Adrenergic Agonists (many thanks to Vickie Poremba, Class of 2012, for providing this lecture transcript).

- Direct action
  - Bind to pre- or post-synaptic receptor \(\rightarrow\) response
- Indirect action – increase NE in synapse
  - Increase release
  - Block uptake
- Mixed action = both of the above

Pharmacophore – catecholamines: change in structure leads to change in activity, distribution, etc.

Structure of Endogenous NT
- two ortho-hydroxyls on benzene (catechol)
- amine (primary, secondary, tertiary)
- R(-) isomer preferred.

QUINOLONE
- inactive form of a catechol
- catechol converts to this easily due to exposure to neutral or alkaline pH, air or light
Biosynthesis

Metabolism

- Major removal by re-uptake
- MAO and COMT
  - Some NE
  - All circulating EPI

\[
\begin{align*}
\text{Tyr} & \xrightarrow{\text{Threonine hydroxylase}} \text{L-Dopa} \\
\text{Dopa} & \xrightarrow{\text{Decarboxylase}} \text{Dopamine} \\
\text{Phenylethanolamine-N-methyltransferase} & \xrightarrow{\text{(Adrenal, same in CNS)}} \text{Epi}
\end{align*}
\]

\[
\begin{align*}
\text{COMT} & = \text{some NE, all EPI. Need catechol (both hydroxyls, ortho) for reaction to take place.}
\end{align*}
\]
MAO = need 2 H’s on alpha carbon because it is an oxidative deamination → end up with aldehyde, which can then be reduced to OH or oxidized to carboxylic acid. MAO-A = prefers serotonin (5-HT), NE, and DA (found in brain, neurons). MAO-B = prefers phenylethylamine (found in platelets, brain, neurons)

Vanillylmandelic acid (VMA) = most common metabolite; after both COMT and MAO

SAR = Structure Activity Relationships

GENERAL STRUCTURE
- R1 determines alpha/beta activity => increase size of R1 = decreased alpha, increased beta
  - R = H, NE
  - R = C\textsubscript{6}H\textsubscript{5}, EPI
  - R = \text{isopropyl}
- Alpha receptors = can handle up to methyl on R1, anything bigger = lower potency
  - Receptor affinities: NE > EPI >> ISO
- Beta receptors = have hydrophilic region so can accommodate bulk/extra chains on R1 (e.g. tert-butyl or isopropyl)
  - Receptor affinities: ISO >> EPI > NE
- 1° amine = mostly alpha
- 2° amine = alpha/beta mixed if methyl; mostly beta if bulkier
- Quaternary amines => great loss in activity

- **R3,4,5 (direct vs. indirect activity)**
  - All hydroxyls = very close to NE and EPI => potent direct activity
  - 3 + 4 hydroxyls = still direct but less potent
  - Any other hydroxyl pattern => more indirect

- Optimal chain distance = 2 carbons; >2 = antagonist

- **R2 (alpha carbon)**
  - H or CH₃
  - Usually CH₃ → increases indirect activity (decreases direct activity), increases CNS activity (decrease peripheral potency), inhibits MAO → degraded slower → increased duration of action
  - Anything > CH₃ abolishes alpha-action:

- **Example:** alpha-ethyl NE is a bronchodilator.
- No catechol and alpha-CH₃ = CNS stimulation. Prototype = amphetamine

- **R3 (beta carbon)**
  - OH = chirality; enhances alpha and beta activity, more direct action, decreases CNS stimulation in non-phenolic cmpds, must have correct stereochemistry
  - H = increases CNS stimulation, increases volatility (inhalers)

- **R4,5**
  - both OH = catechol; not much CNS stimulation, decreased stability (prep at pH 5.5, add antioxidants like ascorbic acid, protect from air, light)
  - 4 or 5 OH = less potent than catechol, weak CNS activity, also not metabolized by COMT
  - both H = more indirect activity and more CNS stimulation
  - different than OH or H → antagonist
Agents that interfere with the synthesis of catecholamines

- Alpha-methyl-DOPA = competitive inhibitor of DOPA decarboxylase. Also a substrate and slowly converted to alpha-methylNE, which is a false NT and can act as an alpha-2 agonist in the CNS.

\[
\alpha\text{-methylDOPA (Aldomet®)} \xrightarrow{\text{DOPA decarboxylase}} \alpha\text{-methyl dopamine} \xrightarrow{\text{dopamine-\(\beta\)-hydroxylase}} \alpha\text{-methyl norepinephrine}
\]

\[\text{Alpha-methyltyrosine = inhibits tyrosine hydroxylase; inhibits synthesis of NE and EPI}\]

Drugs that affect catecholamine storage and release

- Guanethidine and guanadrel are neuronal blockers that inhibit the release of NE from sympathetic nerve terminals by decreasing sensitivity of the neuronal membrane.
- The rauwolfia alkaloids (reserpine, deserpidine, and rescinnamine) block the transporter responsible for uptake of NE into the storage vesicles.
Antidepressants

- **MAO inhibitors**
  - seldom used
  - cause mood elevation (even in normal subjects)
  - Caution when using adrenergic drugs
  - React with everything
    - Example: Wine and cheese contain tyramine → Tyramine + MAO inhibitor = HTN crisis

\[ R_1 \quad R_2 \quad R_3 \quad R_4 \quad \text{MAO} \quad \rightarrow \quad R_1 \quad R_2 \quad R_3 \quad R_4 \]

**MAO inhibitors.**

**Alpha-agonists**

\[ \text{Dipivefrin} = \text{tert-butyl carbonyl esters; makes it more stable because it can't form quinolone. This is used as prodrug for glaucoma; hydrolyzed to EPI in aqueous humor} \rightarrow \text{increases outflow of aqueous humor and decreases production of aqueous humor} \rightarrow \text{decreases IOP – about 40x more effective than EPI.} \]

**Why use a prodrug?**

- Increased absorption, distribution
- Increased stability
- Mask taste or odor
- Increase duration of action
- Decrease metabolism
- Decrease GI upset

Phenylephrine = not a COMT substrate. Longer DOA (2x EPI), mixed alpha agonist, some selectivity for alpha-1. Used as a nasal decongestant.

