Pharmacology of the Sympathetic Nervous System

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Neurons of the ANS

Adrenergic Nerve Terminal

MAO vs COMT

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

Inhibitors: Tranylcypromine, Pargyline
  Depression

Inhibitors: Clorgiline
  Selective MAO-A

Inhibitors: Selegiline
  MAO-B
Adrenergic Agents – Relative Selectivity

<table>
<thead>
<tr>
<th>RECEPTOR</th>
<th>TISSUE</th>
<th>ACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha1</td>
<td>Coronary blood vessels, heart</td>
<td>Constriction, dilatation</td>
</tr>
<tr>
<td>EPI &gt;&gt; NE &gt;&gt; ISO</td>
<td>Contraction, relaxation</td>
<td></td>
</tr>
<tr>
<td>Alpha2</td>
<td>Platelets, smooth muscle</td>
<td>Aggregation, inhibition of lipolysis</td>
</tr>
<tr>
<td>NE &gt; EPI &gt;&gt; ISO</td>
<td>Contraction, relaxation</td>
<td></td>
</tr>
<tr>
<td>Beta1</td>
<td>Heart, smooth muscle</td>
<td>Force, rate, conduction velocity</td>
</tr>
<tr>
<td>ISO = EPI = NE</td>
<td>Release, relaxation</td>
<td></td>
</tr>
<tr>
<td>Beta2</td>
<td>Smooth muscle, lung</td>
<td>Relaxation, relaxation</td>
</tr>
<tr>
<td>ISO &gt; EPI &gt; NE</td>
<td>Smooth muscle, relaxation</td>
<td></td>
</tr>
<tr>
<td>Alpha4</td>
<td>Fat cells</td>
<td>Lipolysis</td>
</tr>
</tbody>
</table>

Adrenergic / Cholinergic Agents

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>G Protein</th>
<th>2nd Messenger</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1</td>
<td>Effector tissues, smooth muscle, glands</td>
<td>Gq</td>
<td>Ca++, IP3, DAG</td>
</tr>
<tr>
<td>α2</td>
<td>Nerve endings, smooth muscle</td>
<td>Gi</td>
<td>cAMP</td>
</tr>
<tr>
<td>β1</td>
<td>Cardiac muscle, juxtaglomerular apparatus</td>
<td>Gs</td>
<td>cAMP</td>
</tr>
<tr>
<td>β2</td>
<td>Smooth muscle, lung</td>
<td>Gs</td>
<td>cAMP</td>
</tr>
<tr>
<td>β3</td>
<td>Adipose cells</td>
<td>Gs</td>
<td>cAMP</td>
</tr>
<tr>
<td>D1, D3</td>
<td>Renal, vascular SM, brain</td>
<td>Gs</td>
<td>cAMP</td>
</tr>
<tr>
<td>D2, D3, D4</td>
<td>Brain, cardiovascular</td>
<td>Gi</td>
<td>cAMP</td>
</tr>
</tbody>
</table>

Phospholipase C

G-Protein coupled receptors

Alpha1-receptors

Cholinergic
M1
M3
M5

Hepatocyte

Adrenergic

β2-AR

↑ cAMP

protein kinase A

phosphorylase kinase

β1-AR

IP3 / DAG

Ca++ / PKC

Ca++-dependent
phosphorylase K.

phosphorylase a

glycogenolysis

↑ glucose-1-P

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 – septic shock)
- Precursor of NE and EPI
- Activates dopamine- (low dose), beta1- (moderate dose), alpha1-receptors (high dose)
- 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, metaproterenol, salmeterol (LABA)
  terbutaline, ritodrine
  
  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, pirenteronol
  
  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-methylidopa (pro-drug), guanfacine
  
  Uses: chronic hypertension (CNS action)
  Opioid withdrawal (decrease severity)

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

Dexmedetomidine: CNS action, 2A selectivity, iv for sedation/analgesia in surgery, less respiratory depression, increasing use. Caution: hypovolemic patient

Tizanidine: CNS action to ↓muscle spasticity, CYP1A2

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**Alpha₂-Adrenoceptors**

CNS: hypotension, bradycardia, sedation, analgesia and ↓ muscle spasticity

Peripheral: ↓ salivation, ↓ secretion, ↓ bowel motility, contraction of vascular smooth muscle, diuresis

**Dopamine Agonists**

- **Fenoldopam:**
  - D₁A-agonist, no action on α₁- or β-receptors
  - used for acute hypertension
  - iv short-term infusion (<48 hrs)
  - SE: ↑ ocular pressure, ↑ HR

- **Bromocriptine, Pramipexole:**
  - Parkinson’s Disease
  - Restless leg syndrome (RLS)
  - SE: drowsiness

**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 options:**
  - MAO inhibitors:
  - Dopamine agonists: bromocriptine pramipexole
  - L-Dopa
  - Anticholinergics: benztropine
  - Decarboxylase inhibitor: carbidopa
  - COMT inhibition

**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)

**Tachyphylaxis**

1. Release of NE/DA from neurons
2. Inhibition of monoamine transmitter uptake
3. Binding to extracellular receptors
4. Inhibition of MAO

**Amphetamine Action**

1. Release of NE/DA from neurons
2. Inhibition of monoamine transmitter uptake
3. Binding to extracellular receptors
4. Inhibition of MAO
Indirectly-acting Sympathomimetics (cont.)

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**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)

**Tyramine Interaction with MAO Inhibitors**

- **Can cause hypertensive crisis (↑BP, ↑HR)**

- **Aged cheese & red wine are rich in tyramine**

**Table: MAO vs COMT**

<table>
<thead>
<tr>
<th></th>
<th>MAO</th>
<th>COMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location in cell</td>
<td>Mitochondrial outer membrane</td>
<td>Cytosol</td>
</tr>
<tr>
<td>Location in body</td>
<td>Symp. nerve, placenta (MAO_A)</td>
<td>Liver, kidney, brain (MAO_A, MAO_B)</td>
</tr>
<tr>
<td>Effect of inhibition on NE levels</td>
<td>Increases NE level in symp. neuron, potentiates release of tyramine-like drugs</td>
<td>None/Minor effect</td>
</tr>
<tr>
<td>Inhibitors</td>
<td>Pargyline, tranylcypromine (non-selective)</td>
<td>Tolcapone, Entacapone, Pyrogallol</td>
</tr>
<tr>
<td>Clinical use of inhibitors</td>
<td>Depression (non-selective or MAO_A-selective)</td>
<td>Parkinson’s D</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>
<td>None, liver failure</td>
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  - Anticholinergics: benztropine
  - COMT inhibition

**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
  - beta2-selective agents eg. albuterol

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

- **Nasal Congestion** (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)
  - Acute: fenoldopam (D1A-agonist)

- **Shock** (Hypotension, need to treat cause)
  - dopamine (DOC), epinephrine, NE
  - blood loss, cardiac failure, septic shock
  - ↓tissue perfusion, need to maintain BP, cerebral flow

- **Congestive Heart Failure** (acute)
  - dobutamine, (dopamine)

- **Cardiac Heart Block & Cardiac Arrest**
  - epinephrine or isoproterenol

Therapeutic uses: Sympathomimetics 3

- **Parkinson’s Disease**
  - Inhibitors: MAO-B: selegiline, COMT: tolcapone
  - D-agonists: pramipexole Precursor: L-Dopa

- **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: - amphetamines
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**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