein removes lipophilic substrates directly from the plasma membrane



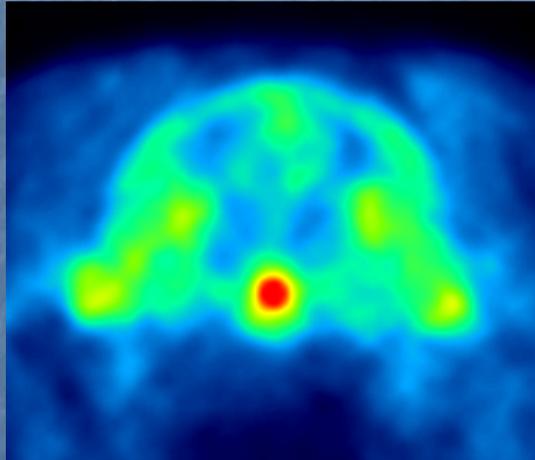
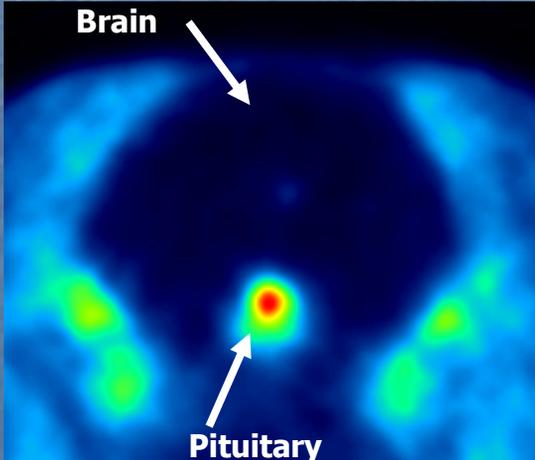
[¹¹C]dLop: brain uptake much higher in P-gp KO than in wild type mice



P-gp blockade increases uptake of [¹¹C]dLop in monkey brain but not in pituitary.

