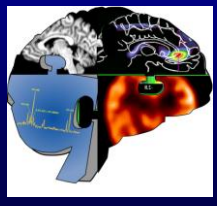
PET Imaging of P-gp:

an efflux transporter at blood-brain barrier

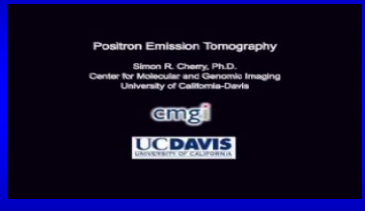


Robert B. Innis, MD, PhD
Molecular Imaging Branch
National Inst. Mental Health

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. **[^{11}C]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. **[^{11}C]dLop may measure function of P-gp in disease.**
   * **Increased function may cause drug resistance in cancer and epilepsy.**

Positron Emission Tomography



PET vs. MRI

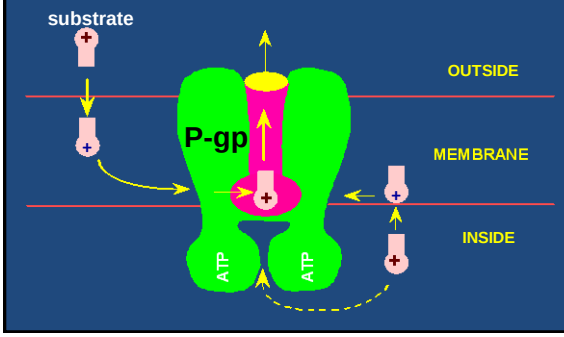
	PET	MRI
Spatial Resolution	2 – 6 mm	<< 1 mm
Sensitivity	10^{-12} M	10^{-4} M
Temporal Resolution	minutes	<1 sec

Radionuclide (^{11}C): high sensitivity
Ligand (raclopride): high selectivity
Radioligand [^{11}C]raclopride: high sensitivity & selectivity

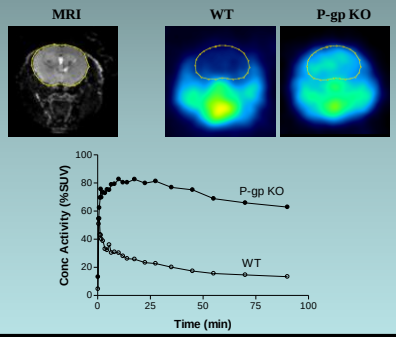
P-glycoprotein (P-gp) Efflux Transporter

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

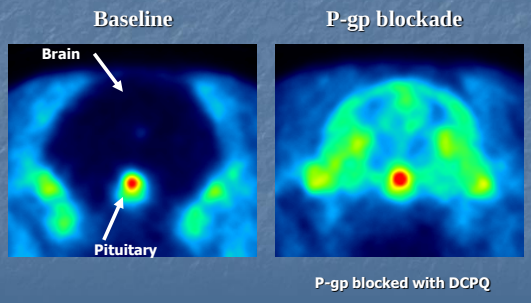
P-glycoprotein removes lipophilic substrates directly from the plasma membrane



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

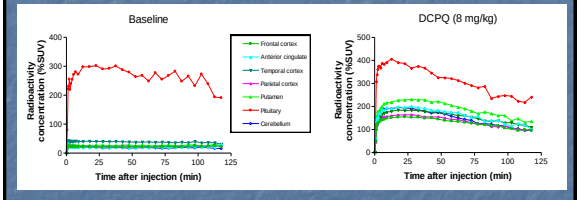


P-gp blockade increases uptake of [^{11}C]dLop in monkey brain but not in pituitary.

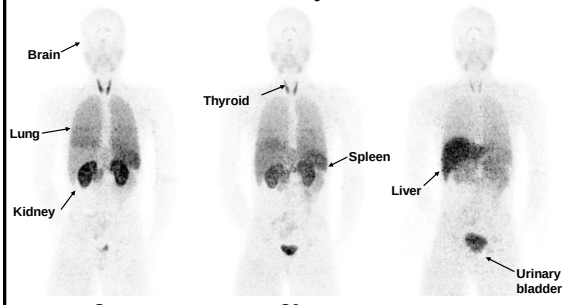


[^{11}C]dLop in Monkey Brain

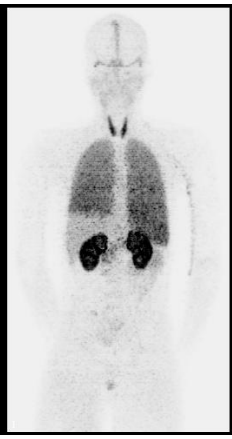
P-gp blockade increases brain uptake but no effect on pituitary



