Pharmacology of the Sympathetic Nervous System I
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Sympathetic Nervous System
Norepinephrine (NE) = Noradrenaline (NA)
Epinephrine (EPI) = Adrenaline (AD, ADR)
Noradrenergic = Adrenergic
Isoproterenol = Isoprenaline (ISO)

Adrenergic Nerve Terminal

Noradrenergic Neuron

Steps in the synthesis of dopamine, norepinephrine and epinephrine

Neuronal (Uptake1) vs Extraneuronal (Uptake2)

Neuronal Uptake
70-80%
- Cocaine
- TCA
- MAO

Extraneuronal
10-20%
- COMT

MAO vs COMT

<table>
<thead>
<tr>
<th>MAO vs COMT</th>
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<tbody>
<tr>
<td>MAO (A, B)</td>
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Release by tyramine-like drugs
**Inhibitors:**

- **Pyrogallol, Tropolone**

**MAO vs COMT**

Inhibitors: Non-selective

- Depression: Tranylcypromine, Pargyline

**Depression**

Inhibitors: Selective

- Parkinson’s: MAO-A Clorgiline

- MAO-B: Selegiline

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**Metabolism of Catecholamines**

Major Metabolites

- VMA

**VMA, MOPEG**

- MAO

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

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**Receptor Subtypes**

**α-Receptors**

- α1A

- α1B

- α1C

- α1D

- α2A

- α2B

- α2C

- α2D

**β-Receptors**

- β1

- β2

- β3

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**Second Messengers**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
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<tr>
<td>α1-Receptors</td>
<td>smooth muscle, glands</td>
</tr>
<tr>
<td>α2-Receptors</td>
<td>nerve endings, some smooth muscle</td>
</tr>
<tr>
<td>β-Receptors</td>
<td>heart, coronary blood vessels, kidney</td>
</tr>
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**Phospholipase C**

G-Protein coupled receptors

- Adrenergic

- Alpha1-receptors

- Cholinergic

- M1

- M3

- M5

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**Adrenergic Agents – Relative Selectivity**

**Receptor**

**Tissue**

**Actions**

- **α1**

  - smooth muscle, glands

  - Gq

  - ↑Ca²⁺, ↑IP₃, DAG

  - Contraction, dilation

- **α2**

  - nerve endings, some smooth muscle

  - Gi

  - ↓cAMP

- **β1**

  - cardiac muscle, juxtaglomerular apparatus

  - Gs

  - ↑cAMP

- **β2**

  - smooth muscle, lung

  - Gs

  - ↑cAMP

- **β3**

  - adipose cells

  - Gs

  - ↑cAMP

- **D1, D5**

  - renal, vascular smooth muscle, brain

  - Gs

  - ↑cAMP

- **D2, D3, D4**

  - brain, cardiovascular

  - Gi

  - ↓cAMP

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**Phospholipase C**

- Sympathetic outflow causes release of NE and norepinephrine, which activates α1-receptors to cause Ca²⁺ release and contraction of smooth muscle.
Adenylate Cyclase

G-Protein coupled receptors

Stimulate All Beta-receptors D1, D5-receptors

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

Stimulate

β2-AR

IP3 / DAG

Ca++ / PKC

↑ cAMP

β

Glucose-1-P

β2-AR

↑ glycogenolysis

Inhibit

α1-AR

IP3 / DAG

Ca++ / PKC

↓ protein kinase A

↓ phosphorylase kinase

↓ phosphorylase a

↓ glycogenolysis

Hepatocyte

norepinephrine / epinephrine

β2-AR

IP3 / DAG

Ca++ / PKC

Ca++-dependent phosphorylase K.

phosphorylase a

glycogenolysis

↑ glucose-1-P

Vasculature

norepinephrine / epinephrine

α1-AR

β2-AR

IP3 / DAG

Ca++ / PKC

Vasoconstriction

Increase resistance

Decrease resistance

Increase BP

Decrease BP

Catecholamines

A. Norepinephrine (limited use, pressor agent, shock)

• Activates: both α, β1, β2, β3 (weakest)
• Substrate for MAO & COMT, does not cross BBB

B. Epinephrine (DOC - Allergic reaction)

• Activates both α, β1, β2, β3 (weakest)
• Substrate for MAO & COMT, does not cross BBB

C. Dopamine (DOC – shock)

• Precursor of NE and EPI
• Activates α1, dopamine receptors
• Substrate for MAO & COMT, does not cross BBB

D. Isoproterenol (asthma, cardiac stimulant)

• Activates all β receptors
• Substrate for COMT, does not cross BBB

Non-Catecholamines – Beta agonists

• Selective β2-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 β1-agonists: dobutamine, prenalteron

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

Non-Catecholamines – Alpha agonists

• Selective α1-agonists: methoxamine, phenylephrine, metaraminol (direct & indirect actions, orally active)

Uses: hypotension or shock, nasal decongestant

• Selective α2-agonists: clonidine, α-methylidopa (prodrug), guanfacine

Uses: hypertension (CNS action)

opioid withdrawal (decrease severity)

Side effects: impotence, dry mouth, rebound HT
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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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 (ie. 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)

MAO vs COMT

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<tr>
<td>Location</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 + MAOB)</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>Most tissues, not in sympathic nerve</td>
</tr>
<tr>
<td>Effect of inhibition on NE levels</td>
<td>Increases NE level in symp. neuron, potentiates release by tyramine-like drugs</td>
<td>No effect</td>
</tr>
<tr>
<td>Inhibitors</td>
<td>Pargyline, tranylcypromine (non-selective)</td>
<td>Clorgyline (MAOA-selective)</td>
</tr>
<tr>
<td>Clinical use of inhibitors</td>
<td>Mental depression (non-selective or MAOA-selective)</td>
<td>Parkinson's disease (MAOB-selective)</td>
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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:
  benzhexol
  Decarboxylase inhibitor:
  carbidopa
  Amantadine: inhibit D-uptake, M-rec; NMDA-block, release dopamine
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

bronchoconstriction
Secretions
↓Blood pressure
Epinephrine
  - bronchodilation
  - vasoconstriction
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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 isoproterenol

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