Baseline

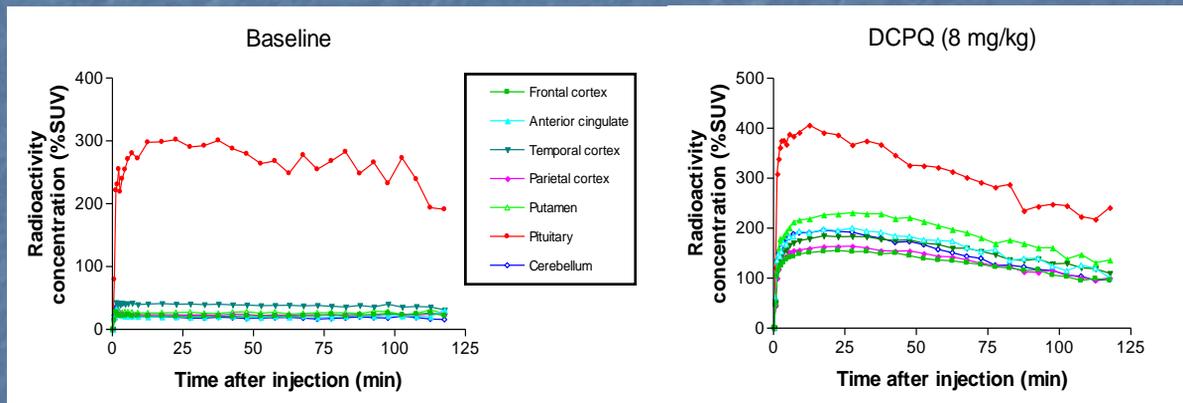
P-gp blockade

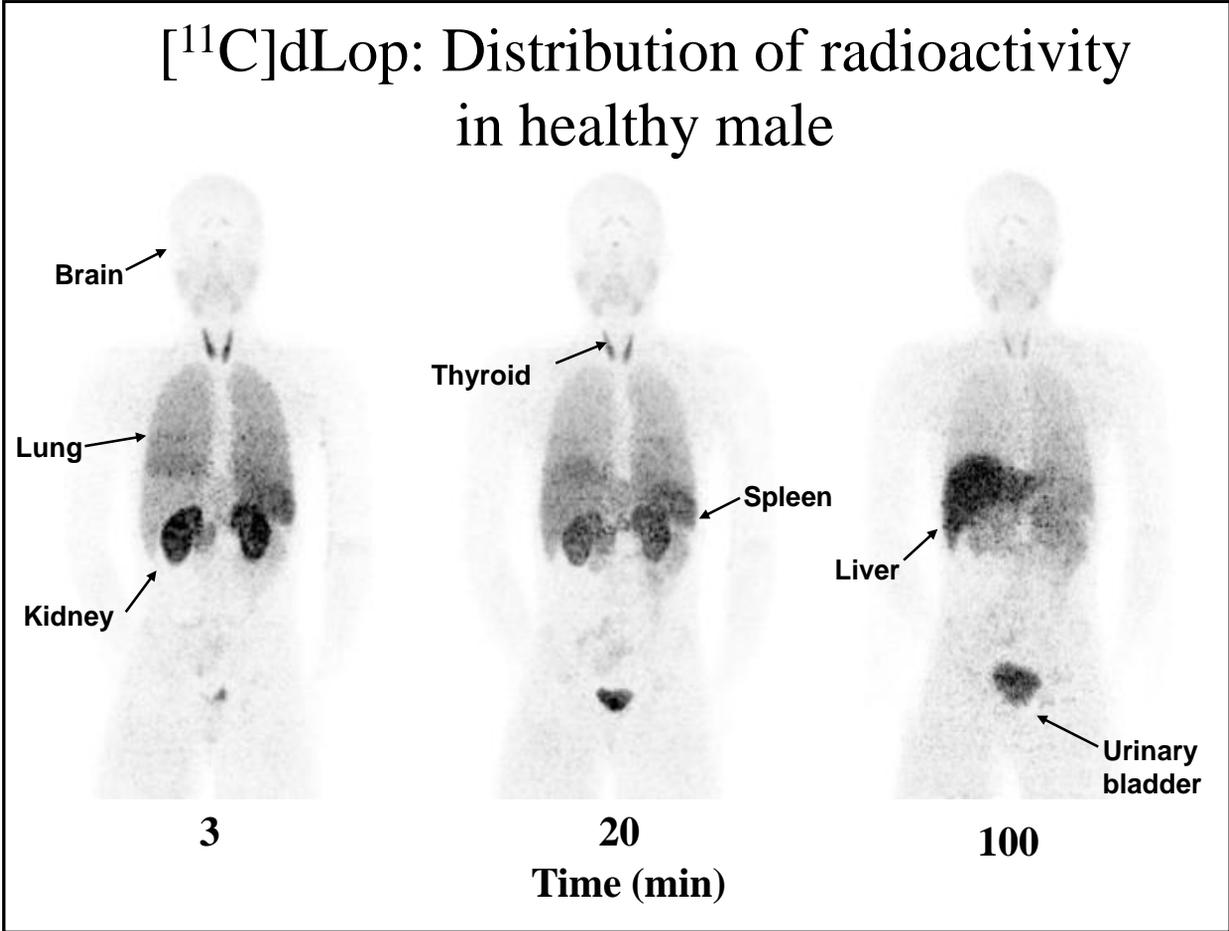


P-gp blocked with DCPQ

[¹¹C]dLop in Monkey Brain

**P-gp blockade increases brain uptake
but no effect on pituitary**



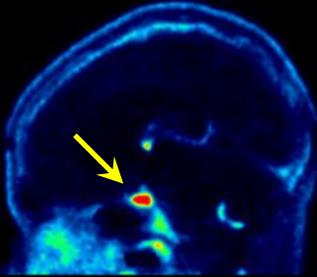


**Summed early images
(0 – 3 min) show
blood pool.**

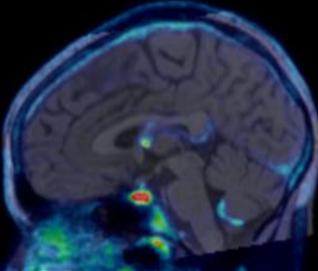


Minimal brain uptake of [¹¹C]dLop in healthy human brain

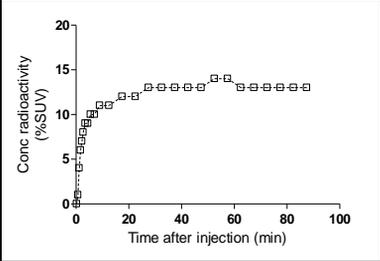
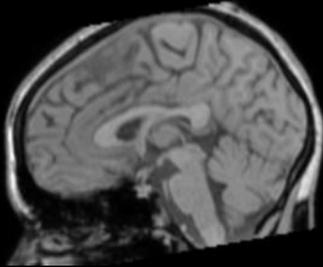
PET

