**Pharmacology of the Sympathetic Nervous System**

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**Sympathetic Nervous System**

Norepinephrine (NE) = Noradrenaline (NA)
Epinephrine (EPI) = Adrenaline (AD, ADR)
Noradrenergic = Adrenergic
Isoproterenol = Isoprenaline (ISO)

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**Adrenergic Nerve Terminal**

**Noradrenergic Neuron**

- Neuronal (Uptake1) vs Extraneuronal (Uptake2)
  - **Neuronal Uptake (Uptake1)**
    - 70-80%
    - Cocaine
    - TCA
    - MAO
  - **Extraneuronal Uptake (Uptake2)**
    - 10-20%
    - COMT

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**MAO vs COMT**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine (DA)</td>
<td>Norepinephrine (NE)</td>
</tr>
<tr>
<td>Serotonin (5-HT)</td>
<td>Norepinephrine (NE)</td>
</tr>
<tr>
<td>Histamine</td>
<td>Noradrenergic (NE)</td>
</tr>
<tr>
<td>MAO</td>
<td>MAO</td>
</tr>
<tr>
<td>DA, 5-HT, NE</td>
<td>DA, 5-HT, NE</td>
</tr>
<tr>
<td>Liver, kidney, brain</td>
<td>Liver, kidney, brain</td>
</tr>
<tr>
<td>Liver, kidney, brain</td>
<td>Liver, kidney, brain</td>
</tr>
<tr>
<td>Most tissues</td>
<td>Liver, kidney, brain</td>
</tr>
<tr>
<td>Not in symp. nerve</td>
<td>Not in symp. nerve</td>
</tr>
<tr>
<td>Release by tyramine-like drugs</td>
<td>Released, not in symp. nerve</td>
</tr>
</tbody>
</table>

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Inhibitors: Pyrogallol, Tropolone
Inhibitors: Non-selective
Depression: Tranylcypromine, Pargyline
Inhibitors: Selective
Depression: MAO-A Clorgiline
Parkinson's: MAO-B Selegiline

**MAO vs COMT**

**Metabolism of Catecholamines**

Major Metabolites: VMA, MOPEG

**Receptor Subtypes**

- α-Receptors 1948
- β-Receptors
  - 70's
  - 60's

**Adrenergic Agents – Relative Selectivity**

<table>
<thead>
<tr>
<th>RECEPTOR</th>
<th>TISSUE</th>
<th>ACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1</td>
<td>vessels smooth muscle</td>
<td>contraction</td>
</tr>
<tr>
<td></td>
<td>papillary dilator muscle</td>
<td>contraction (dilation)</td>
</tr>
<tr>
<td></td>
<td>proximal smooth muscle</td>
<td>relaxation</td>
</tr>
<tr>
<td></td>
<td>distal smooth muscle</td>
<td>relaxation</td>
</tr>
<tr>
<td></td>
<td>intestinal smooth muscle</td>
<td>relaxation</td>
</tr>
<tr>
<td></td>
<td>intestinal sphincters</td>
<td>relaxation</td>
</tr>
<tr>
<td>α2</td>
<td>NE &gt; EPI &gt;&gt; ISO</td>
<td>contraction</td>
</tr>
<tr>
<td></td>
<td>nerve terminals (NE &amp; Ach)</td>
<td>inhibit transmitter release</td>
</tr>
<tr>
<td></td>
<td>platelets</td>
<td>aggregation</td>
</tr>
<tr>
<td></td>
<td>fat cells</td>
<td>inhibition of lipolysis</td>
</tr>
<tr>
<td>β1</td>
<td>heart</td>
<td>↑ force, rate, conduction velocity</td>
</tr>
<tr>
<td></td>
<td>coronary blood vessels</td>
<td>dilation</td>
</tr>
<tr>
<td></td>
<td>kidney</td>
<td>relaxation</td>
</tr>
<tr>
<td>β2</td>
<td>bronchial smooth muscle</td>
<td>relaxation</td>
</tr>
<tr>
<td></td>
<td>uterine smooth muscle</td>
<td>relaxation</td>
</tr>
<tr>
<td></td>
<td>intestinal smooth muscle</td>
<td>relaxation</td>
</tr>
<tr>
<td></td>
<td>vascular smooth muscle</td>
<td>relaxation</td>
</tr>
<tr>
<td></td>
<td>liver glycogenolysis</td>
<td>facilitation of release</td>
</tr>
<tr>
<td>β3</td>
<td>NA nerve terminals</td>
<td>lipolysis</td>
</tr>
</tbody>
</table>

