

1. Select one of the substances below: Provide as a complete a description of the toxico/pharmacokinetics and toxico/pharmacodynamics as possible. Support your description with at least two references, one of which must be from a published book or a journal article.

VALPORIC ACID (VPA): Valporic acid is a short chain fatty acid that is derived from the natural occurring substance valeric acid and is mostly used for the treatment of epilepsy and seizures. 87-95% of VPA is bound to protein which gives it a low clearance rate according to Leppik and Birnbaum (1).

There are three pathways of VPA metabolism that have been identified in humans which include glucuronidation, beta oxidation, and cytochrome P450 mediated oxidation. As previously stated, VPA is a fatty acid so it can be metabolized in the mitochondria which is illustrated wonderfully in figure 1 in the article by Ghodke-Puranik, Thorn, Lamda, Leeder, Song, Birnbaum, Altman and Klein (2).

VPA can act on the gamma amino butyric acid aka GABA levels in the brain, it can block voltage-gated ion channels, and can also act as an HDAC inhibitor which is a new exciting revelation according to Ghodke-Puranik and associates in there article on the pharmodynamics and pharmokinetics of VPA (2).

If the GABA inhibitory mechanism is impaired or malfunctioning this can lead to convulsions and seizures. This of course, is exactly why efforts to control this pathway through anti epileptic drugs has been such a priority. VPA may also have anti epileptic capabilities by blocking voltage-gated sodium, potassium, and calcium channels which would reduce the high frequency firing of neurons and thus decrease seizures which was highlighted in the review by Johannessen in 2003 (3). VPA is currently being looked into for its anti tumor properties as well with its ability to inhibitor of HDAC1.

References

1. Review: Epilepsy in the elderly.
Leppik IE, Birnbaum AK
Ann N Y Acad Sci. 2010 Jan; 1184(1):208-24.

PK: AD= M=
PD:
Ref:
2. Valproic acid pathway: pharmacokinetics and pharmacodynamics
Yogita Ghodke-Puranik, Caroline F. Thorn, Jatinder K. Lamba, J. Steven Leeder, Wen Song, Angela K. Birnbaum, Russ B. Altman and Teri E. Klein
3. Review: Valproate: past, present, and future.
Johannessen CU, Johannessen SI
CNS Drug Rev. 2003 Summer; 9(2):199-216.

2. Select one of the cytochrome P450 enzymes below in the (a) through (d) list, and describe it as thoroughly as possible in points (i) through (v) below. You should cite at least one reference to a peer-reviewed publication or to a monograph for the course. For any information you put in your response, ensure that it is sourced/referenced. Your response will be compared to the information in the reference

