Pharmacology of the Sympathetic Nervous System I

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Neurons of the ANS

Adrenergic Nerve Terminal

Noradrenergic Neuron

Neuronal (Uptake1) vs Extraneuronal (Uptake2)

MAO vs COMT

<table>
<thead>
<tr>
<th></th>
<th>MAO</th>
<th>COMT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location in cell</strong></td>
<td>Mitochondrial outer membrane</td>
<td>cytosol</td>
</tr>
<tr>
<td><strong>Location in body</strong></td>
<td>symp. nerve, placenta (MAOα)</td>
<td>most tissues, not in sympath. nerve</td>
</tr>
<tr>
<td></td>
<td>platelets</td>
<td></td>
</tr>
<tr>
<td></td>
<td>liver, kidney, brain (MAOα + MAOβ)</td>
<td></td>
</tr>
<tr>
<td><strong>Effect of inhibition on NE levels</strong></td>
<td>Increases NE level in symp. neuron, potentiates release by tyramine-like drugs</td>
<td>minor/no effect</td>
</tr>
</tbody>
</table>
**MAO vs COMT**

**MAO**

- Inhibitors: Tolcapone, Pyrogallol
  - Parkinson’s D with L-Dopa (rarely used, liver failure)

**COMT**

- Inhibitors: Non-selective Depression
  - Tranylcypromine, Pargyline

- Inhibitors: Selective Depression
  - Selegiline

**COMT vs MAO**

**RHO**

\[
\begin{align*}
\text{COMT} & \quad \text{MAO} \\
\text{H}_2 \text{H}_2 & \quad \text{H}_2 \text{H}_2 \\
\text{CH}_3\text{O} \quad \text{R} & \quad \text{R} \\
\text{N} & \quad \text{CO} \quad \text{H} \\
\text{R} & \quad \text{C} \quad \text{O} \\
\text{R} & \quad \text{C} \quad \text{O} \\
\text{O} & \quad \text{CH}_2\text{OH}
\end{align*}
\]

**Metabolism of Catecholamines**

**Major Metabolites**

- VMA
- MOPEG

**Metabolism by either MAO or COMT, inactivates drug**

**Receptor Subtypes**

<table>
<thead>
<tr>
<th>α-Receptors</th>
<th>1948</th>
<th>70’s</th>
<th>α1-Receptors</th>
<th>90’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>α2-Receptors</td>
<td></td>
<td></td>
<td>α2A, α2B, α2C, α2D</td>
<td></td>
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- **PLC**
- \(\text{TCP}^{++}\)
- \(\text{TIP}_{2}\)
- \(\text{DAG}\)

\[\begin{align*}
\text{A/C} & \quad \text{cAMP} \\
\text{A/C} & \quad \text{cAMP}
\end{align*}\]

**Second Messengers**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>G Protein</th>
<th>2nd Messenger</th>
</tr>
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<tr>
<td>α1</td>
<td>Effector tissues: smooth muscle, glands</td>
<td>Gq</td>
<td>(\text{TCP}^{++}, \text{TIP}_{2}, \text{DAG})</td>
</tr>
<tr>
<td>α2</td>
<td>Nerve endings, smooth muscle</td>
<td>Gi</td>
<td>(\text{iAMP})</td>
</tr>
<tr>
<td>β1</td>
<td>Cardiac muscle, juxtaglomerular apparatus</td>
<td>Gs</td>
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<tr>
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</tr>
<tr>
<td>β3</td>
<td>Adipose cells</td>
<td>Gs</td>
<td>(\text{cAMP})</td>
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<td>D1, D2</td>
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<td>D3, D4</td>
<td>Brain, cardiovascular</td>
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**Phospholipase C**

- **G-Protein coupled receptors**
- **Adrenergic Alpha1-receptors**
- **Cholinergic**
  - M1
  - M3
  - M5

**Adrenergic Agents – Relative Selectivity**

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<th>TISSUE</th>
<th>ACTIONS</th>
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<tr>
<td>Alpha2 EPI &gt;&gt; NE &gt;&gt; ISO</td>
<td>smooth muscle contraction</td>
<td>smooth muscle relaxation</td>
<td></td>
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<tr>
<td>Alpha2 NE &gt;&gt; EPI = ISO</td>
<td>glandular tissue contraction</td>
<td>glandular tissue relaxation</td>
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### Adenylate Cyclase