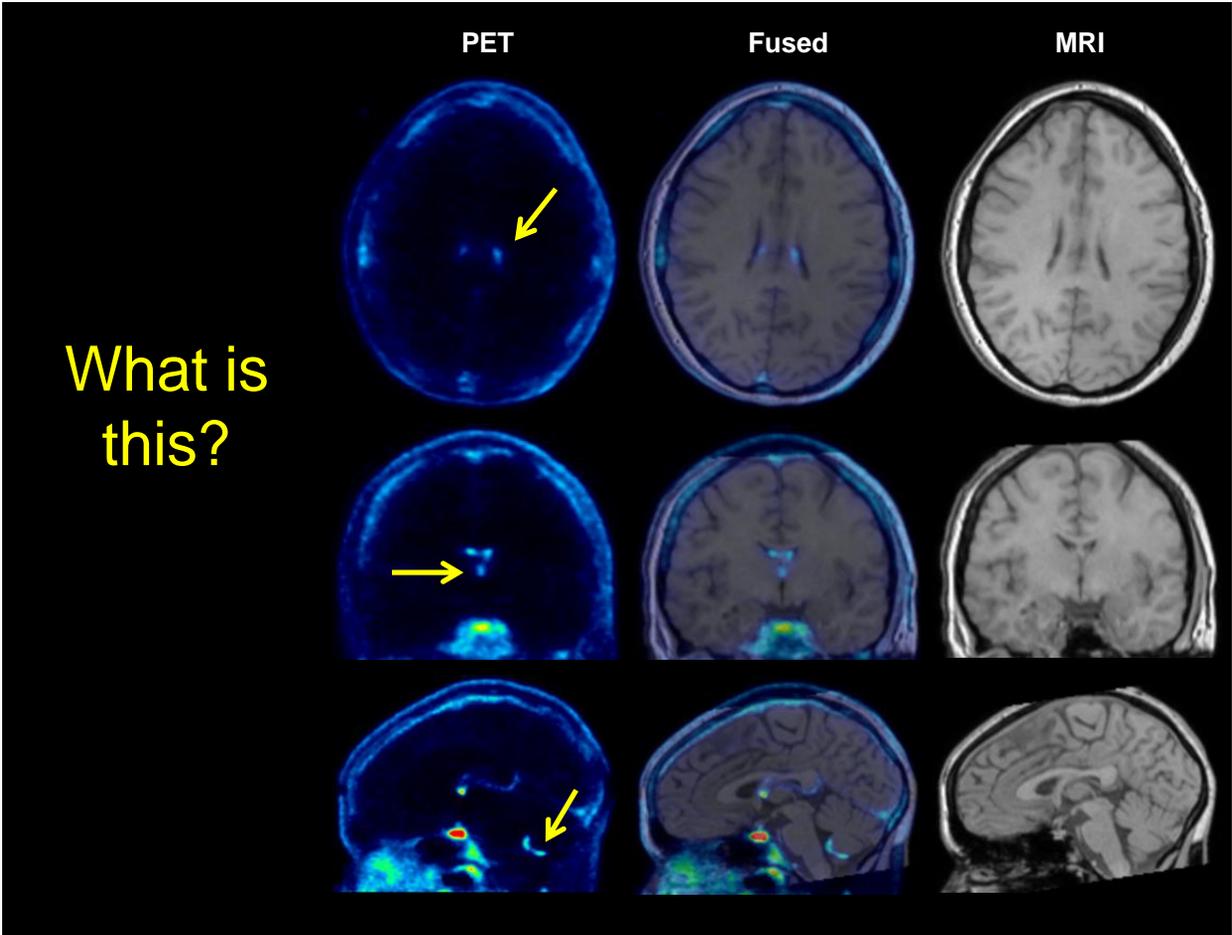


Fused



MRI



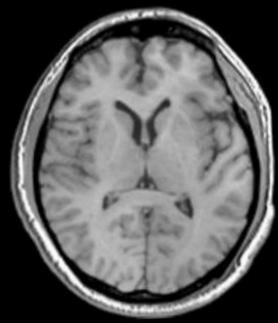
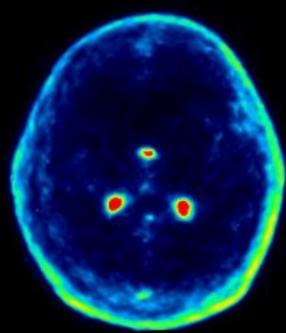