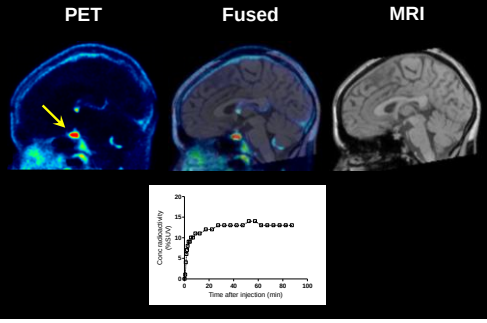
[^{11}C]dLop: Distribution of radioactivity in healthy male

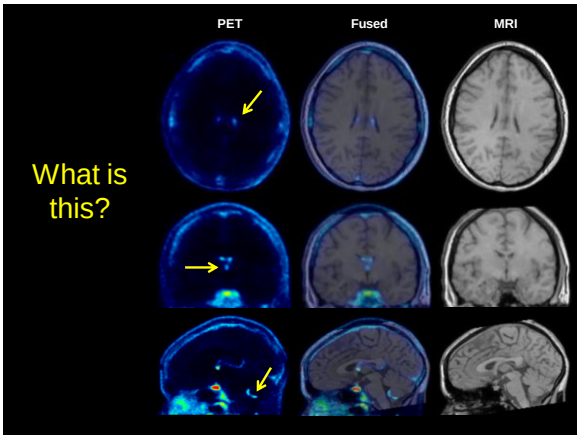


Summed early images (0 – 3 min) show blood pool.

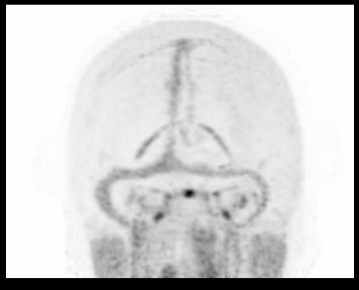


Minimal brain uptake of [^{11}C]dLop in healthy human brain

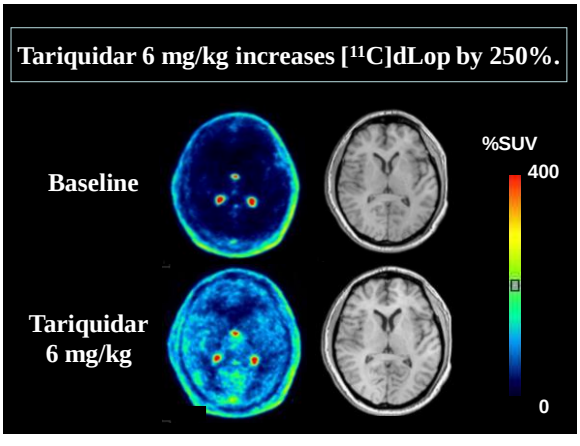




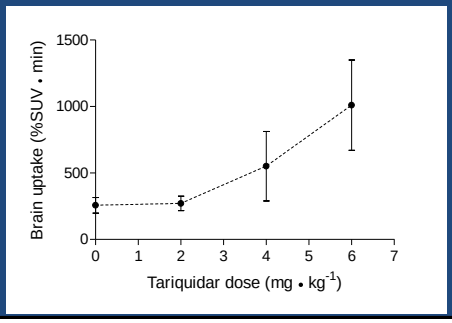
Extended summed images (0 – 10 min) show blood pool and tissue accumulation.



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



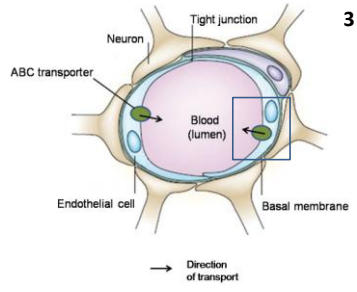
Brain uptake of [^{11}C]dLop increases dose-dependently after inhibition of P-gp.



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.

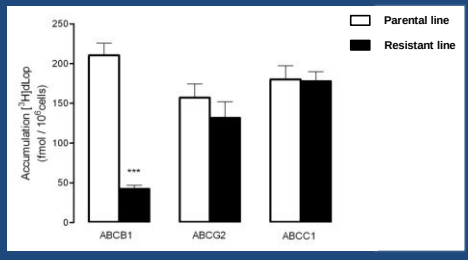
ABC transporters at the blood-brain barrier



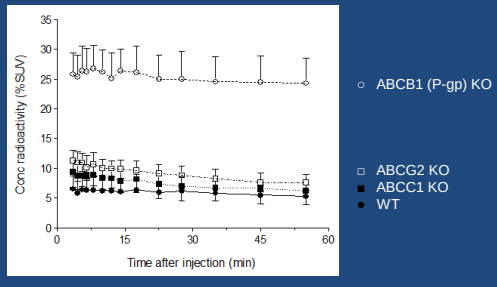
3 most common:
- **ABCB1 (P-gp)**
- **ABCC1**
- **ABCG2**

