ADRENERGIC RECEPTOR ANTAGONISTS:
ALPHA RECEPTOR BLOCKERS

General PC/MC: Understand the term "antagonist" and how an antagonist is similar to an agonist, and how an antagonist differs from an agonist? (Affinity and intrinsic activity)

MC Objective: How has the structure of NE been modified to yield alpha-receptor antagonists:

- NOTE: Hundreds of compounds have been developed which possess alpha-receptor antagonist activity. The minimal “pharmacophore” for alpha antagonist activity consists of at least one aromatic ring linked to a tertiary amine by a 2 to 4 atom chain. The atoms of the chain may consist of carbon and/or heteroatoms:

![Diagram of pharmacophore](image)

- Historically the ergot alkaloids were among the first alpha-receptor antagonists discovered. Identify the active “pharmacophore” in these compounds. What are the primary uses for the ergots today?
• NOTE: A number of drugs designed to express their therapeutic actions at “other” neurotransmitter receptor targets also function as alpha-receptor antagonists. For example, many antimuscarinic, antihistaminic, phenothiazine antipsychotic and tricyclic antidepressant drugs are ALSO capable of antagonizing the actions of NE at alpha-1 receptors. Note the alpha-antagonist pharmacophore present in these compounds!

General PC/MC Objective: Drugs capable of antagonizing the action of an agonist at its receptor may do so by “reversible” or “irreversible” mechanisms:

- Reversible and irreversible antagonists are similar in their actions in that both have the structures necessary to be recognized by and initially reversibly interact with the receptor.
- Irreversible antagonists differ from reversible antagonists in that they contain a functional group capable of chemically reacting with a nucleophile present on the receptor and thereby form a covalent bond, providing prolonged (non-competitive) inhibition.
- Thus, in addition to the basic pharmacophore required for receptor interaction, an irreversible antagonist must have an electrophilic group capable of reacting with a nucleophile present on the receptor. Also, the electrophilic group of the irreversible antagonist must be positioned properly to react with the receptor nucleophile!

Reversible Antagonist \( \rightleftharpoons \) Receptor

Irreversible Antagonist \( \rightleftharpoons \) Receptor  \( \rightarrow \) Irreversible Antagonist \( \rightarrow \) Receptor
MC/PC Objective: Characterize the pharmacologic properties of the irreversible alpha-receptor antagonist phenoxybenzamine (POB, Dibenzyline™):

- POB contains the basic "pharmacophore" for to bind to alpha-adrenergic (and other) receptors and function as an antagonist. The pharmacophore includes an aromatic ring (at least one) and tertiary amine linked by a chain of 2-4 atoms.
- POB and other haloethylamines are chemically reactive compounds because they have a nucleophilic nitrogen atom two carbon atoms from a good leaving group (Cl). This functionality reacts internally at elevated pHs to form an electrophilic aziridinium ion which can alkylate receptor nucleophiles (see mechanism below).
- POB is marketed as a HCl salt that is chemically stable. In the salt form the nitrogen atom cannot react!
- At physiologic pH POB can exist in the unprotonated form which can react to form an aziridinium ion (see below)?
- In the receptor bound form, the "aziridinium ion" is properly positioned to react with a nucleophilic group present on the alpha-receptor, forming a covalent bound. This results in "irreversible" receptor antagonism.

![Mechanism Diagram]

- POB has a relatively long therapeutic half-life (days) as a result of covalent bond formation with the receptor.
- POB has a relatively short (minutes) plasma half-life as a result of rapid distribution to target tissues and elimination.
- POB is NOT selective in its receptor action? It can also produce antagonism at muscarinic, histamine-1 and serotonin receptors.
- POB’s use is primarily limited to treatment of pheochromocytoma. Why?
- Beta-blockers often used with POB to treat pheochromocytoma. Why?
- The oral activity of POB relatively low due to hydrolysis and inactivation in the gut.
NOTE: POB derivatives lacking a reactive beta-haloethylamine group may be capable of functioning as reversible antagonists at alpha receptors, but DO NOT produce irreversible blockade since they cannot "react" and form a covalent bond with the receptor!

\[
R \xrightarrow{(C)n-N-R'} R'' \\
\text{Alpha-Antagonist Pharmacophore (Protonated Tertiary Amine)} \\
\xrightarrow{\text{Phenoxybenzamine Analogue: Reversible Antagonist}}
\]

MC/PC Objective: Describe the development, chemical and pharmacological properties of the imidazoline antagonists:

