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Question #1: Describe pharmacokinetics and pharmacodynamics of (c) Valproic acid?

Definitions:
Pharmacodynamics is often summarized as the study of what a drug does to the body
Pharmacokinetics is the study of what the body does to a drug.
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. It is widely used in pediatric epilepsy because of its multiple mechanisms of action and acceptable safety profile [Article:10319910]. The dose requirements for VPA are highly variable that are age specific to the patient. [Article:10594867] Interactions with other drugs are common which is why therapeutic drug monitoring is commonly used. Life-threatening adverse drug reactions include hepatoxocity [Articles:21038416, 21544075], teratogenicity [Article:21521026] and pancreatitis [Article:15526953]. Children appear to be at increased risk for severe hepatotoxic reactions to VPA. The risk of fatal hepatotoxicity is highest (approximately 1:600) in children less than two years of age receiving concurrent anticonvulsant therapy. (Valproic Acid Pathway, Pharmacokinetics, 2015)

Pharmacokinetics
Valproic Acid binds to protein (87-95%) which means that it stays in the body longer and has a low clearance rate of 60 mL/hr/kg [Article:20146700]. VPA can be eliminated via three metabolic processes: glucuronidation, beta oxidation in the mitochondria (which are the major pathways accounting for 50% and 40% of dose respectively), and cytochrome P450 mediated oxidation [Articles:2112956, 18838507, 20089352]. VPA is a fatty acid which can be broken down via in the mitochondria. Breaking down VPA into its metabolites can be hepatotoxic. A protein metabolic cycle called carnitine facilitates and brings VPA across liver mitochondria membrane. (Valproic Acid Pathway, Pharmacokinetics, 2015)

The pathways inside the mitochondria are as follows: (Valproic Acid Pathway, Pharmacokinetics, 2015)

1. Oxidation: medium-chain acyl-CoA synthase catalyzes the formation of valproyl-CoA (VPA-CoA)
2. 2-methyl-branched chain acyl-CoA dehydrogenase converts VPA-CoA to 2-propyl-valproyl-CoA (2-ene-VPA-CoA) through (ACADSB)[Article:2112956]. Isovaleryl-CoA dehydrogenase (IVD) catalyzes 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].
3. 2-ene-VPA-CoA is further converted to 3-hydroxyl-valproyl-VPA (3-OH-VPA-CoA) by an enoyl-CoA hydratase and crotonase (ECSH1)
4. 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].

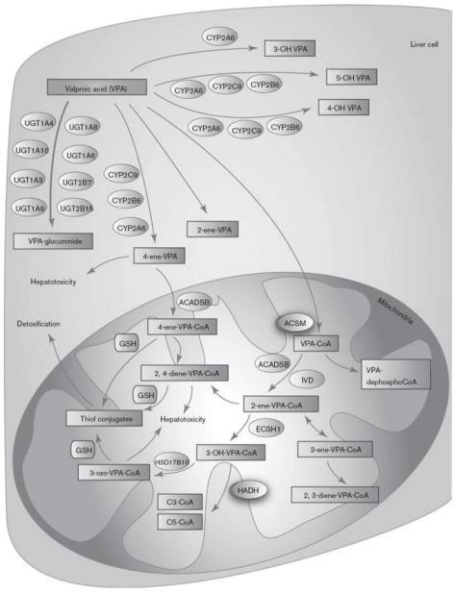
It is still not conclusive whether the beta-oxidation of VPA is complete in mitochondria. In CYP-mediated oxidation of VPA, CYP2C9 and CYP2A6 are the main enzymes. CYP2B6 has been shown to form metabolites in vitro but at a very small level. The key CYP-mediated branch of the VPA pathway is the generation of the metabolite 4-ene-VPA by CYP2C9, CYP2A6 and CYP2B6 [Articles:9353388, 16945988]. In addition these metabolizing enzymes also mediate the metabolism of VPA to the inactive 4-OH-VPA and 5-OH-VPA [Article:14597963]. CYP2A6 also contributes partially to the formation of 3-OH-VPA [Article:16945988]. Combination therapy of the DNA methyltransferase inhibitor 5-azacytidine (5-AZA) and VPA as treatment for myelodysplastic syndromes (MDS) demonstrated that carriers of the CYP2C19 variant, CYP2C19*2 required higher VPA doses to achieve the target therapeutic plasma concentration, indicating that CYP2C19 is also involved in the VPA pathway [Article:19638460]. (Valproic Acid Pathway, Pharmacokinetics, 2015)

