Pathology 438 Midterm Examination due: by 1:00 PM, 6 May 2015
Spring 2015
NAME _____

The electronic responses to this examination are due at 1:00 PM on Wednesday, 6 May 2015. Submit them to shalloran@lifewest.edu.

You are not allowed to consult with classmates or any individuals *other than* the instructor as you research, prepare and compose your responses to the questions posed in this examination. You may use the information available from lecture content (slides) in MOODLE, the LCCW library, reference books and course text books, and on-line resources. Please proofread and organize your work and assemble the exam before submitting it.

Some answers require you to include a citation of the sources you consult to formulate your response. Format your citation according to MLA or APA standards. (If you wish, you can use the built-in Word feature that formats your references: under the References tab, use Insert Citation and fill in the fields as much as possible. Later you will use Bibliography->Insert Bibliography at the point of the cursor. You might learn how to use Section Break too in order to insert bibliographies under separate answers. I have put in section breaks in this document between questions.)

By working the examination and submitting it for grading you are agreeing to work independently of all other individuals and you are certifying that all the responses and answers to the examination questions are your own work.

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1. Select one of the substances below: (a) OR (b) OR (c). 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.
   a) doxorubicin
   b) clonidine
   c) valproic acid

(Ghodke-Puranik)

(Loscher)

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

i. Provide a description of the type of substrates it metabolizes and give an example of one substrate it is known to metabolize.
ii. Explain the mechanism of catalysis (you can even draw the steps)
iii. Provide the names of any substances known to inhibit the cytochrome, if any
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
v. Provide, if any, known enzyme kinetic parameters: turnover/catalysis rate, etc

(a) CYP3A4
(b) CYP2C9
(c) CYP1A1
(d) CYP2D6

(Horn JR PharmD)

(Various)

(Kumar V)

3. Select (a) or (b) or (c) to answer:

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.

b) Hepatocytes have several different efflux transporters in the plasma membrane that forms the canalicular wall. In the literature there are many original articles and reviews of these canalicular efflux transporters. Pick two of the transmembrane proteins, give their names, describe what substances are known to be transported by them (or class of substances). Explain what is known about their function and include any details of known mechanisms (the "molecular machinery and gears"), such as cellular substrates required to make them work. Summarize what is known about how they are regulated: what turns them on or off, or what increases or decreases their activity, including regulation of gene expression, or signaling pathways the modify protein activity and/or de novo synthesis.

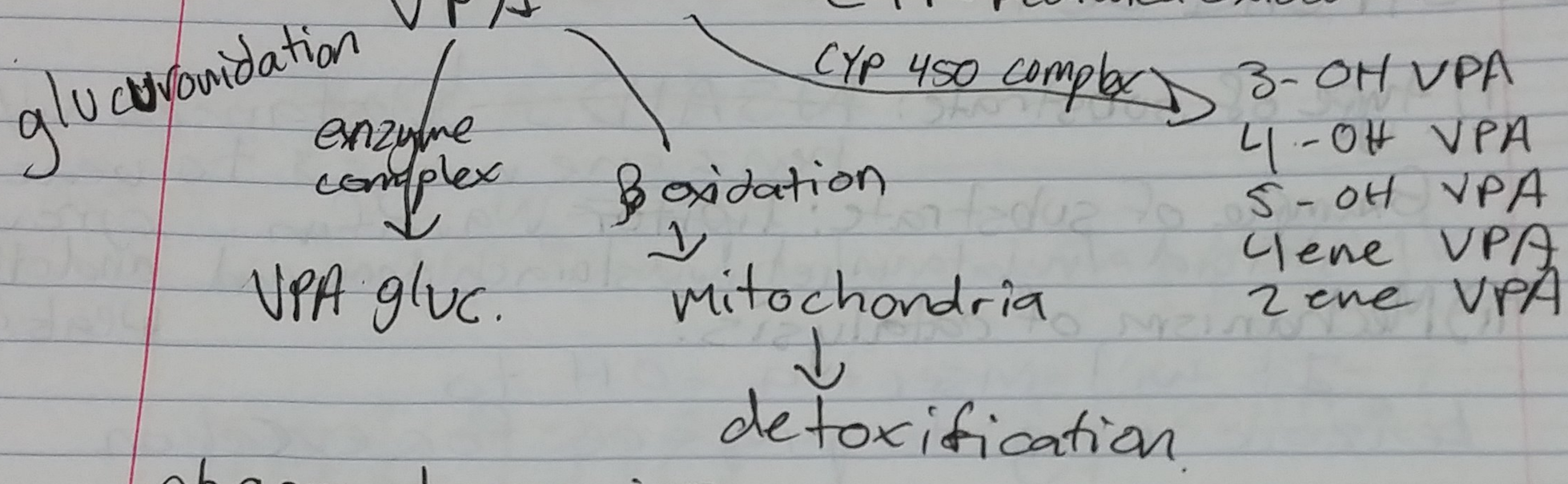
c) Search for a nephrotoxic substance (toxicant, poison or drug). Explain what part(s) of the nephron it disrupts (describe the mechanism of toxicity). Describe how normal kidney physiology would be disrupted for the parts of the nephron affected. Describe how the

