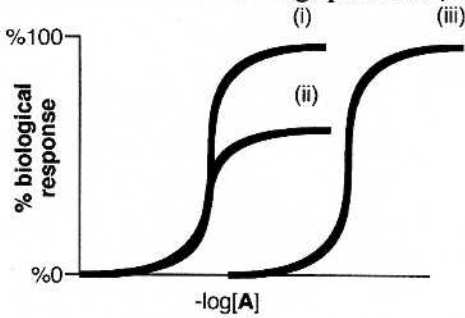


1) To answer the following questions, consider the dose-response curves shown below. (8 points)



(i) Agonist A alone. (ii) Agonist A in the presence of a fixed concentration of compound B. (iii) Agonist A in the presence of a fixed concentration of compound C.

8

a) With respect to agonist A, how would you characterize the action of compound B?

Non-competitive ANTAGONIST (4)

b) With respect to agonist A, how would you characterize the action of compound C?

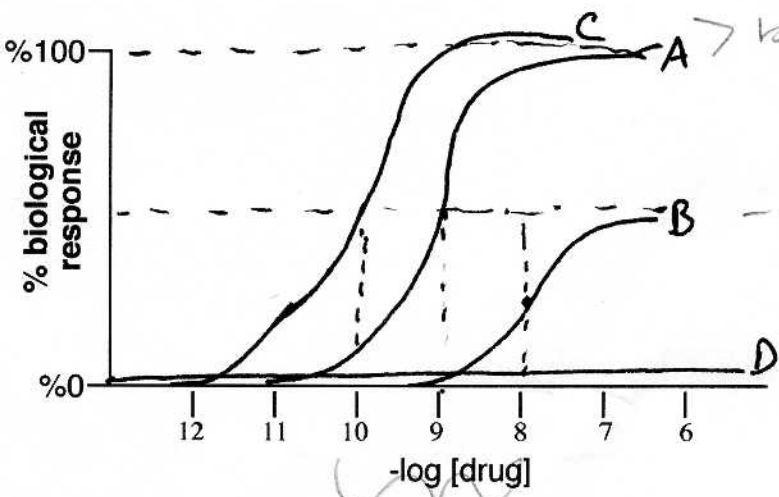
Competitive ANTAGONIST (4)

1/2 credit for antagonists

2) In the space provided, draw dose-response curves (on the same plot) for the following four conditions. (12 points)

- A) An endogenous agonist with an $EC_{50} = 10^{-9}$ (100% activity)
- B) A partial agonist with $1/10^{\text{th}}$ the affinity and $1/2$ the intrinsic activity of the endogenous agonist
- C) An agonist with the same intrinsic activity as the endogenous agonist but with an affinity 10 times greater than that of the endogenous agonist.
- D) an antagonist (alone) of the endogenous agonist

12



If curves are backwards, but all correct 9/12

both up to 100% 1/3 if it doesn't

-50% \Rightarrow 1/3 H 17 is not

3 \rightarrow not flat = 0 of flat, but not zero = 2/3

one point off if not netten

20

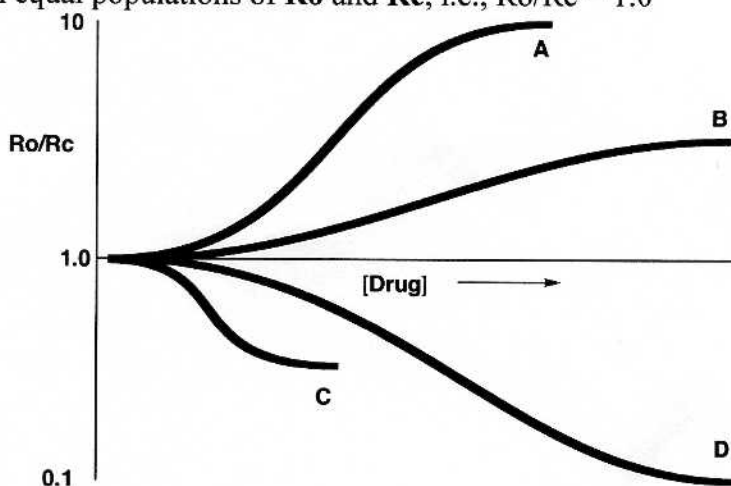
- 3) Assume that the eudismic ratio for a chiral drug is 1 at receptor X and 1000 at receptor Y. Provide 2 explanations that could account for the difference in the selectivity of receptors X and Y.