**Phospholipase C**

Sympathetic nerve causes release of NE at α2 receptors to cause Ca++ release and contraction of smooth muscle.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>G Protein</th>
<th>Second Messenger</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

**Second Messengers**

- α1A, α1B, α1C, α1D
- α2A, α2B, α2C, α2D
- β1, β2, β3, 90's
- ↑Ca++
- ↑IP$_3$
- ↑cAMP
- DAG

**Phospholipase C**

G-Protein coupled receptors

Adrenergic
- Alpha1-receptors

Cholinergic
- M1
- M3
- M5
Adenylate Cyclase

G-Protein coupled receptors
- Stimulate All Beta-receptors
  - D1, D5-receptors
- Inhibit Alpha2-receptors
  - D2, D3, D4-receptors
  - M2, M4-receptors

Hepatocyte

- norepinephrine / epinephrine
  - IP3 / DAG
  - Ca++ / PKC
  - ↑ glucose-1-P
glycogenolysis

- β2-AR
  - ↑ cAMP
  - protein kinase A
  - phosphorylase kinase
  - phosphorylase a
glycogenolysis

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 – Beta agonists

- 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, pirenalbetaline

  - 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 (prodrug), guanafacine

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

  - Side effects: impotence, dry mouth, rebound HT

Vasculature

- norepinephrine / epinephrine
  - IP3 / DAG
  - Ca++ / PKC
  - Vasoconstriction
  - Increase resistance
  - Increase BP

- β2-AR
  - ↑ cAMP
  - Vasodilation
  - Decrease resistance
  - Decrease BP

- α1-AR
  - Decrease resistance
  - Decrease BP

Non-Catecholamines – Alpha agonists

- DOC
  - Drug of Choice

Non-Catecholamines – Beta agonists

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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)

Indirectly-acting Sympathomimetics (cont.)

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- **Tyramine** (not a drug, interaction with MAO inhibitors)

**Neuronal Uptake Inhibition**

- Inhibit neuronal uptake (Uptake1)
- 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, amitriptyline)
  - High dose: block alpha- & M-rec.
- Atomoxetine (used for ADHD)
- Guanethidine (competes for uptake)

**Parkinson's Disease**

- **General population:** 1:1000, over 60 1:75
- **Tremor, stiffness, or slowness, 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: benztropine
  - Decarboxylase inhibitor: carbidopa
  - Amantadine: inhibit D-uptake, M-rec, NMDA-block, release dopamine

**MAO vs COMT**

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<thead>
<tr>
<th>MAO</th>
<th>COMT</th>
</tr>
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<tbody>
<tr>
<td>Platelets</td>
<td>(MAOg)</td>
</tr>
<tr>
<td>Liver, kidney, brain</td>
<td>(MAOg + MAo)</td>
</tr>
<tr>
<td>Increased to block uptake, decreased release by tyramine-like drugs</td>
<td></td>
</tr>
<tr>
<td>Decreased (MAOe-selective)</td>
<td></td>
</tr>
<tr>
<td>Selegiline (MAOe-selective)</td>
<td></td>
</tr>
<tr>
<td>Atomoxetine (MAOe-selective)</td>
<td></td>
</tr>
<tr>
<td>Decreased (MAOe-selective)</td>
<td></td>
</tr>
<tr>
<td>Increased (COMT-selective)</td>
<td></td>
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<tr>
<td>Carbidopa (COMT-selective)</td>
<td></td>
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<tr>
<td>Increased (COMT-selective)</td>
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Tyramine Interaction with MAO Inhibitors
Can cause hypertensive crisis (↑BP, ↑HR)

Aged cheese & red wine are rich in tyramine

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

Tyramine Interaction with MAO Inhibitors
Can cause hypertensive crisis (↑BP, ↑HR)

Aged cheese & red wine are rich in tyramine

Therapeutic uses: Sympathomimetics 1
- Asthma (major use)
  - bronchodilation with ↓airway resistance
  - β2-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

Epinephrine

Anaphylaxis
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, α-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 isoproteol

Therapeutic uses: Sympathomimetics 3

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