nephrotoxic substance is detoxified (metabolism? elimination? both?) What doses or concentration levels are required to obtain the toxic effect?

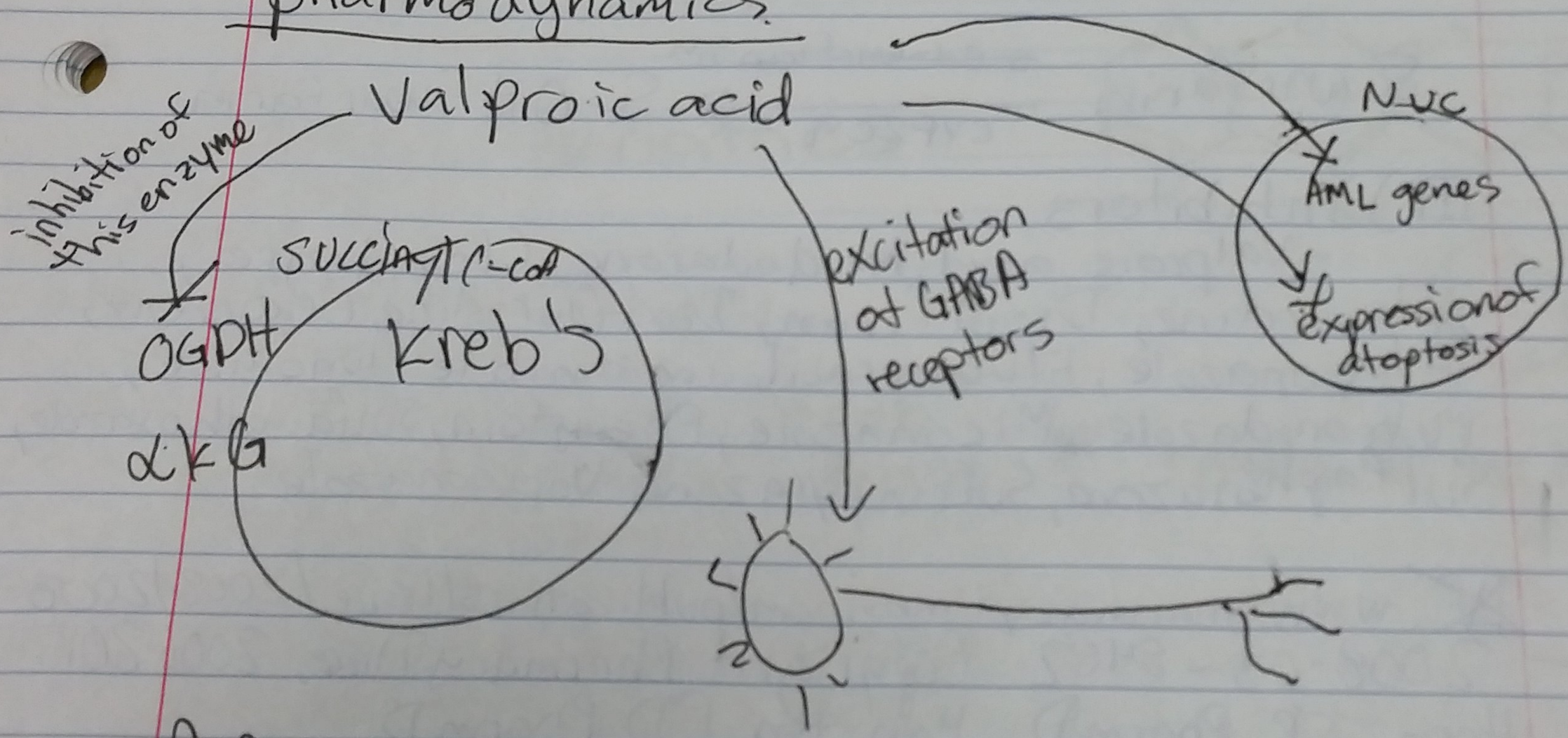
(http://jpet.aspectjournals.org/content/316/3/1195.full)

