P-glycoprotein at the blood-brain barrier
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**Permeability---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.
ATP – binding cassette (ABC) transporters at the blood-brain barrier

Images
ATP – binding cassette (ABC) transporters at the blood-brain barrier

Images

3 most common classes:
- P-glycoprotein (P-gp/ABCB1)
- Multidrug resistance protein (Mrp1/ABCC1)
- Breast cancer resistance protein (Bcrp/ABCG2)

Limits drug delivery

Increases function:
- Drug-resistant epilepsy
- HIV infection of brain
- Multidrug resistant cancer

Dysfunction:
- Alheimer disease

Why study (ABC) transporters at the blood-brain barrier?

- Understanding now changes in P-gp expression impact disease states
- Can we take advantage of transport inhibitors to improve drug delivery (Snatch victory from the jaws of defeat)
- Patient imaging/diagnosis preferable to post-mortem imaging
Why study (ABC) transporters at the blood-brain barrier?

Article
Pardridge. 2005. NeuroRX 2: 3-14
Many factors affect brain penetration – logP

Figure 31.3.
Many factors affect brain penetration – logP

Graph showing active uptake and efflux transport

Renal Cell Carcinoma:
Tariquidar increases uptake of 99m TC-Sestamibi in metastasis of thigh

Images showing baseline and after Tarquidar
How to study P-gp using imaging?

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

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

Image of baseline and P-gp blockade
Brain uptake of [11C]dLop increases after p-gp inhibition and is trapped in monkey brain.

Graph
[11C]dLop: Distribution of radioactivity in healthy male x-ray image
What is this?

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

Image of brain scan
Tarquidar 6mg/kg increases [11c]dLop by 250%

Image of brain at baseline and with Tariquidar 6 mg/kg

Graph showing brain uptake and the amount of Tariquidar
Thesis Work of Pavitra Kannan:
PhD student at NIH/ Karolinska program

1. [11c]dLop is a selective substrate of p-gp.
Accumulation of [3H]dLop is lowest in ABCB1 (P-gp) expressing cells.

Graph

Kannan Drug Metab Disp 2010
Uptake of [11c]dLop is highest in brains of p-gp knockout mice.

Graph

Kannan Drug Metab Disp 2010
Summary

1. P-glycoprotein (p-gp): efflux transporter in many organs and can block entry of drugs in brain.

2. [11c]dLop is substrate selective for p-gp in mice, monkey, and man.

3. P-gp at blood-brain barrier acts rapidly and with high capacity to block entry of [11c]dLop.

4. Function of P-gp in humans can be measured with [11c]dLop at baseline and after inhibition.

5. Models are important for predicting and understanding the potential for a drug to cross the blood-brain barrier.
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