Rebecca Wilder
Toxicology
Spring 2015

MIDTERM

1. **Valproic Acid** (VPA) is a branched short-chain fatty acid derived from naturally occurring valeric acid. VPA is used in the treatment of epilepsy and seizures but also migraine, bipolar, mood, anxiety and psychiatric disorders. Recent work has explored its use as an adjuvant agent in cancer, HIV therapy, CLL and neurodegenerative disease because of its action as histone deacetylase (HDAC) inhibitor. VPA is available in oral, rectal and injectable dosage forms.

   The drug label carries a black box warning for life-threatening adverse drug reactions (ADR) including hepatoxocity, teratogenicity and pancreatitis. Although VPA hepatotoxicity may occur at any age, the risk of fatal hepatotoxicity is greatest in children less than two years of age receiving concurrent anticonvulsant therapy. Hyperammonemia is also a documented ADR of VPA.

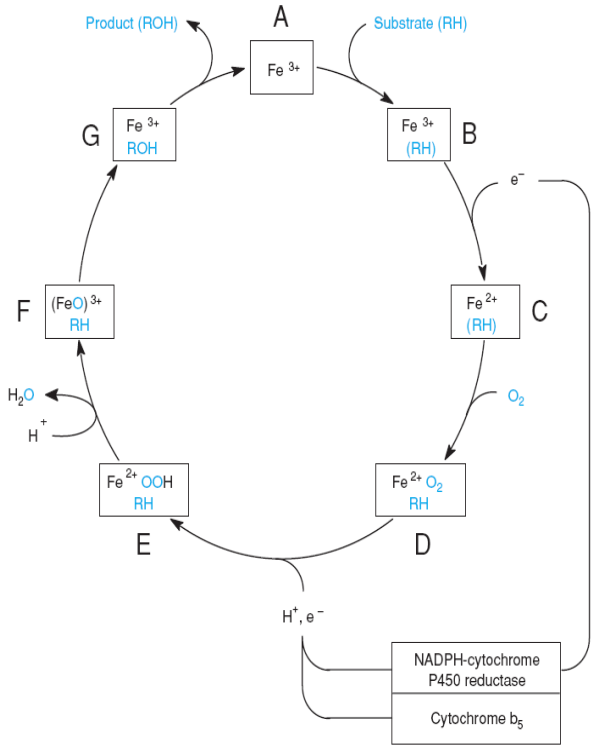
   There are 3 routes of VPA metabolism in humans: glucuronidation, beta oxidation in the mitochondria, and cytochrome P450 (CYP) mediated oxidation. Valproate-glucuronide is the major urinary metabolite of VPA (approximately 30-50%) VPA can be metabolized via endogenous pathways in the mitochondria.

   > "VPA crosses the membrane of liver mitochondria via the facilitation of carnitine. Inside the mitochondria, the first step of oxidation is the formation of valproyl-CoA (VPA-CoA) catalyzed by medium-chain acyl-CoA synthase (coded for by the genes ACSM1-5) [Article:21843514]. VPA-CoA is then converted to 2-propyl-valproyl-CoA (2-ene-VPA-CoA) through 2-methyl-branched chain acyl-CoA dehydrogenase (ACADSB)[Article:2112956]. Isovaleryl-CoA dehydrogenase (IVD) was also recently reported to catalyze this step [Article:21430231]. VPA-CoA also gets converted in to VPA-dephospho-CoA , though the exact phosphatase mediating this reaction has not been identified [Article:15483197]. 2-ene-VPA-CoA is further converted to 3-hydroxyl-valproyl-VPA (3-OH-VPA-CoA) by an enoyl-CoA hydratase, crotonase (ECSH1) and then 3-OH-VPA-CoA is metabolized to 3-keto-valproyl-CoA (3-oxo-VPA-CoA) through the action of 2-methyl-3-hydroxybutyryl-CoA dehydrogenase (HSD17B10)[Articles:1988037, 21843514]"

REFERENCES
Cytotoxic activity of valproic Acid on primary chronic lymphocytic leukemia cells. - PubMed - NCBI. (2015). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/25923087

Ghodke-Puranik Yogita, Thorn Caroline F, Lamba Jatinder K, Leeder J Steven, Song Wen, Birnbaum Angela K, Altman Russ B, Klein Teri E. "Valproic acid pathway: pharmacokinetics and pharmacodynamics" *Pharmacogenetics and genomics* (2013).

2. Over 100 therapeutic drugs are metabolized by CYP2C9, including drugs with a narrow therapeutic index such as warfarin and phenytoin and other routinely prescribed drugs such as acenocoumarol, tolbutamide, losartan, glipizide, and some nonsteroidal anti-inflammatory drugs. By contrast, the known extrahepatic CYP2C9 often metabolizes important endogenous compound such as arachidonic acid, 5-hydroxytryptamine, and linoleic acid.



Substrates are largely NSAIDS, and strong inhibitors include St. Johns wort and Valproic Acid

REFERENCES
CYP2C9 - Wikipedia, the free encyclopedia. (n.d.). Retrieved May 6, 2015, from http://en.wikipedia.org/wiki/CYP2C9

3. The article, Women and Prescription Drugs: The Gender Gap Tightens by Dr. David Sack, M.D. focuses on the history of addiction being a mans disease, but now women are caught up and surpassing them with the use of prescription drugs, but also with the revelation that drugs affect men and women differently.

"Today, prescription painkillers are a drug of choice among women, in part because women are more likely to suffer from chronic pain…Women are more often prescribed painkillers and for longer periods of time than men. In fact women are 50% more likely to leave their doctors office with a prescription even if they have the same condition."

"Drugs' negative effects strike women harder and faster than men. For example, alcohol does as much damage to womens's bodies in four years as it does to men's bodies in 14 years."

"…because of physiological differences such as women's slower metabolism and ratio of fat to water in the body. These differences cause women's bodies to hold onto drugs and alcohol longer…"

REFERENCES
Sack, M.D., D. (n.d.). Women and Prescription Drugs: The Gender Gap Tightens | David Sack, M.D. Retrieved from http://www.huffingtonpost.com/david-sack-md/prescription-drug-abuse_b_3756121.html