

Pharmacy 408
Principles of Drug Action and Therapeutics VIII

Study Guide and Questions -Chemistry of Non-Steroidal Anti-inflammatory drugs (NSAIDS) and Cytokines

The following study guide and questions are provided to help you study for my section on the Chemistry of Non-Steroidal Anti-Inflammatory Drugs (NSAID's), and to help you prepare for the exam. The answers for these study questions can be found in my lecture handouts (Lectures 1 and 2) and in additional material covered during the lectures e.g. the PowerPoint presentation and associated handout. In this way, you should be able to master this material. Please keep in mind that I will NOT ask you to draw structures, but you should be able to recognize the functional classes of the compounds, and should know the important features of the pharmacophores discussed during lecture and in your handouts. By no means will I be able to test you on all of the questions below...that would take way to much time. However, if you go through these questions it should help to make you more prepared for exam questions.

NSAIDS

1. Upon stimulation of a Mast Cell, what does the Mast Cell release that causes inflammation? We covered this in Lecture 2, but it is applicable to both lectures.
2. Draw the structure of arachidonic acid as well as the cyclic endoperoxide products (PGG₂ and PGH₂) of the cyclooxygenase and peroxidase reactions.
3. What enzyme(s) catalyze(s) the conversion of arachidonic acid to PGH₂? How many enzymes and reactions are involved, and how many molecules of oxygen are required?
4. What is the site (i.e. enzyme activity) of action of NSAID's?
5. What are the chemical classifications of the NSAID's?
6. What drug(s) discussed in class inhibit cyclooxygenase reversibly and irreversibly?
7. Draw the complete mechanism of action of acetylsalicylate? Draw the structure of acetylsalicylate and the products of its mechanism of action. What active-site residue, i.e. amino acid, of cyclooxygenase does acetylsalicylate act upon?
8. Draw the base (building block) structure for the Salicylate Derivatives. What functional portion of the salicylate derivatives are responsible for their anti-inflammatory action? Why does salicylamide not have anti-inflammatory action?
9. Draw the base structure of the Para-amino phenol derivatives. Draw the structure of acetaminophen.
10. Why does acetaminophen have weak anti-inflammatory action? Do you think it should even be classified as an NSAID's?
11. Why is Cox-3 believed to be the enzyme target for Acetaminophen Action? What are the four observations that the studies report to support the Cox-3 hypothesis?
12. Draw the basic structure of an arylalkanoic acid (e.g indole and indene acetic acids, heteroaryl acetic acids and propionic acids). Show where the carboxylic

acid is located. Show where the chiral center is located (i.e where the active S(+) form is located). Remember, when this position is R(-) it is much less active as an inhibitor. How many carbons can you have for good activity? When this carbon has an R-group attached (i.e. a 2-methyl) what are these compounds classified as?

13. Draw the structure for indomethacin. What NSAID's classification is it?
14. Draw the structure for diclofenac. What NSAID's classification is it?
15. Draw the structure for ibuprofen. What NSAID's classification is it? Circle the propionic group and the portion of the group that designates it a "profen". Is there chirality within the propionic group? Does chirality change its activity?
16. Draw the structure of piroxicam. What NSAID's classification is it? Circle the portion of the molecule that places piroxicam in this class.
17. Explain the structural differences between Cox-1 and Cox-2 as well as their differences in origin. This involves knowing the amino acids in the active site that are different, knowing the differences in the primary amino acid sequence, and knowing the differences in the size of the active site pocket. This is important for understanding how drugs are designed to target Cox-2 and not Cox-1.
18. Explain the current concept of the Cox-2 to Cox-1 ratio and Cox-2 selectivity. What advantage is there to Cox-2 selective drugs? What disadvantage is there to Cox-2 selective drugs?
19. Explain the cardiovascular effects of Cox-2 inhibitors and why it is important to maintain a dynamic balance between PGI₂ production in vascular endothelial cells and TxA₂ production in platelets.
20. Explain the similarity between the pharmacophore model based on indomethacin, to that of the pharmacophore model of the Coxibs.

CYTOKINES

1. Considering the progression of rheumatoid arthritis (RA), what is the relationship between Inflammation, Disability and Radiographs with the duration of the Disease?
2. What is a cytokine and where do they come from?
3. What are the major, "PRO"-inflammatory cytokines discussed in class?
4. What are the major, "ANTI"-inflammatory cytokines discussed in class?
5. What is the cytokine hierarchy?
6. The two "key" inflammatory cytokines involved in RA discussed in class are TNF α and IL-1. What are the protein properties, where are they produced, and what do they do?
7. How do TNF α and IL-1 lead to joint damage in RA patients?
8. What does TNF α function in a cell? How is TNF α produced? What is the role of TNF α converting enzyme (TACE)? How many TNF α receptors are there? Upon binding of TNF α to each of the receptors, what signal transduction mechanisms are stimulated or repressed? (You need to know thoroughly how TNF α works and why its inhibition is important).
9. What are the possible, general strategies for inhibition of cytokine action?
10. What are the current strategies for inhibition of cytokine action via drugs?

11. What are the four major protein-based drugs discussed in class? How are these proteins produced? Are these proteins human derived, mouse derived, or chimeras?
12. What are the specific mechanisms-of-action of each of the major protein drugs? How are they similar or different in the way they inhibit cytokine action?
13. Why is it important to treat RA patients early and aggressively with drugs that inhibit cytokine action? How would these patients benefit from early treatment versus starting therapy later, after RA has set in?
14. What are the small molecule approaches to Anti-TNF α Therapy?
15. What potential advantages could a small molecule TACE inhibitor such as BMS-561392 have for patients? Think of dosing, side-effects and the economics associated with such treatment. What impact could a small molecule drug have on beginning early treatment for RA?
16. What is Abatacept (Orencia) and how does it work?
17. What new class of biological drugs does Abatacept establish?