
α Agonists
- Phenylethanolamine Derivatives: As discussed in the previous lecture, these substituted phenethylamines are reminiscent of NE. Their structure-activity relationships determine their selectivity
  - (1) Catechol Moiety: Required for α2 agonists. Without it, the phenylethanolamine is α1 selective. Ex: PE
  - (2) Small α-carbon alkyl group: α2 receptors can accommodate these substituents via its hydrophobic binding pocket, whereas α1 receptors cannot. Ex: Methylpiperine
- α1-Selective Agonists: Imidazoline Derivatives are the best example of α1 agonists. They have no β activity
  - Structure: The compounds involve an Imidazoline ring connected to an aryl group via one or two atoms.
    - The aromatic ring has an ortho-substitution, conferring α1 selectivity.
  - Drugs and Indication: Tetrahydrozoline (Visine) and Naphazoline (Privine) as topical nasal decongestants and eye drops.
- α2-Selective Agonists
  - Receptor Activity: α2 receptors are located in the brain, thus, drugs reaching them must be able to cross the BBB. α2 receptors are located presynaptically. Upon activation, they turn down the tone. They are used to relieve pressure, whether in HT (clonidine) or in glaucoma.
  - Ortho,Ortho Halogens: confer the α2 selectivity
    - (1) Structure: Selectivity is conferred by the 2 bulky ortho functionalities. For example, the dichloro ortho-substitutions on Clonidine prohibit coplanar conformations. The substituents produce steric hindrance, forcing the aryl and imidazoline rings into orthogonal positions. As a result, these structures are α2 selective
    - (2) Ionization: Additionally, the ortho-halogens function as EWG, lowering the pKa of the imidazole from 12 to 8, promoting the un-ionized neutral structures capable of crossing the BBB.
      - Brimonidine (Alphagan): Albeit α2-selectivity, these cannot cross the BBB. Used for glaucoma
        - Bromine group prevents BBB passage
      - Apraclonidine (Iopidine): Albeit α2-selectivity, these cannot cross the BBB. Used for glaucoma
        - Amine group prevents BBB passage
- Mixed α-Agonists
  - Bulky Tert-butyl: The presence of a bulky tert-butyl group at the para-position of the aryl ring greatly diminishes the affinity of the drug for α2 receptors. Thus, drugs like Oxymetazoline (Afrin) are used as topical nasal decongestants and eye drops to act at α1 receptors.

α-Adrenergic Receptor Antagonists
- Irreversible: Compounds capable of irreversibly binding to α-adrenergic receptors are antagonists and can be used to cease/knock-out vasoconstriction. Most frequently irreversible α-adrenergic antagonists are used to target α1, but there are some that target α2.
  - Phenoxymethylamine (Dibenzyline): Has reactive Aziridine intermediate, nucleophilic attack by the receptor active site Cys or Ser residue will cause irreversible alkylation, relatable to nitrogen mustard anticancer agents.
    - Produces a complete blockade in the periphery, long-acting. Patient will be at hypotensive risk.
- Imidazoline-type: These compounds are non-specific, non-selective antagonists. Phentolamine and Tolazoline are potent, nonselective α-antagonists indicated for pheochromocytoma.
  - Tolazoline (Priscoline): This drug spins with free rotation. For the sake of practice, if we added a ortho-methyl, it would become an α1 agonist. Add 2 ortho-methyls, it would be α2 agonist
- α1-Selective Antagonists: α1 agonists cause vasoconstriction, raising BP (see Midodrine). α1-selective antagonists can be used to induce vasodilation helping to lower blood pressure. These are reversible
  - Quinazolines – containing a 4-amino-6,7-dimethoxyquinazoline ring system
    - (1) Quinazoline ring system is essential for the activity and binding
    - (2) The piperazine ring acts as a connection element for the R group
    - (3) The identity of the R group determines the T1/2 and other pharmacokinetic properties
      - Prazosin: T1/2 = 2-3h. Flat aromatic furan ring makes it metabolically accessible to amidases
      - Terazosin: T1/2 = 12h. Tetrahydrofuran is much bulkier, slowing amidase activity
  - Uroselective α1-antags: Alfuzosin is a failed anti-hypertensive, but its functionally uroselective activity makes it useful for the treatment of benign prostatic hyperplasia (BHP). Short T1/2, it is ER formulated.
    - Phenylethanolamines: Tamsulosin + Silodosin are also used to treat BPH
- **α2-Selective Antagonists**: Recall the α2 agonists operate at the presynaptic α2 autoreceptors, turning down the adrenergic tone. α2 antagonists inhibit the negative feedback loop, thereby increasing the adrenergic tone!!
  - **Herbal Alkaloids**: Though not FDA approved, Yohimbine and rauwolscine (← say that word) are natural alkaloids isolated from *Pausinystalia* bark and roots. They express greater selectivity for the α2 receptor, though there is some residual α1 antagonistic activity as well. These compounds are used as aphrodisiacs and weight loss… at your own frisky risk.

**β-Agonists**
- β-adrenergic agonists are far more important and efficacious in the treatment of HT than α-agonists. Similar to α-adrenergic receptors, there are subtypes to the β receptors that we have already encountered. β1 receptors are prevalent in the heart, whereas β2 receptors are present in the bronchial smooth muscles of the lungs.
  - **β1 Agonist Activity**: Increases heart contractility and rhythm
  - **β2 Agonist Activity**: Induces bronchodilation, helping to relieve constriction and improve aspiration

**Isoproterenol**: This is our plain β-agonist. It is non-selective, acting at both β1 and β2 receptors. Its appearance suggests it would have α-adrenergic activity, but the isopropyl group makes it β-selective.