(8 points)

1) The chiral center is not involved in the binding interactions in receptor X but is in Y. (4)

2) Receptor X involves only 2 (less than 3) binding interactions with respect to the chiral center whereas receptor Y involves at least 3. (4)

- 4) Suppose there are two conformations of a certain neurological receptor that are responsible for signaling your brain whether or not your kidneys are full; i.e., whether or not you need to visit the restroom. Let's call the open form of the receptor **R_o** (in this conformation, it signals your brain to find a restroom quickly because it implies that your kidneys are full. **R_c** is the closed conformation of the receptor; i.e., no signal sent to brain. The normal resting state of the receptor when the kidneys are not full is **R_c**. Now let's say that you suffer from a certain disorder in which the ligand for the receptor is overproduced. When this ligand binds to the receptor, it induces a conformational change promoting the open form of the receptor (**R_o**). As a result, you feel the need to find a restroom all the time. Working with the isolated receptor, you experimented with various concentrations of the endogenous endocrine ligand (**A**) and several drugs (**B, C, D**) as possible treatments for this disorder, which are represented graphically below. In each case, a fixed amount of endogenous ligand was initially added to the assay to cause the receptor to be in equal populations of **R_o** and **R_c**; i.e., $R_o/R_c = 1.0$

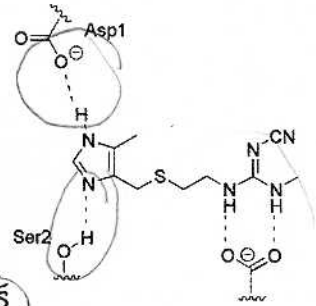


- i) Which drug is most effective at lowest concentration? C 4
- ii) Which drug appears to be a partial agonist of the endogenous ligand? B 4
- iii) Assuming there are not untoward side effects at high concentration, which drug appears to be the most effective? D 4

(12 points)

9) Below is shown a hypothetical binding model for cimetidine to H₂, a known histamine receptor. (20 points)

Binding Model of Cimetidine to H₂



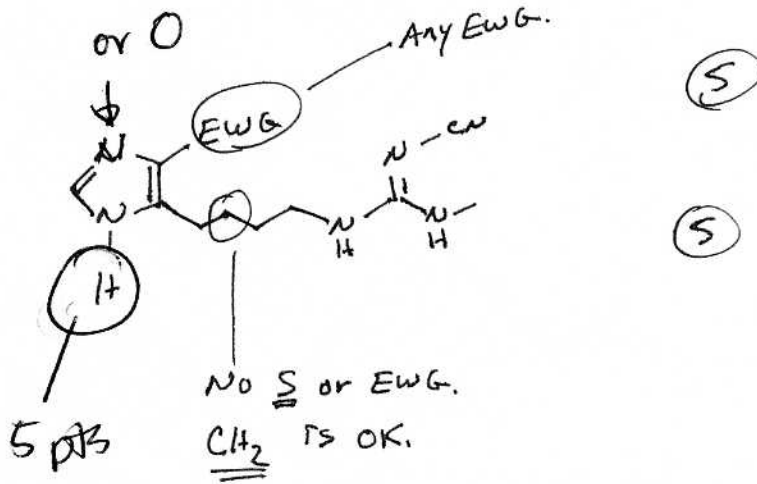
A) Recently, a new histamine receptor, H₆, was found. When **cimetidine** is used as an antagonist for H₆ it was found to be 20-fold **less** potent. Inspection of the amino acid sequence of H₆ revealed that Asp1 had been mutated into a serine and Ser2 had been mutated into an aspartate. Given this information, rationalize this receptor's insensitivity to **cimetidine**.

10 pts

There is a mismatch in the H-Bonding between cimetidine and the receptor with respect to the imidazole ring.

B) Suggest a new compound based on **cimetidine** that might restore antagonism against H₆. Include a rationale for the structure of your new compound.

10 pts



5) In general, the neurotransmitter systems we examined had a number of similarities, especially how drugs (agonists or antagonists) interfered with these systems. Which aspect of the cholinergic (acetylcholine) system differs from the other systems we studied (i.e. adrenergic, histaminergic, dopaminergic)? ³

(5 points) ACh is destroyed after its interactions with the target receptor and is NOT Recycled through a reuptake mechanism. ₂

6) If a disease state involved *decreased* concentrations of a neurotransmitter (other than acetylcholine), what pharmacological methods would be potentially effective?

(5 points) Inhibit metabolism (catabolism) ^{+ 2 for a second}
 Inhibit reuptake ^{+ 3 for 1}
 Give FALSE neurotransmitters (agonists)

7) If a disease state involved *increased* concentrations of a neurotransmitter (other than acetylcholine), what pharmacological methods would be potentially effective?

(5 points) Give ANTAGONIST ^{3 for 1}
 Give FALSE neurotransmitters (partial agonists) ^{+ 2 for a second}
 Block fusion of ^{Storage} vesicles to pre-synaptic cell-membrane.

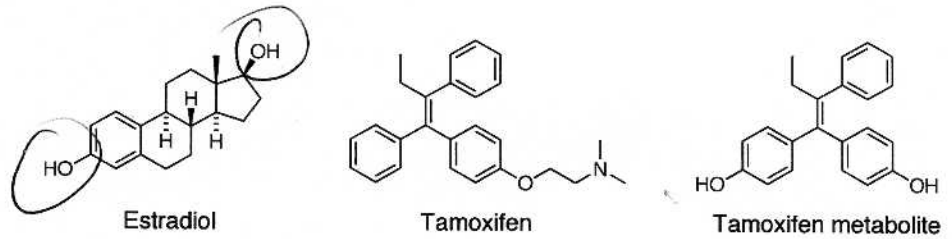
8) Neurotransmitters and steroid hormones both interact with specific receptors. How do hormones such as estrogen differ in their mode of action from neurotransmitters?

(5 points) ^{intracellular - transported to nucleus}

Hormones	Neurotransmitters
* Cytosolic Receptors	* Receptors on cell surface (GPCRs)
* Cause protein transcription	Do not directly cause protein transcription
Receptor/complex transported to nucleus.	

Hormone → cellular nucleus ^{3 for 1}
 → intracellular receptor ^{2 for a second}
 in cell → DNA → protein transcription →
 • regulate protein transcription

- 10) Tamoxifen is an antagonist of the estrogen receptor while its metabolite is an agonist. Briefly provide a rationale for this observation.
(4 points)



4) The metabolite is capable of the same H-bonding interactions as Estradiol through the 2-OH groups.

- 11) Dr. Gerber lectured on what topic? B
A) GCPR **B) GPCR** C) CPR-G D) PCR-G
(4 points)

- 12) Despite the variety of G-protein coupled receptors that are specific for various neurotransmitters, what major structural feature do these proteins share?
(4 points) 7 transmembrane domains.

- 13) How many subunits do G-proteins contain?
(4 points) 3

- 14) What is the major difference between the action of the α_s -subunit of the G_s -protein from the action of α_i -subunit of the G_i -protein? What secondary chemical messenger is regulated by these two different proteins?
(4 points)

- 4)
- ① α_s stimulates adenylate cyclase
 - ① α_i inhibits adenylate cyclase
 - ② cAMP is regulated by these