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

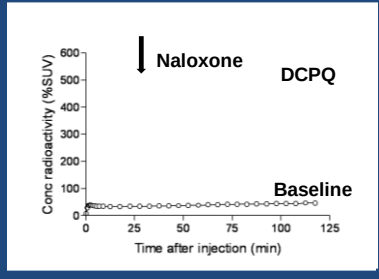
Accumulation of [^{3}H]dLop is lowest in ABCB1 (P-gp) expressing cells



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

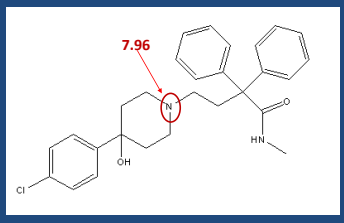


Brain uptake of [^{11}C]dLop increases after P-gp inhibition and is trapped



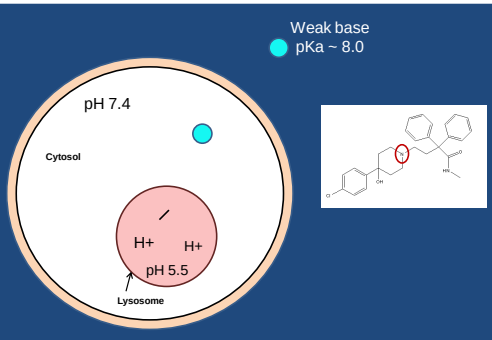
DCPQ 16 mg/kg Naloxone 5 mg/kg

Structure of dLop: weak base

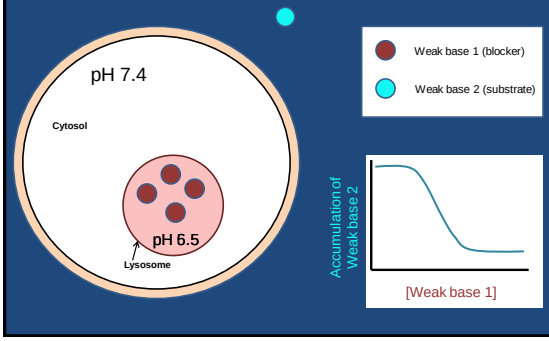


dLop

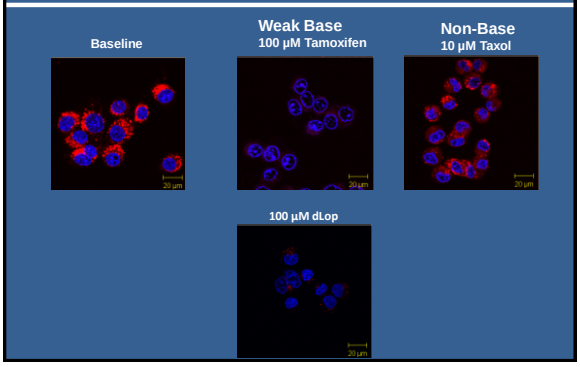
Hypothesis: lysosomal trapping



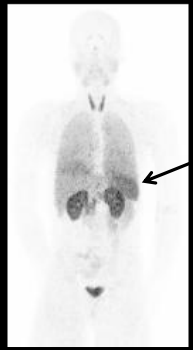
Competition with other weak bases



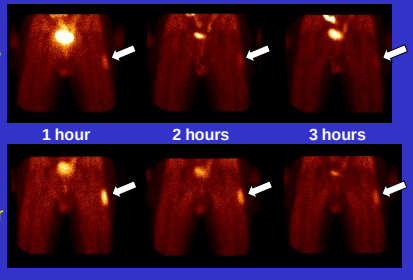
Displacement of Lysotracker Red by other weak bases



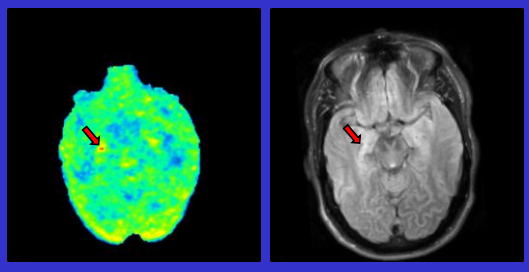
What is organ above left kidney?



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



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



Summary

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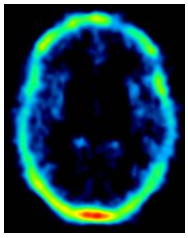
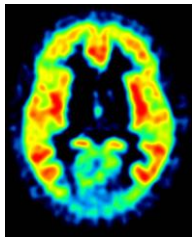
Self-Assessment Quiz: True or False?

- 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 [^{11}C]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