- Tolazoline lacks the alpha-agonist activity observed for naphazoline and clonidine, but possesses weak alpha-receptor antagonist activity. Tolazoline also possesses weak antimuscarinic and histaminic actions? Tolazoline is marketed as the HCl salt.
- What is the primary therapeutic indication for tolazoline HCl?
- Why should tolazoline not be used in patients with gastric acid hypersecretory disease?
- Phentolamine \((\text{Regitine})\) lacks the alpha-agonist activity observed for naphazoline and clonidine, and is a more potent alpha-antagonist than tolazoline due to enhanced receptor affinity (the additional aromatic ring present on this compound).
- Phentolamine is NOT selective for alpha-1 versus alpha-2 receptors, and is also capable of blocking muscarinic receptors and promoting histamine release.
- Phentolamine is marketed as a mesylate salt \((\text{CH}_3\text{SO}_3^-)\)? Why?
- Why is phentolamine used to diagnose or treat \textit{pheochromocytoma}?
- Why is phentolamine in combination with papaverine used in impotence?
- Why should phentolamine not be avoided in patients with gastric acid hypersecretory disease?
General MC Objective: Extensive structure-activity relationships have been published for compounds acting as antagonists at alpha-receptor subtypes. We will not review these here since relatively few alpha-antagonist drugs are used in the US. This course and these notes will simply review the more significant drugs that display some degree of selectivity at alpha-receptor subtypes such as the quinazolines, yohimibine and tamsulosin.

MC/PC Objective: Describe the development, chemical and pharmacological properties of the quinazoline antagonists:

- The key structural features present in the quinazolines that contribute to alpha-receptor binding and antagonism include the aromatic ring, the basic guanidino structure and the amide group.

- The primary pharmacologic and therapeutic advantage of the quinazolines over other alpha-antagonists is that they are relatively selective for alpha-1 receptors. They DO NOT block alpha-2 receptors or other neurotransmitter receptors at therapeutic concentration! They also do not promote histamine release! Thus they can produce peripheral dilation without increasing heart rate or cardiac output.
The quinazolines generally are well tolerated. Like other alpha-adrenergic blocking agents, however, they may cause a "first dose phenomenon", characterized by marked hypotension (especially postural hypotension) and syncope with sudden loss of consciousness with the first few doses. How is this managed?

The quinazolines are used to treat hypertension and benign prostatic hyperplasia (BPH). Explain the rationale for their effectiveness in these disorders:

NOTE: Quinazoline efficacy in BPH results from their ability to produce relaxation of smooth muscle by blockade of alpha-1-adrenoceptors in the bladder neck and prostate. Because there are relatively few alpha-1 receptors in the bladder body, these drugs are able to reduce the bladder outlet obstruction without affecting bladder contractility.

The quinazolines differ only in the nature of the amide group (R) in the structure. These structural differences effect primarily pharmacokinetic (rather than pharmacologic) properties as illustrated in the table below.

### Pharmacokinetics of Alpha-1-Adrenergic Blockers

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Prazosin</th>
<th>Terazosin</th>
<th>Doxazosin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral bioavailability</td>
<td>45% to 65%</td>
<td>90%</td>
<td>65%</td>
</tr>
<tr>
<td>Affected by food</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Peak plasma level, time</td>
<td>1 to 3 hrs</td>
<td>1 to 2 hrs</td>
<td>2 to 3 hrs</td>
</tr>
<tr>
<td>Protein binding</td>
<td>92% to 97%</td>
<td>90% to 94%</td>
<td>98%</td>
</tr>
<tr>
<td>Half-life</td>
<td>2 to 3 hrs</td>
<td>9 to 12 hrs</td>
<td>22 hrs</td>
</tr>
<tr>
<td>Excretion: Bile/feces</td>
<td>&lt; 90%</td>
<td>60%</td>
<td>63%</td>
</tr>
<tr>
<td>Excretion: Urine</td>
<td>&lt;10%</td>
<td>40%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Oral bioavailability: All three quinazolines display comparable chemical stability and solubility in the gut, and all are well absorbed from the GI tract. However, they differ in the extent of first pass metabolism as indicated by the bioavailability data. Prazosin is the most "planar" quinazoline and is most efficiently metabolized ("first pass" effect) by oxidative enzymes of the liver (see "metabolism" below). Hence displays the lowest oral bioavailability! It should be noted that several of the metabolites formed retain alpha-blocking and therefore therapeutic activity. Terazosin has higher oral bioavailability than the other quinazolines because it is least efficiently metabolized (minimal first pass metabolism).
- **Metabolic Profiles:** The quinazolines are metabolized to varying degrees by oxidative-O-demethylation (OOD), oxidative-N-dealkylation (OND) and, to a lesser extent, hydrolysis. The OOD and hydrolysis metabolites retain some receptor binding activity and contribute to therapeutic activity. The extent of metabolism effects elimination since these more polar metabolites are more readily eliminated, and conjugated (and eliminated as conjugates) than the parent drug. Note that prazosin is most efficiently (rapidly) metabolized.

