Drug Transporters

Objectives:
- List major drug transporters involved in drug disposition: P-gp, PepT1, and OATPB1
- Describe tissue distribution and representative substrates of major transporters
- Describe how inhibition of drug transporters alters drug disposition
- Describe how drug transporters affect drug efficacy and toxicity

Drug concentration does not equal the amount of drug actually in the tissues

P-Glycoprotein (P-gp)
- Major Efflux Transporter (Think of pumps pointing to direction of sites of drug elimination)
- Location: Intestines, Kidneys, Placenta, & Blood Brain Barrier
- Substrates: Anticancer drugs, Anti-HIV drugs, Immunosuppressants, Statins, & Opioids (Think of Role of Substrates on Transporter; What’s the Effect?)
- Inhibitors: Anti-HIV drugs, Anti-infective, & Some Cardiovascular Drugs (Think of Role of Inhibitor; Blocks the Transport out of Cells)
- Note: There is some overlap with substrates and inhibitors of P-gp; there is competitive inhibition happening
  - What is the effect if you have a substrate and inhibitor co-administered
- Blood-Brain Barrier: p-gp inhibitors increase the amount of drug in the brain
- In the liver, p-gp substrates are influenced by biliary excretion
- P-gp is a fetal protectant system in the placenta

Peptide Transporter 1(PEPT1)
- Peptide=Proteins (Look for Amino Acids or Proteins for Transporter)
- Peptide Uptake Transporter in Intestines
- Substrate: Dipeptide & Tripeptides, Beta-Lactams
- Can be used to increase oral absorption
  - Acyclovir vs. Valacyclovir (Valine allows transport into tissues unlike acyclovir)

Organic Anion Transporting Protein (OATP)
- Another Uptake Small Molecules Transporter (Look for smaller drug molecules versus BIG molecules)
- Location: All over the body (Blood-Brain Barrier, Hepatocytes, Small Intestines, Skeletal Muscle, Placenta, Kidneys)
- Statins=major substrate of OATP
- Blocking OATP pathway in liver can increase risk of myopathy and rhabdomyolysis (both side effects of statins)
- This is caused by OATP being blocked in the liver (decreasing statin liver concentration, increasing plasma concentration)
- You will have lower efficacy (drug not being taken up by target organ) & myopathy (muscles take up drug from plasma)
- OATP does have genetic polymorphs which can cause the above inhibition

Highlighted are the various drug transporters showing their directions to better understand their effects

References: