ADRENERGIC PROBLEM SET 7 KEY

1. The role of the amino moiety of the aryloxypropanolamines in beta-receptor binding:
Which compound below has the highest beta-receptor affinity?

Answer: Compound B. A is a primary amine and would have reduced affinity due to the absence of N-alkyl functionality. Compound C is inactive because the nitrogen is part of an amide group and therefore is non-basic and not-ionized at physiologic pH: a requirement for beta-receptor binding!

2. The role of chirality and the side chain hydroxyl group: Which compound below has the highest beta-receptor affinity?

Answer: Compound B: Compounds A and B both possess the basic aryloxypropanolamine structure for beta-receptor affinity, including a beta-OH group on a chiral carbon. In compound A the stereochemical orientation of this group is "R", while it is in the proper "S" orientation in Compound B. Compound C does not possess a beta-OH group, so it would not have optimal receptor affinity.

3. The role heteroaromatic aryl groups in activity: Which compound below has the highest beta-receptor affinity?

Answer: Compound C: As noted on page 51 of our notes, heteroaromatic aryloxypropanolamines tend to be "more potent" because they have higher affinity for some beta-receptors. It appears that the "heteroatoms" present in these systems may facilitate binding by direct interactions, or by altering the electronic character of the aromatic ring so that it binds with higher affinity. Only Compound C has a heterocyclic aromatic ring of the three compounds above.
4. The role of the aryl group in intrinsic sympathomimetic activity (ISA): Which compound below is mostly likely to have ISA?

Answer: All of these compounds are "regioisomers" - they have the same functionality, but different bonding positions, in this case the amide group off the aromatic ring is located at the 4- (A), 3- (B) and 2- (C) positions. Compound C would be most likely to have ISA since "ortho" (2) substitution is most commonly associated with this pharmacologic property.

5. The role of the aryl group in beta-1 receptor selectivity: Which compound below has the highest beta-1 receptor selectivity?

Answer: Again, all of these compounds are "regioisomers" - they have the same functional groups, but different bonding positions. In this case the amide group off the aromatic ring is located at different positions in the three compounds; at the 4- (A), 3- (B) and 2- (C) positions. Compound A would be most likely display the highest degree of beta-1 receptor selectivity since aryloxypropanolamines containing 4-substituents with a polar moiety bind with greater affinity to these receptors.
6. Beta-blocker structure and lipophilicity: Rank the following compounds in terms of lipophilicity (high, intermediate and low):

INTERMEDIATE   HIGH (Least polar)   LOW (Most polar)

7. For the compounds in questions 6. above, answer the following question:

a. Which would distribute to the CNS most readily? **B: Most Lipophilic!**
b. Which would undergo the highest degree of 1st pass metabolism? **B: Least polar/"flat"**
c. Which would be most highly bound to plasma proteins? **B: Most Lipophilic!**
d. Which would be beta-1 receptor selective? **None: Non has a "para"-polar group!**
e. Which may undergo cytochrome-mediated OND? **All have same amino group**
f. Which may undergo aromatic hydroxylation by CYP P450? **All ("reactive" para**
g. Which may undergo metabolism by hydrolysis? **None: No esters or amides!**
h. Which would be absorbed most efficiently from the GI tract? **B: Most Lipophilic!**

8. Analyze the structures of the compounds shown below and circle the appropriate response or responses. There may be more than one correct answer, or no correct answer (“None”):

a. Which compounds are chiral? **Answer: A, B and C.** All of the aryloxypropanolamine beta-blockers have a chiral secondary alcohol in the side chain, so they can exist as two enantiomeric forms. Only the S-enantiomer possesses optimal affinity for beta-receptors. (see page 51)

b. Which compounds have intrinsic sympathomimetic activity? **Answer: B and C.** There is not always a clear-cut relationship between structure and properties such as these, but generally those aryloxypropanolamines with an "ortho" substituent display some degree of ISA, although it is very low for propranolol (C) (see page 51).
c. Which compound has the greatest beta-1 receptor selectivity? **Answer:** A. Aryloxypropanolamines with 4-alkyl substituents with a polar functional group typically show the highest selectivity for beta-1 versus beta-2 receptors as antagonists (see notes on page 51, etc.)

d. Which compound is most lipophilic? **Answer:** C. The "aryl" portion of this beta blocker is composed entirely of non-polar C and H functionality; there are no electronegative atoms or dipolar groups on the aryl portion, thus its polarity is low, or lipophilicity is relatively high.

e. Which compounds are metabolized by aromatic hydroxylation? **Answer:** B and C. Both of these compounds have an aryl ring with an "open" (unsubstituted) 4-position. As discussed in Adrenergic Problem Set 3 in more detail, this position is electron rich ("para" to oxygen with a +R electronic effect), and sterically accessible. Thus it is a prime substrate for cytochrome oxidation!

f. Which compound is most extensively absorbed from the GI tract? **Answer:** C. It is the most lipophilic compound as discussed in D. above and thus would be most efficiently absorbed. Remember, these agents are being absorbed by passive diffusion in the small intestine, so lipophilicity is a major determinant of efficiency for this process.

g. Which compounds are capable of functioning as beta-2 antagonists? **Answer:** A, B and C. All beta-blockers are capable of functioning as antagonists at beta-2-receptors. Don't confuse this with selectivity! The beta-1 selective antagonists have relatively higher affinity for beta-1 versus beta-2 receptors. But all beta-blockers can block beta-1 and beta-2 receptors!