CYP1A1

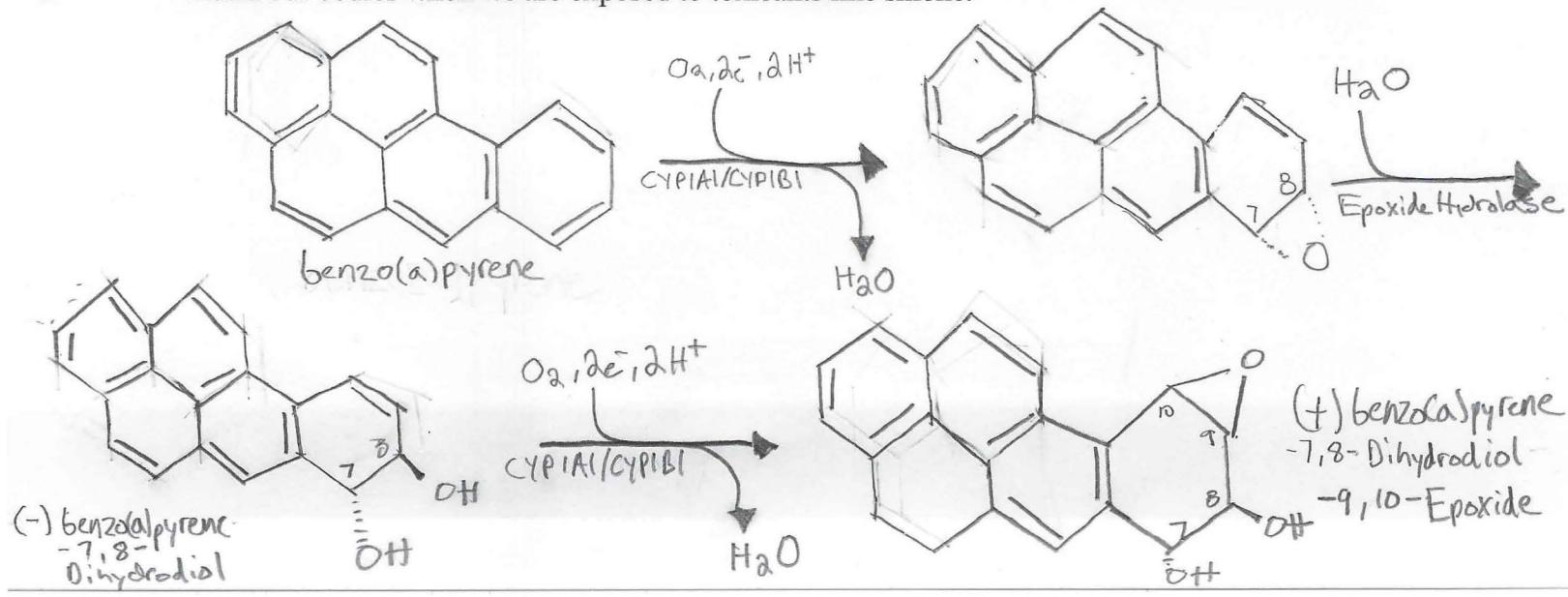
- i. Provide a description of the type of substrates it metabolizes and give an example of one substrate it is known to metabolize.

According to Walsh, Sklarz, and Scott CYP1A1 is an extrahepatic monooxygenase that is involved in the metabolism of drugs and endogenous substrates but it also is responsible for the activation of certain toxins and environmental pollutants. Some of these substrates include arachidonic acid, eicosapentoic acid, estradiol, and melatonin. CYP1A1 detoxifies polycyclic aromatic compounds. While CYP1A1 is responsible for the metabolism of these substrates it is more well known for being one of the most important enzymes in bioactivation of procarcinogens to generate reactive metabolites. CYP1A1 is also the primary cytochrome P450 enzyme that activates benzo(a)pyrene which is highlighted in my drawing below under section 2.

I found it very interesting that CYP1A1 is the main microsomal enzyme responsible for activation of polycyclic aromatic hydrocarbons which is what happens when you smoke, eat charbroiled meat, or are exposed to smog or exhaust. CYP1A1 has been discovered to play a significant role in this carcinogenic process.

- ii. Explain the mechanism of catalysis (you can even draw the steps)

According to the text, Cytochromes P450 Metabolic and Toxicological Aspects edited by Ioannides, CYP1A1 is an inducible enzyme which is upregulated by the aryl hydrocarbon receptor. In humans it can be induced by consuming charbroiled meat or vegetables or by smoking cigarettes or being exposed to too much car exhaust. Below is a drawing of how CYP1A1 is involved in the metabolism of benzo(a)pyrene which then yields the carcinogenic benzo(a)pyrene-7,9-dihydrodiol-9,10-epoxide. This is the same carcinogenic that is taking place within our bodies when we are exposed to toxicants like smoke.



- iii. Provide the names of any substances known to inhibit the cytochrome, if any
Dietary Flavanoids, fluoroquinolones, Ellipticine and macrolides are all inhibitory and oxidative stress can also down regulate CYP1A1.
- iv. If its gene and/or protein structure is known, describe the domains (functional parts or features) of the enzyme, and any molecular detail/features that are interesting or significant to the enzyme's function

Walsh, Scklarz, and Scott described the structure of CYP1A1 as a 2.6 degree alpha structure with the inhibitor alpha naphthoflavone (ANF). They go on to describe the binding of ANF at an enclosed active site, and these active sites have distinct features that may underlie the functional variability of these enzymes. They also note a 5 residue disruption of the F helix but I was not able to really understand what they were talking about here but it was deemed significant by Walsh and colleagues.