Ephedrine and Pseudoephedrine = structure/stereochemistry affect activity
- 2 chiral centers = 4 possible isomers
- Fischer projections:
  - Large groups on same side = erythro (more potent)
  - Large groups on opposite sides = threo
- Ephedrines are more potent than pseudoephedrines
- No MAO metabolism because of alpha methyl
- No COMT and high CNS activity because no catachol
- Used as nasal decongestants

Phenylpropanolamine (OFF MARKET)
- Used to be the drug of choice for nasal decongestion
- Taken off market due to dosing issues; supposed to be 25 mg TID-QID but was formulated into Dextarin, 75 mg tablet and that caused huge problems = gross misuse of a drug
- Drug had high CNS penetration → anorexigenic

2-aminoheptane (Tuaminoheptane) = inhaled vasoconstrictor, potency > ephedrine

IMIDAZOLINES

Naphazoline = good decongestant, equipotent to ephedrine in alpha-potency. Used as nasal spray, which can be addictive due to rebound congestion.

Tetrahydrozaline = “gets the red out”; Visine; topical vasoconstrictor
Alpha-antagonists

- Adrenergic block
  - Block post-synaptic receptors/block action of NT
  - Competitive
  - Non-competitive
- Inhibit release of NT centrally or at pre-synaptic receptors; no interference with released NT

Phenoxybenzamine = has an aziridine ring. Once it binds with alpha-receptor, a NU in receptor attacks aziridine => covalent bond => irreversible blockade
- Slow onset of action (about an hour even IV) and 3-4 day duration of action
- Used for peripheral vascular disease, Raynaud’s Syndrome

Imidazolines (like naphazoline, tolazoline, phentolamine) can be considered reversible antagonists because they are very weak alpha-agonists and so via competitive action inhibit activity of NE and EPI. Examples:

Ergot alkaloids = complex mix
- Complex; some alpha stimulants, some alpha blockers, some CNS stimulants, some oxytocic
- From the fungus Claviceps purpurea
- Ergotism = St. Anthony’s Fire = gangrene; arms and legs turn black and fall off (due to vasoconstriction/no blood flow). There is also psychosis associated with this, due to LSD resemblance:
- All natural ergot alkaloids = alpha-agonists = vasoconstriction
- Synthetic analogs = 9,10 dihydro (saturated) → alpha block

Ergotoxins (ergaloid mesylates) = 9,10-dihydro (saturated) → alpha blockers; used for peripheral vascular disease and Alzheimer’s (not too good). 3 components:

- **Dihydroergocristine**: \( R = \text{CH}_2 - \bigcirc \)
- **Dihydroergocryptine**: \( R = \text{CH}_2 - \bigtriangledown \)
- **Dihydroergocornine**: \( R = \bigtriangledown \)

Ergotamines = unsaturated = vasoconstrictor = use in migraines (acute tx). Cafergot = Ergotamine (1 mg) + caffeine (100mg). Caffeine potentiates ergotamine.
Prazosin = alpha-1 blocker

Yohimbine = alpha-2 blocker

Clonidine = alpha-2 agonist; centrally mediated alpha block

**Beta-agonists**

- Non-selective = not good; too many undesirable effects
- B2-selective = bronchodilator; asthma

Isoproterenol = non-selective, direct beta agonist; substrate for COMT and MAO; causes bronchodilation and is also a powerful cardiac stimulant so don’t use IV, not ideal for asthma either

*Resorcinol type* = like a catechol but with meta hydroxyls. Not a substrate for COMT = longer duration than catechols. Large N substituent = direct toward beta-2 receptors. Examples:

Terbutaline = bronchodilator
Metaproterenol = beta-2 selective bronchodilator

**Salicyl alcohol type** = has a hydroxyl and a CH$_2$-OH; eliminate COMT metabolism and increases beta-2 activity

Example:

Albuterol/Ventolin = beta-2 stimulant, no COMT metabolism

**Beta-antagonists**

DICHLOROISOPROTERONOL = Chlorines in place of catechol OHs, larger group on N; first beta-blocker discovered

- **Beta-1 blockade** = decrease workload on heart
- Used as agents to treat cardiac disease, angina, glaucoma, decrease BP, and decrease mortality post-MI

\[
\text{Pharmacophore – beta-1 blockers}
\]

- Bulky R-group directs toward beta
- Stereochemistry must match ISO (R config)
- X group can be nothing or O-CH$_3$
- Aryl can be napthyl or phenyl (phenyl must be substituted, but no phenols)

Propranolol = prototype; non-selective so not very good and can’t be used in asthma. Marketed as racemic; R-(-) 100x more potent.
Primary metabolite of propranolol.

Nadolol = similar to propranolol; long-acting, less CNS

Atenolol = beta-1 selective, ok in asthma

Metoprolol = similar to atenolol

Acebutolol \(\rightarrow\) first pass effect \(\rightarrow\) gets deaminated and N-acetylated \(\rightarrow\) diacetolol = active metabolite