- **Elimination profiles:** Terazosin and doxazosin display more "balanced" excretion profiles than prazosin. They are eliminated to a greater extent by BOTH biliary and renal processes.

- **Terazosin and doxazosin display significantly longer half-lives than prazosin. Since all of these compounds are ultimately extensively metaboized, and are similarly bound by plasma proteins (90-98%), the difference in half-lives probably results from the increased biliary component of elimination for terazosin and doxazosin, and particularly biliary recycling which conserves drug.
MC/PC Objective: Describe the development, chemical and pharmacological properties of the yohimbine:

- Yohimbine is a natural product obtained from *Pausinystalia yohimbe* bark. As the Figure above illustrates, it contains the basic pharmacophoric groups for alpha-receptor antagonist binding.

- Receptor Selectivity: Yohimbine particular functionality allows it to function as a selective, competitive alpha-2 (versus alpha-1) receptor antagonist. As a result it inhibits the release of NE from presynaptic storage sites. Yohimibine is not completely selective in its neurochemical actions. For example, it also functions as a 5-HT receptor antagonist.

**NOTE:** Why is yohimibine used to treat male impotence? Also, which peripheral side effects (CV, renal) result from antagonism at alpha-2 receptors? Does this drug penetrate the BBB and produce CNS side effects (see pharmacology notes)?

- Epimerization: Yohimbine is subject to epimerization at the carbon atom adjacent to the methyl ester. Do you know why this reaction occurs? (see examples presented earlier in the course). Epimerization results in a change in receptor selectivity, and the epimer formed is an alpha-1 receptor antagonist?
MC/PC Objective: Describe the development, chemical and pharmacological properties of the tamsulosin (Flomax™):

- **Receptor Binding Profile**: Tamsulosin contains the basic pharmacophoric groups for alpha-receptor antagonist binding. Its particular functionality allows it to function as a selective, competitive alpha-1a-receptor antagonist, and it displays high selectivity being 10-40X more potent as an antagonist at alpha-1a receptors than alpha-1b-receptors.

  NOTE: based on this receptor binding selectivity, tamsulosin has utility in the treatment of benign prostatic hypertrophy (see pharmacology notes)

- **Stereochemistry**: Tamsulosin is chiral and the R-enantiomer is the more active than the S-enantiomer as an alpha-1a receptor antagonist.

- **Bioavailability**: Tamsulosin is sufficiently stable and soluble and lipophilic to allow for high absorption from the GI tract. Also this drug does not contain functionality that is readily metabolized, and thus it does not undergo extensive first pass metabolism. Therefore this drug displays high oral bioavailability (>90%).

- **Half-life**: Tamsulosin has a relatively long therapeutic half-life (15 hours) since it is not extensively in activated by metabolism and not rapidly eliminated.

 ![Alpha-Antagonist Pharmacophore (Protonated Tertiary Amine)](attachment:image) Tamsulosin
ADDITION QUESTIONS AND PROBLEMS

1. For the compounds shown below circle the appropriate response or responses. There may be more than one correct answer, or no correct answer (“None”):

   ![Chemical structures A, B, and C]

   a. Which compounds would form a reactive aziridinium ion?...........A   B   C   None
   b. Which compounds are chiral bases?...............................................A   B   C   None
   c. Which compounds could antagonize NE at alpha-1-receptors?......A   B   C   None
   d. Which compound produces longest acting alpha blockade?...........A   B   C   None
   e. Which compounds are predominantly ionized in plasma?..............A   B   C   None

2. Why is dibenamine a potent, long-lasting alpha-antagonist?

   ![Dibenamine]

3. Based on structural differences and chemical properties, explain why terazosin has higher oral bioavailability and a longer duration of action than prazosin?

   ![Chemical structures Prazosin and Terazosin]