VPA Elimination:
VPA is eliminated through urine as valproate-glucuronide which accounts for approximately 30-50%) [Article:18838507]. One study shows that "in vitro studies of human liver microsomes and purified recombinant proteins have reported glucuronidation of VPA by UGT1A3, UGT1A4, UGT1A6, UGT1A8, UGT1A9, UGT1A10, UGT2B7 and UGT2B15 [Articles:15761113, 18838507, 17687269." Other studies have disputed the role of UGT2B15, suggesting that VPA inhibits UGT2B15 but is not glucuronidated by it [Article:12732356]. UGT1A1 does not have activity against VPA in vitro [Articles:12732356, 18838507]. (Valproic Acid Pathway, Pharmacokinetics, 2015)

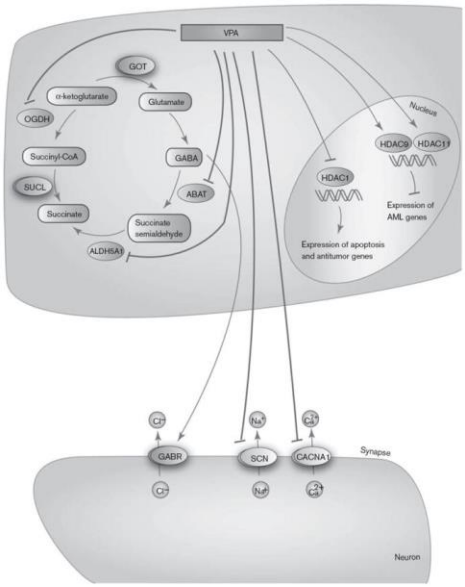
Pharmacokinetics
VPA and Seizures
VPA acts on γ amino butyric acid (GABA) levels in the brain, blocks voltage-gated ion channels, and also inhibits HDAC. These pathways can help decrease the number of convulsions a person experiences.
Antiepileptic drugs like VPA aim to control GABA pathways because impairment of GABAergic inhibitory activity can lead to convulsions. GABA is formed from α-ketoglutarate through the tricarboxylic acid cycle and metabolized to succinate semialdehyde by GABA transa-minase (*ABAT*) and then to succinate by succinate semialdehyde dehydrogenase (*ALDH5A1*). α-Ketoglutarate can also be converted to succinyl CoA through the action of α-ketoglutarate dehydrogenase (*OGDH*), shunting it away from the formation of GABA. Ex-vivo and in-vitro studies have shown that VPA inhibits *ABAT* and *ALDH5A1*, both of which are involved in the GABA degradation pathway. One in-vitro study also showed that *OGDH* was inhibited by high concentrations of VPA [24].
Besides increasing GABA levels, VPA may also have antiepileptic activity by reducing the high-frequency firing of neurons by blocking voltage-gated sodium, potassium, and calcium channels (including those coded for by *CACNA1C, CACNA1D, CACNA1N*, and *CACNA1F* and the *SCN* gene family) [24,25]. (Ghodke-Puranik, 2014 Apr)

VPA and Cancer
VPA was recently shown to inhibit HDAC1 as well as other HDACs that may increase the expression of genes involved in apoptosis and antitumor action. Therefore, VPA is now under

consideration to be a potential antitumor agent. It is being considered for other ways it can help cancer patients too. (Valproic Acid Pathway, Pharmacokinetics, 2015)



Graphic representation of the candidate genes involved in valproic acid (VPA) pharmacokinetics. A fully interactive version of this pathway is available online at PharmGKB at http://www.pharmgkb.org/pathway/PA165964265. CYP, cytochrome P450.