**G-Protein coupled receptors**

- **Stimulate**
  - All Beta-receptors
  - D1, D5-receptors

- **Inhibit**
  - Alpha2-receptors
  - D2, D3, D4-receptors
  - M2, M4-receptors

### Vasculature

**norepinephrine / epinephrine**

- α1-AR
  - IP3 / DAG
  - Ca++ / PKC
  - Vasoconstriction
  - Increase resistance
  - Increase BP

- β2-AR
  - ↑cAMP
  - protein kinase A
  - Vasodilation
  - Decrease resistance
  - Decrease BP

### Catecholamines

A. **Norepinephrine** (limited use, pressor agent, shock)
   - Activates: both alpha, beta1, beta2, beta3 (weakest)
   - Substrate for MAO & COMT, does not cross BBB

B. **Epinephrine** (DOC - Allergic reaction)
   - Activates both alpha, beta1, beta2, beta3 (weakest)
   - Substrate for MAO & COMT, does not cross BBB

C. **Dopamine** (DOC – shock)
   - Precursor of NE and EPI
   - Activates alpha1, dopamine receptors
   - Substrate for MAO & COMT, does not cross BBB

D. **Isoproterenol** (asthma, cardiac stimulant)
   - Activates all beta receptors
   - Substrate for COMT, does not cross BBB

### Non-Catecholamines

- **Selective beta2-agonists:**
  - albuterol, ritodrine, metaproterenol, terbutaline

  Uses: asthma, premature labor

  Oral: Onset 1-2 hrs, duration 4-6 hrs
  Inhal: Onset 5-10 min, duration 3-4 hrs (fewer side effects)

- **Adverse effects:** cardiovascular (↑HR, ↓BP)

- **Selective beta1-agonists:**
  - dobutamine, prenalternol

  Uses: Congestive heart failure
  Increase force, no change in HR or oxygen demand

### Non-Catecholamines – Alpha agonists

- **Selective alpha1-agonists:**
  - methoxamine, phenylephrine, metaraminol (direct & indirect actions, orally active)

  Uses: hypotension or shock, nasal decongestant

- **Selective alpha2-agonists:**
  - clonidine, α-methyldopa (prodrg), guanfacine

  Uses: hypertension (CNS action)
  opioid withdrawal (decrease severity)

  **Side effects:** impotence, dry mouth, rebound HT

### Drug of Choice

- **None effective orally**
- **Do not cross BBB**
- **Actions brief**

- **DOC**
  - Drug of Choice
Indirectly-acting Sympathomimetics (displace transmitter)

- Amphetamine, methamphetamine, methylphenidate
  - CNS stimulant, performance enhancer, physical & mental abuse
  - Alertness, mood, self-confidence, concentration, psychological dependence, tolerance, tachyphylaxis
- Uses: ADHD, appetite suppression (?), narcolepsy
- Toxicity: cardiovascular, restlessness, tremor, insomnia
- Ephedrine (mixed)
  - Direct action (alpha- and beta-receptors)
  - Indirect action to release norepinephrine
- Uses: nasal decongestant
- Tyramine (not a drug, interaction with MAO inhibitors)

Sudafed phenylephrine vs pseudoephedrine

Manufacturers, including Sudafed-maker Pfizer Inc., switched to phenylephrine from pseudoephedrine the past year after passage of a law requiring all pseudoephedrine products be sold from behind pharmacy counters.

Crystal Meth Drug Abuse

After 1.5 years of drug use

Indirectly-acting Sympathomimetics (cont.)

- Amphetamine, methamphetamine, methylphenidate
  - CNS stimulant, performance enhancer, physical & mental abuse
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Neuronal Uptake Inhibition

- Inhibit neuronal uptake (Uptake 1)
- Can prevent the action of indirectly acting agents (e.g. amphetamine) and can potentiate the effects of NE (i.e. not removed from synaptic junction).
- Neuronal Uptake 1: 70-80%
- Cocaine
  - Tricyclic antidepressants (Imipramine, amitriptylline)
  - High dose: block alpha- & M-rec.
- Atomoxetine (used for ADHD)
- Guanethedine (competes for uptake)
Tyramine Interaction with MAO Inhibitors

Can cause hypertensive crisis (↑BP, ↑HR)

Aged cheese & red wine are rich in tyramine

FIG. 7

Tyramine Interaction with MAO Inhibitors

Can cause hypertensive crisis (↑BP, ↑HR)