- v. Provide, if any, known enzyme kinetic parameters: turnover/catalysis rate, etc

I imagine if you continue to be exposed to toxic substances like cigarette smoke, smog, exhaust and charbroiled foods then the turnover rate would continually increase. On the other hand if you reduce your exposure to these toxins then you can greatly reduce your risk of developing cancer in the future. I do not believe I am fully grasping the enzymes effects or kinetic parameters but I did take away a good bit of information from this midterm that I can research further and apply in my practice.

References

1. Human Cytochrome P450 1A1 Structure and Utility in Understanding Drug and Xenobiotic Metabolism. Agnes A. Walsh, Grazyna D. Szklarz, and Emily E. Scott
First Published on March 18, 2013, doi: 10.1074/jbc.M113.452953
May 3, 2013 The Journal of Biological Chemistry, 288, 12932-12943.
2. Cytochromes P450 Metabolic and Toxicological Aspects, Edited by Costas Ioannides
- 3.

- a) Find at least one report/article that discusses the differences in how men and women respond to toxicants or drugs. Your search for an article may focus on one particular toxicant/drug or you may summarize an article that treats these differences in a broad survey. In any article you obtain, be sure to indicate at least three significant points, but list all of them if there are more.

Sex, Drugs, and Cognition: Effects of Marijuana
Beth M. Anderson, Ph.D., Matthew Rizzo, M.D., Robert I. Block, Ph.D., Godfrey D. Pearlson, M.D., and Daniel S. O'Leary, Ph.D.
Journal Psychoactive Drugs. 2010 dec;42(4):413-24

The aim of this study was to compare the effects of marijuana on cognition, specifically the differences in cognition between men and women after smoking marijuana. The authors talk

about the fact that there is knowledge that many drugs affect men and women differently, however there are few studies that look at effect of marijuana use on cognition in women. This is one of the reasons the authors chose this study, they wanted to examine the sex differences in the acute effects of marijuana on cognition in 35 males and 35 females who were occasional marijuana users.

Participants for this study were recruited by fliers and by word of mouth in the Iowa City area. I thought it was interesting that they excluded non marijuana users from the study for fear that it may be “the gateway drug,” even though I have seen no research substantiating this claim. The participants were asked to smoke marijuana cigarettes where they were instructed to inhale for 3 seconds, hold their breath for 5 seconds, and give 27 seconds between inhalations. The participants were told to continue this procedure until they finished the marijuana cigarette or until they reached an “uncomfortable” level of highness. This brings up one problem with this study. Not everyone consumed the same amount of marijuana due to the choice to stop the smoking session early if they felt too high. This is an interesting fact to keep in mind because one thing they did find linked to females over males, was the urge to stop the smoking session earlier which could have tainted there results. The study shows that 0% of the men requested to discontinue the active cigarette while 44.4% of the women chose to discontinue the cigarette. This is a big difference and I think the study needs to be conducted again with no option to discontinue use.

The marijuana cigarettes used in this study were provided by the national institute of drug abuse and were given in between subjects, with sex, randomized, double blinded, design. There were two types of cigarettes, one with no THC and one with 2.9% THC. I do like how they used a control group with no THC but I think 2.9% THC is too low and they should have used a THC content closer to 10%. The study had the patients smoke, wait 30 minutes and then perform a variety of tests which included visuospatial processing, trail making, time estimation, and cognitive flexibility which involved task switching. One important and interesting bit of information I found in this article was that there were no differences in heart rate, or cognitive test performance found in those that completed the marijuana cigarette versus those that did not complete it and there were also no sex differences in heart rate found at any time. One interesting fact reported in the article was the fact that women reported more sleepiness than men before cognitive testing but no differences were found at any other point. The final interesting piece I took away was on completion time of tasks. When you asked the control group how long it took them to complete the tasks they underestimated the time compared to the group that smoke the marijuana cigarette who overestimated the time it took for completion.

In conclusion the study found that marijuana did have an impact on selective attention, divided attention, cognitive flexibility, and time estimation. The study found no sex by drug interactions for cognitive testing, but, psychological response to the smoking session was remarkable in that the women wanted to discontinue use at such a greater rate than men. One opportunity for future testing on marijuanas effect on different sexes could be on cognitive flexibility since this study found women that smoked the marijuana cigarette had a slower reaction time to task switching.