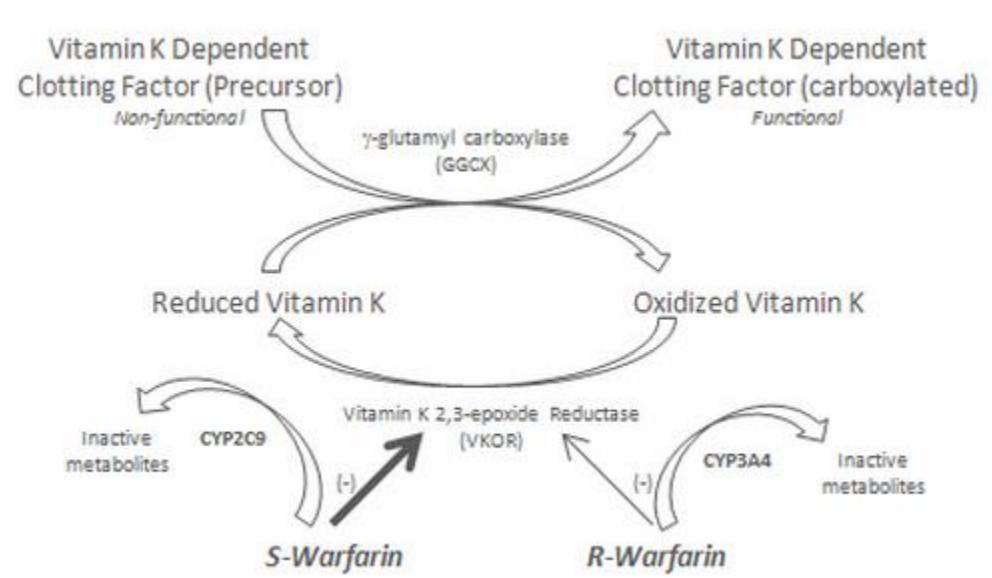


Graphic representation of the candidate genes involved in valproic acid (VPA) pharmacodynamics. A fully interactive version of this pathway is available online at PharmGKB at http://www.pharmgkb.org/pathway/PA165959313.

Question #2: (b) CyP2C9

A. Enzyme cytochrome P-2C9 is largely used to help oxidize xenobiotic and endogenous compounds. It metabolizes any drug that undergoes "Phase I metabolism." (Booven, 2010 Apr) CyP2C9 metabolizes substrates like NSAIDs. An article from PharmGKB says that this enzyme metabolizes the S-Isomer in warfarin, which is the anti-coagulative part of the drug.

B. The mechanism of catalysis: "The structure showed unanticipated interactions between CYP2C9 and warfarin, revealing a new binding pocket, suggesting that CYP2C9 may simultaneously accommodate multiple ligands during its biologic function [Article:12861225]. Structural analysis suggested that CYP2C9 may undergo an allosteric change when binding warfarin." (Gene: CYP2C9, 2015)
    a. Example: (How is warfarin (Coumadin, Jantoven) use influenced by genetic polymorphisms to CYP450 2C9?, 2014)



C. There are competitive inhibitors and noncompetitive inhibitors of CyPC9. Strong active inhibitors are antifungal drugs such as fluconazole, miconazole and antibacterial drugs such as sulfaphenazole and anticonvulsants like Valproic Acid (VPA). Noncompetitive inhibitors are nifedipine, phenethyl isothiocyanate and medroxyprogesterone acetate. (CYP2C9, 2013)

D. Gene and/or protein structure unknown.

E. No known enzyme kinematic parameters.

Question #3: **(a)**

Drug and blockers different in men v. women (Beer, 2013)

1. This study suggests that men and women metabolize steroids like DHEA-S and DHEA in response to insulin may be regulated differently.

2. Reducing circulating insulin with a Ca2+ channel blocker is associated with a rise in serum DHEA-S concentration in women and in men. This is not different between the two sexes.

3. A reduction of fasting serum insulin levels in men also showed a concurrent rise in serum DHEA and DHEA-S levels.

Works Cited

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