**Structural Modifications**
- **Larger Amine Substituents**: Increases in size beyond Isoproterenol’s isopropyl shows preference to β2
  - Colterol: Now tert-butyl, only 1C bigger than Isopropyl, the compound favors β2 > β1
- **Removed β-OH**: β2 agonists require the presence of a β-OH group, without it, they act β1 only
  - Dobutamine: This compound is optically active, eliciting opposing activity at receptors
    - S(-) Isomer: α1 agonist, β1 agonist
    - R(+) Isomer: α1 antagonist, β1 weak agonist
    - Observed clinical effect is a selective β1 agonist
    - Dobutamine is indicated as a cardiac stimulant following surgery or CHF
- **Modified meta-OH**: Additional H-bonding restricts these drugs to β2 agonist

**β2-Selective Agonists**: There are a few methods by which we can confer β2 selectivity.

**Modified meta-OH**: A decent number of the drugs we have discussed have maintained the catechol moiety. β2 selective agonists modify the meta-OH to prevent COMT metabolism, thereby also improving bioavailability. Relative to β1 receptors, β2, have a slightly larger binding pocket to provide hydrogen-binding to the m-substituents. *Albuterol*, a short-acting beta-agonist (SABA) nearly resembles Isoproterenol, with the methoxy at the meta position rather than the catechol.

**Catechol → Meta, Meta**: β2 specificity can also be conferred by moving the 4-OH to 5-OH, producing a *m,m’*(OH)2 structure. *Metaproterenol*, another SABA, nearly resembles isoproterenol, with the catechol moiety adjusted to the meta,meta OHs.

**Small Alkyl Group on α-Carbon**: The addition of an alkyl group to the α carbon will make a β agonist β2 selective. β1 cannot easily accommodate such groups. *Isoetharine* is an example of Isoproterenol made into a β2 selective agonist by adding an ethyl moiety.

**Long-Acting β-Adrenergic Agonists (LABA)**: Not Discussed.

**β-Antagonists**
- **Non-Selective β Antagonists**: Replacement of Isoproterenol’s catechol moiety with chlorine atoms created the lead compound for β-adrenergic antagonist development, *DCI*. The chlorine groups were slightly smaller than the –OH groups, H-bonding ability was halved (Accept vs Donate+Accept). DCI’s partial agonist-antagonist activity was not clinically appealing. Eventually, following:
  - (1) Elongation of ethylamine side chain by an oxymethylene bridge
  - (2) Placement of the oxymethylene bridge at C1 of the naphthyl group
  
  the first non-selective β-adrenergic antagonist was marketed, *Propranolol!*

**1st Generation Beta-Blocker** (Non-selective): Propranolol is lipophilic, penetrates the BBB, eliciting fatigue and potentially even depression as AE

**2nd Generation Beta-Blocker** (Non-selective): To limit BBB penetration, hydrophilic groups were added, producing Nadolol, Pindolol, and Timolol. (Timolol has a different aromatic ring, indicated for glaucoma)

**3rd Generation Beta-Blocker** (β Selective): While the 1st and 2nd generation β-blockers were not a good idea for asthmatics due to β2 antagonism, accomplishment of β1 selectivity in the 3rd generation β-blockers was a major success. **Key to success**: Large para-substituent. Fits in β1, but not β2
  - Caution: 1st and 2nd generation β-blockers are contraX with asthmatics
Indirect-Acting Adrenergic Agonists

These agents increase the concentration of NE at the receptor, without directly interacting with the receptor. As a result, these are not selective. Their structure involves an A group, which can be any aromatic or carbocyclic ring. The ethylamine side chain may be separate, or part of the cyclic ring.

- Activity: (1) Inhibit Reuptake, similar to cocaine. (2) Increase NE Release
- Effect: Recall these are non-selective. Put vaguely, these agents increase the tone of the adrenergic system.
- Amphetamine (Adderall, AMP): CNS Stimulant, aka speed, stimulates the release of NE and other NT such as DA and 5-HT in the periphery/brain. Non-selective action: appetite suppression. (C-II)
- Methamphetamine (Desoxyn, MAMP): More lipophilic CNS stimulant. Highly abused. (C-II)
- 3,4-Methylenedioxyamphetamine (MDMA): aka Ecstasy. Potent, Lipophilic, ~Neurotoxic
  - Neurotoxicity MoA: The methylene of the methylenedioxy group confers excellent lipophilicity and avoidance of COMT. Once in the CNS, CYP with metabolize the methylene, producing the catechol. COMT becomes overwhelmed, leading to the production of orthoquinones and other neurotoxic compounds. Damage to the brain may ensue, as neuronal nucleophiles begin to irreversibly engage the metabolites. It may show benefit in treating PTSD, but its therapeutic window is trash. (C-I)
- Pseudoephedrine (Sudafed, PSE): Non-selective action: Raise BP. (C-V)
- Tyramine: Tyramine is a product of Tyr decarboxylation by L-Amino Acid-Decarboxylase. Tyramine is found in cheese and red wine, capable of inhibiting reuptake of NT. People taking MAOIs should avoid this compound.