Aged cheese & red wine are rich in tyramine

FIG. 7

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<td>Inhibitors</td>
<td>Pargyline, tranylcypromine (non-selective) Clorgyline (MAO\textsubscript{A}-selective) Selegiline (MAO\textsubscript{B}-selective)</td>
</tr>
<tr>
<td>Clinical use of inhibitors</td>
<td>Depression (non-selective or MAO\textsubscript{B}-selective) Parkinson’s disease (MAO\textsubscript{A}-selective)</td>
</tr>
<tr>
<td>Interactions</td>
<td>MAO inhibitors potentiate effects of tyramine (due mainly to blocking metabolism of tyramine by MAO in liver)</td>
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Parkinson’s Disease

- General population 1:1000, over 60 1:75
- Tremor, stiffness, or clumsiness, usually involving one side, difficulty walking, fatigue, depression
- Progressive destruction of the dopaminergic nigrostriatal pathway
- Elevated cholinergic activity

- Treatment:
  - MAO inhibitors:
  - Dopamine agonists: bromocriptine
  - L-Dopa
  - Anticholinergics: benztrapine
  - Decarboxylase inhibitor: carbidopa
  - Amantadine: Inhibit D-uptake, M-rec, NMDA-block, release dopamine

MAOI and Tyramine Crisis

- ↑Blood pressure, ↑Heart rate
- Treatment: α-blocker or labetalol (α, β-blocker)
- Normally dietary tyramine is metabolized by MAO
- With MAO inhibition, octopamine is produced and stored in vesicles with NE
- Aged cheese, red wine are rich in tyramine

Therapeutic uses: Sympathomimetics 1

- Asthma (major use)
  - bronchodilatation with ↓airway resistance
  - β\textsubscript{2}-selective agents eg. albuterol

- Allergic Reactions
  - acute hypersensitivity reactions (food, bee sting, drug allergy)
  - epinephrine (DOC)

- Nasal Decongestant (common use)
  - vasoconstriction (ephedrine, phenylephrine)

- Hypotension (acute)
  - intoxication with antihypertensive agents, spinal anesthesia, hemorrhage
  - phenylephrine, methoxamine, metaraminol
Asthma

- **Albuterol**
- **Terbutaline, Metaproterenol**
- β₂-selective agonists - bronchodilation
- Inhalation vs oral - less side effects
- **Ritodrine** - premature labor

**Therapeutic uses: Sympathomimetics 1**

- **Asthma** (major use)
  - bronchodilation with ↓airway resistance
  - beta²-selective agents eg. albuterol
- **Allergic Reactions**
  - acute hypersensitivity reactions (food, bee sting, drug allergy)
  - epinephrine (DOC)
- **Nasal Decongestant** (common use)
  - vasoconstriction (ephedrine, phenylephrine)
- **Hypotension** (acute)
  - intoxication with antihypertensive agents, spinal anesthesia, hemorrhage
  - phenylephrine, methoxamine, metaraminol

**Therapeutic uses: Sympathomimetics 2**

- **Hypertension** (chronic)
  - centrally acting α₂-receptor agonists (clonidine, α₂-methyl-dopa)
- **Shock** (need to treat cause)
  - dopamine (DOC), epinephrine, NE
  - blood loss, cardiac failure, septic shock, cardiac obstruction
  - inadequate perfusion of tissues, need to maintain BP and cerebral blood flow
- **Congestive Heart Failure**
  - dobutamine (acute)
- **Cardiac Heart Block & Cardiac Arrest**
  - epinephrine or isoproterenol

**Therapeutic uses: Sympathomimetics 3**

- **Ophthalmic**
  - dilate the pupil (phenylephrine)
  - glaucoma (epinephrine)
  - also beta-blocking agents used (common)
- **Uterine Contraction**
  - suppress premature labor
  - ritodrine, terbutaline (not FDA approved)
- **Hyperactivity Disorder (ADHD)**
  - amphetamines, methylphenidate (ritalin)
  - NE uptake inhibition: atomoxetine
- **Others**: obesity, narcolepsy
  - amphetamine-like agents

**Toxic effects of Sympathomimetics**

- Extensions of their receptor-mediated effects
- **Cardiovascular** (main)
  - cardiac stimulation (β-AR, arrhythmias)
  - hypertension (α-AR, hemorrhage)
- **CNS**
  - Especially those that cross BBB (ie. amphetamine)
  - restlessness
  - dizziness
  - insomnia
- **Alpha₂-receptor agonists**
  - dry mouth, sedation, impotence