**Extended summed images (0 – 10 min) show
blood pool and tissue accumulation.**

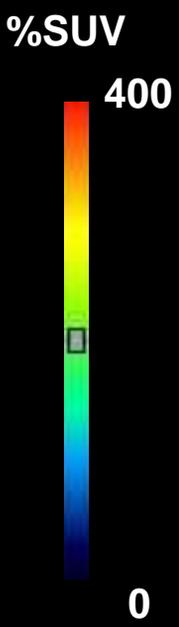
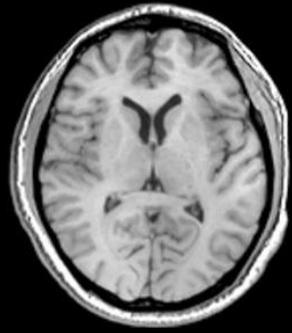
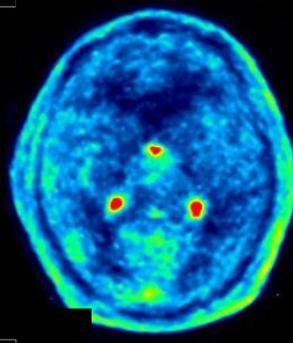


Tariquidar 6 mg/kg increases [¹¹C]dLop by 250%.

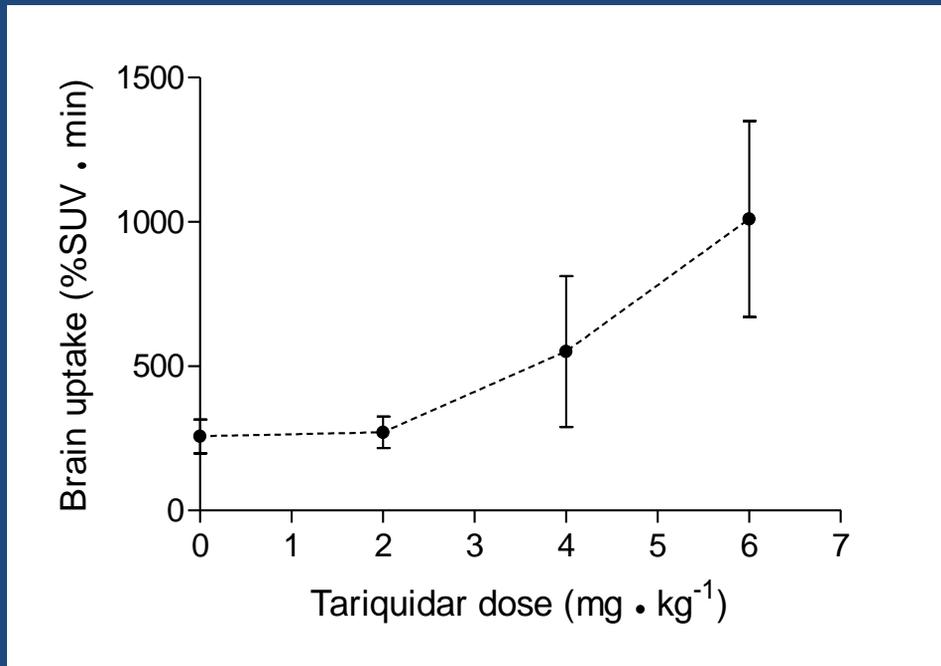
Baseline



**Tariquidar
6 mg/kg**



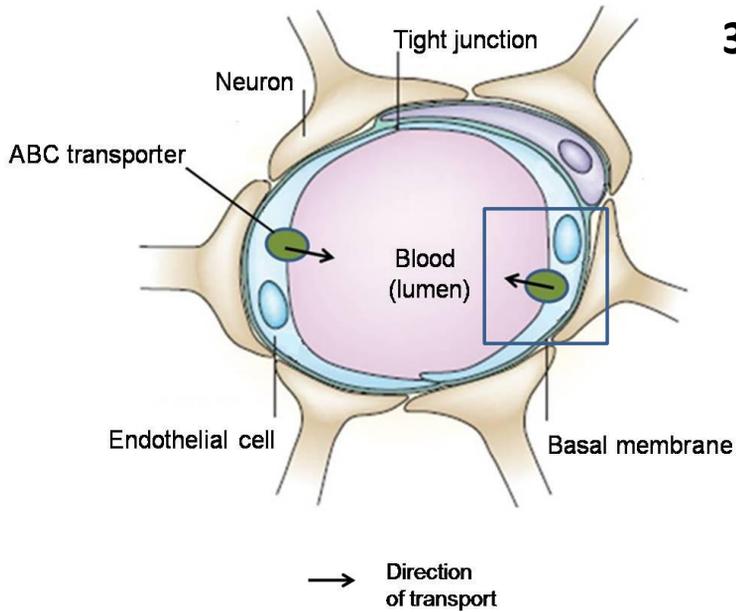
Brain uptake of [^{11}C]dLop increases dose-dependently after inhibition of P-gp.