1) Valproic acid -

pharmokinetics



pharmodynamics



References:

① Valproic acid pathway: pharmacokinetics ; pharmacodynamics -Ghodke-Ryanik, Thorn CF, Lamba JK, Leeder JS ... Pharmacogenet Genomics 2013 Apr. 23(4):236-41

② Basic pharmacology of valproate: a review after 35 yr of clinical

use for the treatement of epilepsy. Lösher
● CNS Drugs 16 (10): 669-694 (2002)

2. CYP ~~3A4~~ 2C9

i) type of substrate: ~~NSAIDs~~ substances w/ benzene rings & toluene groups.
Example of substrate: ~~Tipifor~~ Warafin and other steroids/nebitarin/retinoids/arachidonic acid. weak acids.

ii) Mechanism of catalysis:
-It will insert a -OH to benzoic ring to prepare for excretion

S warfarin $\xrightarrow[\text{CYP2C9}]{\text{~~S-OH-warfarin~~}}$ S-OH-warfarin

III) Inhibitors
-Valproic acid, Amidodarone, Clopidogrel, Delavirdine, Disulfiram, Doxifluridine, Efavirenz, Fluconazole, Fluorouracil, imatinib, leflunomide, Metronidazole, Miconazole, Phenytoin, Sulfamethoxazole, Sulfaphenazone, Sulfinpyrazone, Voriconazole.

~~IV~~. www.pharmacytimes.com/publications/issue/2008/2008-03/2008-03-8462 Copyright Pharmacy Times 2006-2015
Horn JR PharmD, Hansten PD PharmD

IV. It's a series of α helices surrouding a heme group.

www.wikipedia.org/wiki/CYP2C9
It's a ~~pk~~ dilafftin induced enzyme so cocurrent use w a CYP2C9 inhibitor will cause toxicity.

V. The only study I found that evaluated Km for CYP2C9 was performed ~~to~~ 10 yrs ago. Though no confirmed rate was found because of variable, they did find stand alone CYP2C9 performed ~~my~~ sm much slower than with cofactors

8. http://dmd.aspetjournals.org/content/34/11/1903.full DMD Nov 2006 vol. 34 no. 11 1903-1908 Kumar V, Rock D, Warren C, Tracy TS, Wahlstrom J

3. Hydrocodone 131.2 M prescriptions yearly webmd.com/news/20110420/the-10-most-prescribed-drugs.

- Male rats are more sensitive to ~~opioid~~ morphinans
- Male rats appear to have less pain tolerance.
- This sensitivity is independant of estrogen cycle.
- Non-mophinan ~~opiods~~ sm anti nociceptors opiods, fentanyl and methadone did not have the same sex based variance.
- lipophilicity does not play a role in this.
- these results were only true in vivo (vs. in vitro studies).

http://jpet.aspetjournals.org/content/316/3/1195.fi