h. Which compounds may be metabolized by cytochrome OND? **Answer:** A, B and C. All three compounds contain an isopropylamino substituent which may be cleaved by metabolic oxidation. This process can occur by several pathways as discussed in more detail in Adrenergic Problem Set 3.

i. Which compound would distribute most readily to the CNS? **Answer:** C. Again this is the most lipophilic of the three compounds above and therefore most likely to partition across the BBB (a "passive process" for these drugs) and into the CNS.

j. Which compound is most polar? **Answer:** A. Compound A contains a primary amide group with a C=O dipole and N-H dipoles, and thus is relatively polar. Also, the non-polar portion of the "aryl" group of compound A is "smaller" than that of compounds B or C.

k. Which compound has the highest oral bioavailability? **Answer:** Probably B. This is a tough one, but analysis of structures would suggest compound B. Compound C (propranolol) contains a planar, large (naphthyl) aromatic aryl group. This
group enhances absorption (see f. above), but also is a good substrate for oxidative metabolic enzymes. Thus while compound C may be well absorbed, it is extensively metabolized by hepatic (and other) enzymes during first pass", and this reduces oral bioavailability. Compound A is one of the more polar (primary amide) beta-blockers and thus is not absorbed as efficiently as compound C. Because of its polarity and position of the polar group (4-position), compound A is not as extensively metabolized as compound C, but absorption limits bioavailability in this case. Compound B has "intermediate" polarity due to the presence of a secondary amide in the additional ring structure its aryl portion. Thus this compound will be fairly well absorbed, and not extensively metabolized. The combination of good absorption (altho' lower than compound C) and low metabolism (although higher than compound A) results in higher availability for compound B versus A or C.

1. Which compound is most highly bound by plasma proteins? Answer: C. Again this is the most lipophilic of the three compounds above and therefore most likely to have higher binding affinity for some proteins, such as plasma proteins. The non-polar aryl ring in Compound C is more efficiently bound on the surfaces of plasma proteins by van der Waals interactions than the more polar aryl potions of compounds A or B.

m. Which compound may be safest in patients with respiratory disease? Answer: A. As noted in question c. above, aryloxypropanolamines with polar 4-substituents typically show the highest selectivity for beta-1 versus beta-2 receptors as antagonists (see notes). Thus these compounds display lower binding for beta-2 receptors in respiratory tissue and are less likely to block them and complicating asthma.

9. Draw the metabolites formed by cytochrome-mediated benzylic oxidation of metoprolol. Why is the half-life of metoprolol longer in “poor metabolizers”? Also, explain why even though Metoprolol is relatively lipophilic, is displays relatively low oral bioavailability (40-50%).

Answer: As shown in the figure above, metoprolol differs from many other beta-blockers in that it is a "ether-aryloxypropanolamine, containing a sterically unhindered benzylic carbon (carbon adjacent to an aromatic ring). Because they are "activated" through their position relative to the aromatic ring, benzylic carbons in
drug molecules are frequently oxidized to the corresponding alcohols, as shown above. Furthermore, this oxidation process generates a chiral carbon at the site of reaction, so two "enantiomeric" alcohols are possible. In the case of metoprolol, these alcohol products are considerably less potent than the parent drug as beta-blockers.

In "extensive metabolizers" (EMs) there is more efficient (rapid) metabolism of metoprolol by the pathway shown above than is observed in so-called "poor metabolizers" (PMs). Thus a greater fraction of the initial dose is destroyed in EMs than PMs by first pass metabolism. This results in lowered oral bioavailability. Also, "continued" (secondary) metabolism of metoprolol to these less active metabolites occurs more extensively in EMs as the drug cycles and recycles through the liver (and other tissues). Hence, metoprolol has a shorter half-life in slower metabolizers (PMs).

**Additional Question:** Why do the other "ether" aryloxypropanolamine beta-blockers, betaxolol and bisoprolol, have higher oral bioavailabilities than metoprolol?

10. Explain why even though Acebutolol has a half-life of 3-4 hours, its therapeutic effects may persist for more than 10 hours. Be sure to use structures in your answer!

**Answer:** The situation with acebutolol is analogous to that observed with metoprolol in question 4. Above, but the outcome is different! Acebutolol is an "aromatic amide" (anilide) and thus is hydrolyzed more readily (by amidases) than 'typical amides (see Amide Tutorial if you do not know why). The hydrolysis product formed (an "aniline intermediate") is efficiently conjugated by acetylation using an acetylase enzyme and the cofactor acetyl-coenzyme A. The resultant acetamide conjugate, known as diacebutolol, is an active beta-blocker (essentially as active as the parent drug), and is metabolized and cleared more slowly (has a longer half-life up to 10 hours) than the parent drug! Thus while acebutolol itself has a relatively short half-life, it's active metabolite persists in the biologic environment and is capable of producing beta-blockade. This phenomenon illustrates two important points to keep in mind about drug metabolism and drug activity:

- First, to appreciate the role of drug metabolism on pharmacologic or therapeutic activity, it is necessary to understand the structure and activity of the metabolite! If metabolism results in the formation of a product with lower or no
activity, then the more efficiently a drug is metabolized, the shorter the duration of therapeutic effect. However, if the metabolite formed retains activity and is not efficiently cleared by some other means (i.e. elimination by the kidneys), then metabolism may NOT significantly reduce the duration of therapeutic effect. This is illustrated further in the benzodiazepine chapter!!!

• Second: Half-life of a drug is not necessarily related to duration of therapeutic effect. The "actual" plasma half-life of acebutolol is 3-4 hours, but its effects persist far beyond this point (due to the formation of an active, persistent metabolite). Thus if one dosed this drug based solely on half-life, they may be making a serious error!