Thesis Work of Pavitra Kannan

1. [^{11}C]dLop is a selective substrate for P-gp.
2. Retention of [^{11}C]dLop in brain reflects ionic trapping in acidic vesicles.

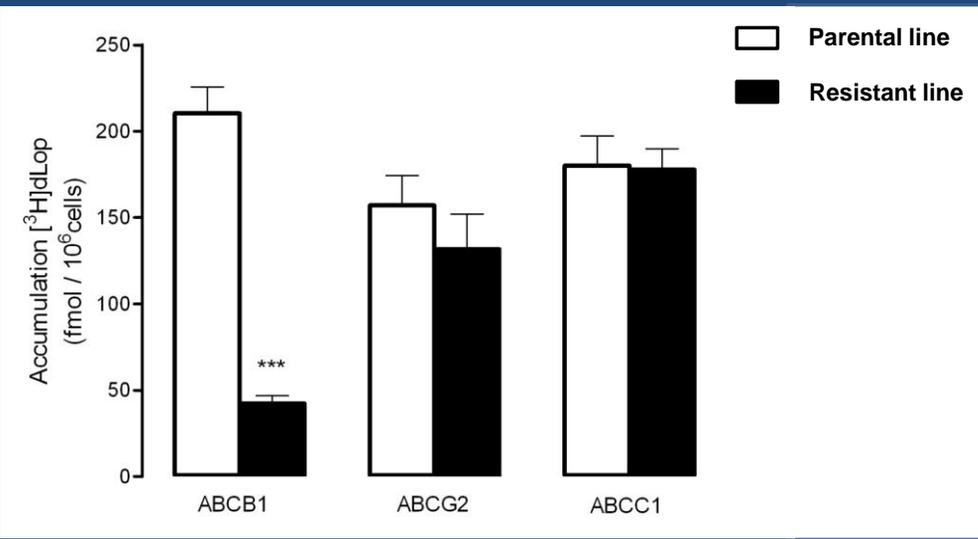
ABC transporters at the blood-brain barrier



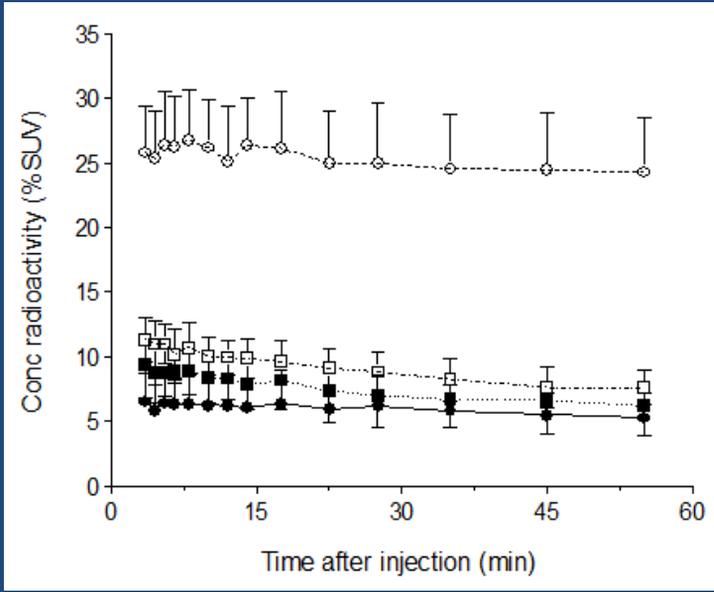
- 3 most common:**
- ABCB1 (P-gp)
 - ABCC1
 - ABCG2

Loscher et al. 2005. Nature Review Neuroscience. Drug resistance in brain diseases

