ADME_3_Drug Transporters

- A drug that is sufficiently lipophilic can easily enter the cell through the process of passive diffusion across the cell membrane. But polar molecules cannot undergo passive diffusion but instead are carried into the cell by carriers. That's why these carriers are known as drug transporters.

- **Drug transporters**: There are a large number of drug transporters that are known to us, but we can generally divide all of them into two families. The first family is collectively known as ATP Binding Transporter Cassettes or ABC transporters. As the name suggests, these transporters use ATP to actively transport polar molecules in and out of cells. The second family is known as the solute carriers or the SLC. The solute carriers differ from the ABC transporters in that they don’t use ATP. Instead, they use facilitated transport or ion coupled transport. The solute carriers can be further divided into two subtypes depending on whether they are specific for anion solutes or cation solutes. These subtypes are known as organic anion transporter proteins or OATP and organic cation transporters (OCT). Of course, within each family and then within each subtype, there are numerous different transporters but we'll just look at a couple of examples.

- **Drug Transporters & Drug Movement**: Drug transporters play an important role in moving drugs in and out of the major organs, including the GI tract, brain, liver, and kidneys. Refer to Figure 1. Due to the blood brain barrier, transporters regulate entry as well as exit or efflux of drugs from the brain. In the GI tract, some transporters serve to import drugs from the lumen into the enterocytes. Others export drug from the enterocytes back into the lumen. In the liver, there are transporters that import drugs from the circulation into the hepatocytes, while other transporters efflux drugs from the hepatocytes to bile. Similarly, the kidneys have transporters that serve to excrete drugs into the tubules.
• **P-Glycoprotein (PGP):** P-glycoprotein or PGP is the most widely studied transporter. It is also known as ABCB1 as well as MDR-1. MDR stands for multidrug resistance; PGP is linked to drug resistance because it plays a major role in efflux of drugs from the body. PGP is located in many major organs, including the GI tract, liver, brain, and kidneys, so its function has a significant impact on the ADME properties of a drug.

• **PGP & GI efflux:** For example, PGP plays a very important role in removing digoxin from the body by effluxing it into the GI tract. As you can see from Figure 2, the drug enters the enterocytes from the basal end. Once inside the enterocytes, digoxin is then rapidly exported out into the lumen by the PGP that is located within the apical surface of the cells. Once inside the lumen, digoxin would be removed along with fecal excretion. Without PGP digoxin levels would build up to dangerous level in blood. If another drug somehow interferes with this efflux, then that also has an impact on the plasma concentration of digoxin.
o **PGP in brain, liver, and kidneys:** Just like in the GI tract, PGP also causes efflux of drugs from hepatocytes in the liver so that the drugs can be eliminated via biliary excretion. In the kidneys, PGP effluxes drugs from the circulation and into urine. In the brain, PGP is an integral part of the blood brain barrier because it effluxes drugs back into the vasculature.

o **PGP & Drug interactions:** PGP effluxes many (but not all) drugs from the body. Therefore, without functional PGP, plasma concentrations of many of these drugs may rise to toxic levels. This can happen if a drug inhibits the function of PGP. For example, Clarithromycin inhibits PGP and can lead to increased plasma concentration of Digoxin, which is a major substrate of PGP.

o **PGP & Drug Resistance:** PGP has an important protective role in that it removes drugs and toxic chemicals from the body, but when it comes to cancer chemotherapy PGP actually presents a challenge. Most other drugs target specific receptors at the surface of the cells, but when it comes to cancer drugs, they actually have to not only enter the tumor cells but the intracellular concentration of these drugs have to be sufficiently high in order to destroy the tumor cells. The problem is that over time, tumor cells can develop resistance to a drug. One way in which they become resistant is that they start making PGP and expressing it in the cell membrane. This way, the cells start effluxing the drug so that high enough intracellular concentrations are not reached. Since PGP can act on many anticancer drugs, a tumor that was previously responding to chemotherapy becomes resistant to multiple drugs. In fact, this is why PGP is also known as MDR-1 for multidrug resistance.

- **OATP1B1 or SLCO1B1:** See Figure 3. OATP1B1 is a solute carrier that is selective for organic anions. Remember that PGP is an active transporter because it uses ATP.
These solute carriers don't use ATP but function by facilitated transport. There are many solute carriers that are involved in transport of drugs in and out of the liver, but OATP1B1 is among the more important ones from the standpoint of drug-drug interactions. This carrier is expressed on the basolateral membrane of the hepatocytes, which is right next to capillaries. Its function is to remove certain drugs from circulation and import them into the hepatocytes where these drugs can be inactivated by metabolic enzymes. For example, the cholesterol lowering drug Simvastatin is among the many drugs OATP1B1 imports into hepatocytes. When OATP1B1 function is compromised, then the plasma concentration of Simvastatin can increase to the point that even a normal dose can cause toxicity.

**Figure 3. OATP1B1.** This transporter removes drugs from the circulation and imports them into hepatocytes where they can be inactivated.