Accumulation of [³H]dLop is lowest in ABCB1 (P-gp) expressing cells

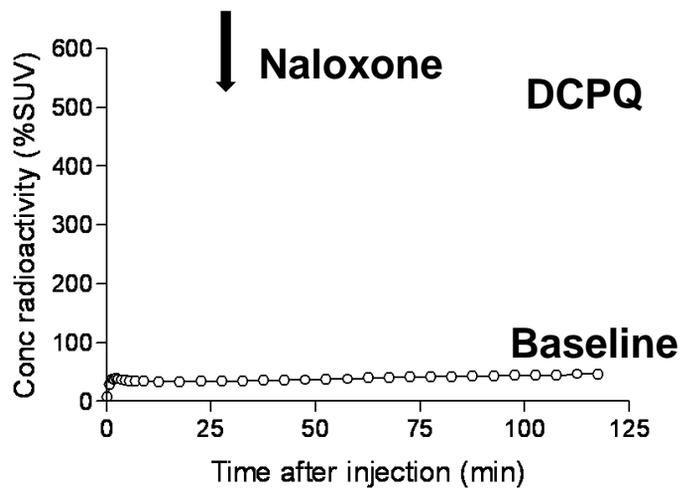


Uptake of [¹¹C]dLop is highest in brains of P-gp knockout mice



- ABCB1 (P-gp) KO
- ABCG2 KO
- ABCC1 KO
- WT

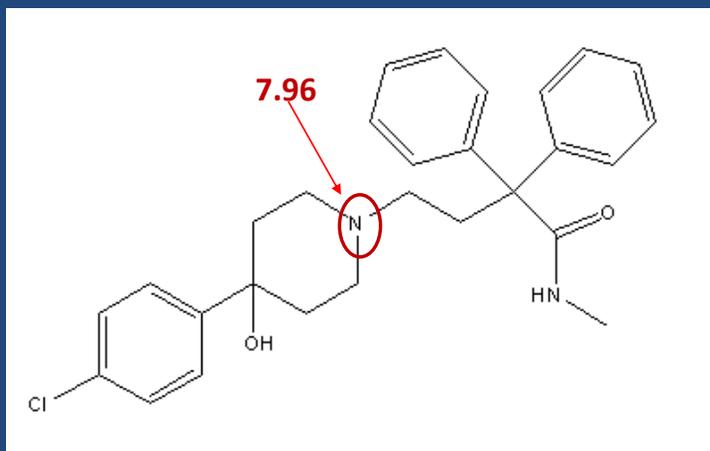
Brain uptake of [^{11}C]dLop increases after P-gp inhibition and is trapped



DCPQ 16 mg/kg

Naloxone 5 mg/kg

Structure of dLop: weak base

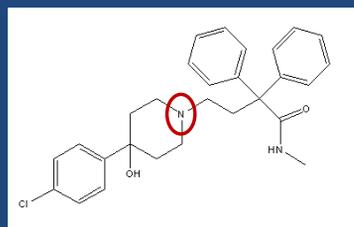
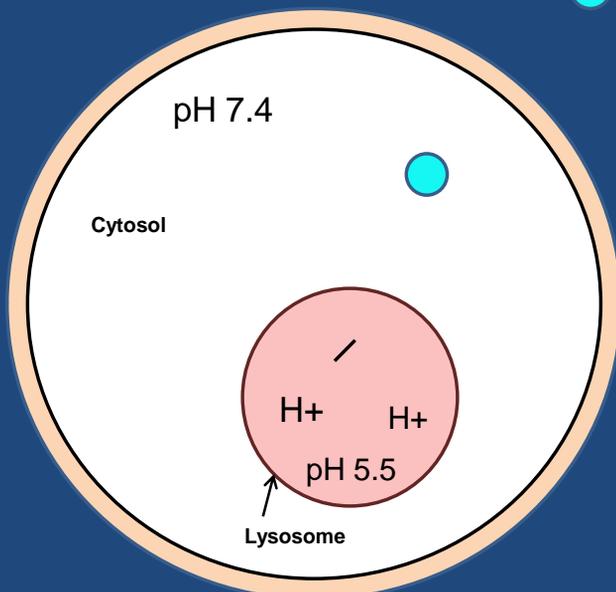


dLop

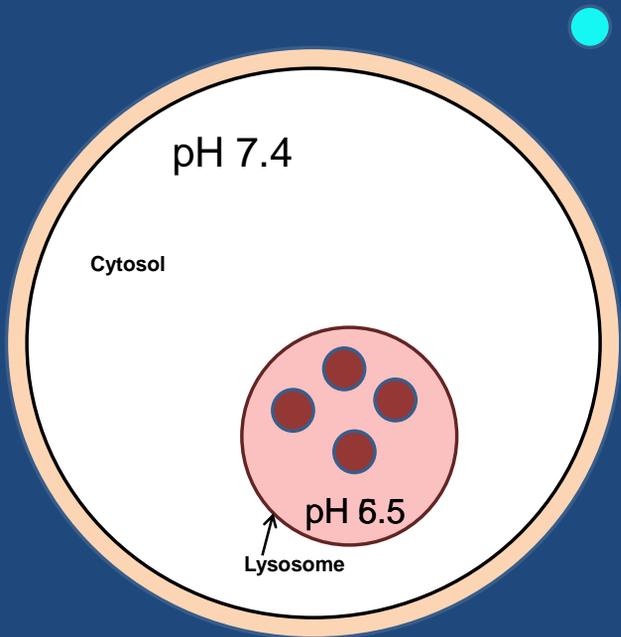
Hypothesis: lysosomal trapping

Weak base

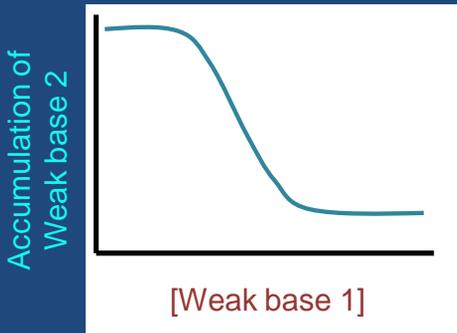
 pKa ~ 8.0



Competition with other weak bases

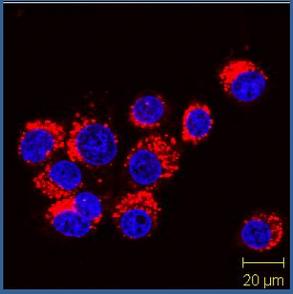


- Weak base 1 (blocker)
- Weak base 2 (substrate)

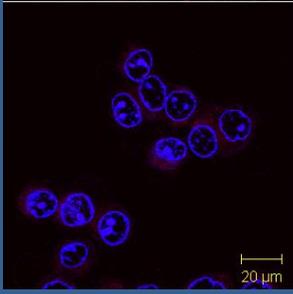


Displacement of LysoTracker Red by other weak bases

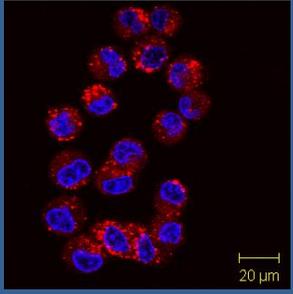
Baseline



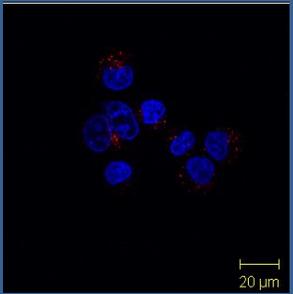
Weak Base
100 µM Tamoxifen



Non-Base
10 µM Taxol



100 µM dLop

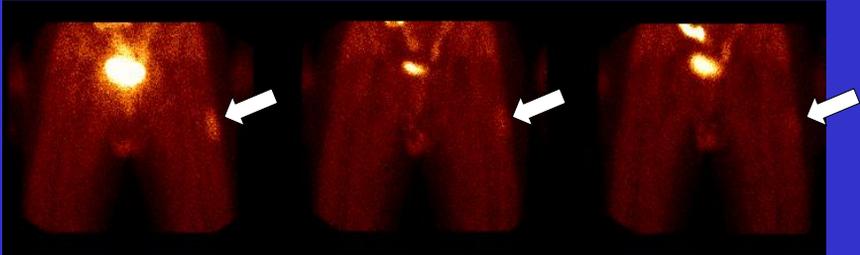


What is organ above left kidney?



Renal Cell Carcinoma: Tariquidar increases uptake of ^{99m}Tc-Sestamibi in metastasis of thigh

Baseline

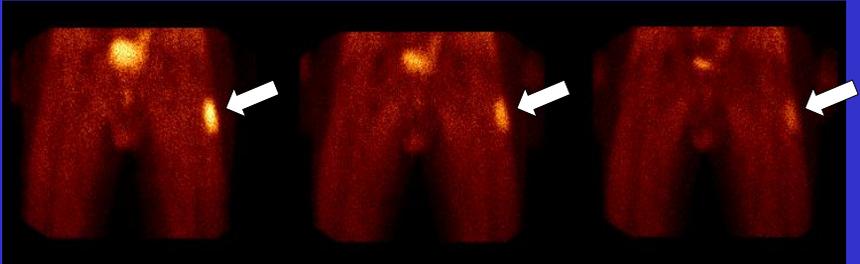


1 hour

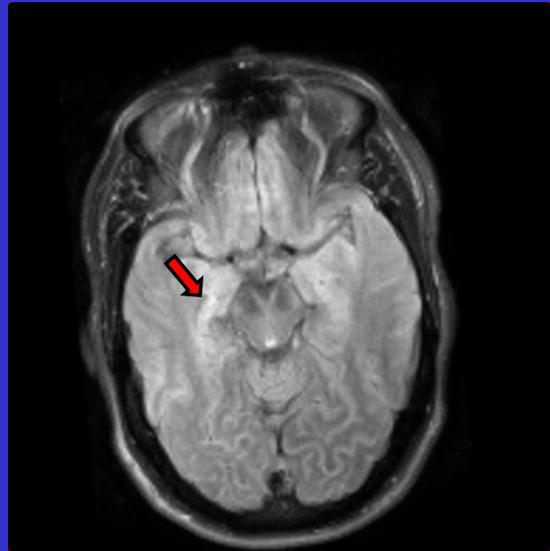
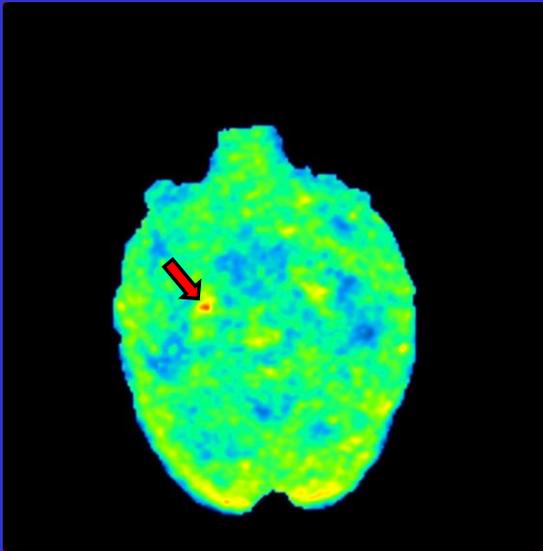
2 hours

3 hours

After
Tariquidar



Translocator protein (marker of neuroinflammatory cells) can localize epileptogenic focus.



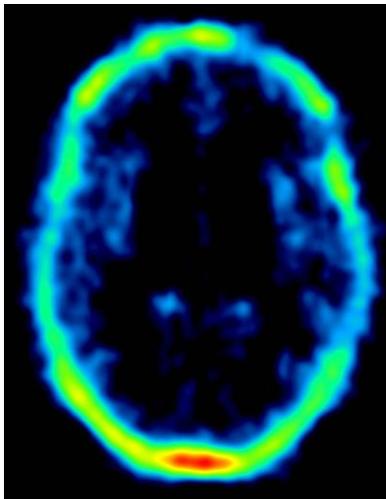
Summary

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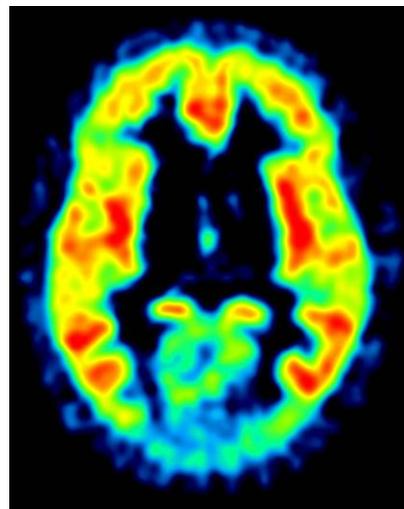
Self-Assessment Quiz: True or False?

- Loperamide, an antidiarrheal drug, lacks central nervous system opiate effects because P-gp (Permeability-glycoprotein) blocks its entry into brain.
- Positron emission tomography (PET) can measure the function of P-gp *in vivo* by using a radiolabeled P-gp substrate such as [¹¹C]loperamide.
- PET can monitor the *in vivo* metabolism of radioligands. By measuring P-gp function, PET can also monitor drug distribution.

Disulfiram: Decreases Skull Activity & Increases Brain Uptake



Baseline



Disulfiram

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