Pharmacology of the Sympathetic Nervous System I

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Neurons of the ANS

Sympathetic Nervous System

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

Adrenergic Nerve Terminal

Steps in the synthesis of dopamine, norepinephrine and epinephrine:

Noradrenergic Neuron

Neuronal (Uptake1) vs Extraneuronal (Uptake2)

Neuronal Uptake
- Uptake 1: 70-80%
- Cocaine
- TCA
- MAO

Extraneuronal Uptake
- Uptake 2: 10-20%
- COMT
MAO vs COMT

<table>
<thead>
<tr>
<th>Location in cell</th>
<th>MAO</th>
<th>COMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitochondrial outer membrane</td>
<td>symp. nerve, placenta, platelets (MAO_A), liver, kidney, brain (MAO_A + MAO_B)</td>
<td>cytosol</td>
</tr>
</tbody>
</table>

**Effect of inhibition on NE levels**
- Increases NE level in symp. neuron, potentiates release by tyramine-like drugs
- Minor/no effect

**Location in body**
- Most tissues, not in symp. nerve

**Inhibitors**
- Depression: Tranylcypromine, Pargyline
- Parkinson's D: Selegiline, Clorgiline
- Non-selective: Tolcapone, Pyrogallol

**Inactivation**
- Metabolism by MAO or COMT

**Metabolism of Catecholamines**

**Major Metabolites**
- VMA
- MOPEG

**Adrenergic Agents – Relative Selectivity**

<table>
<thead>
<tr>
<th>RECEPTOR</th>
<th>TISSUE</th>
<th>ACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha1</td>
<td>most vascular smooth muscle, sympathetic dilator muscle, pilomotor smooth muscle</td>
<td>contraction, relaxation of blood vessels</td>
</tr>
<tr>
<td>Alpha2</td>
<td>some vascular smooth muscle, sympathetic nerve terminals, NE &amp; Ach</td>
<td>contraction, regulation of neurotransmitter release</td>
</tr>
<tr>
<td>Beta1</td>
<td>heart, coronary blood vessels</td>
<td>force, rate, conduction velocity, relaxation of blood vessels</td>
</tr>
<tr>
<td>Beta2</td>
<td>bronchial smooth muscle, uterus smooth muscle, visceral smooth muscle</td>
<td>relaxation, facilitation of release</td>
</tr>
<tr>
<td>Beta3</td>
<td>NA nerve terminals, fat cells</td>
<td>relaxation, facilitation of release</td>
</tr>
</tbody>
</table>

**Second Messengers**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>G Protein</th>
<th>2\textsuperscript{nd} Messenger</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1</td>
<td>Effector tissues: smooth muscle, glands</td>
<td>Gq</td>
<td>TCa\textsuperscript{2}, TIP\textsubscript{3}, 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>TcAMP</td>
</tr>
<tr>
<td>β2</td>
<td>Smooth muscle, lung</td>
<td>Gs</td>
<td>TcAMP</td>
</tr>
<tr>
<td>β3</td>
<td>Adipose cells</td>
<td>Gs</td>
<td>TcAMP</td>
</tr>
<tr>
<td>D\textsubscript{1}, D\textsubscript{2}</td>
<td>Renal, vascular SM, brain</td>
<td>Gs</td>
<td>TcAMP</td>
</tr>
<tr>
<td>D\textsubscript{3}, D\textsubscript{4}</td>
<td>Brain, cardiovascular</td>
<td>Gs</td>
<td>TcAMP</td>
</tr>
</tbody>
</table>
Phospholipase C

Adenylate Cyclase

G-Protein coupled receptors

Stimulate All Beta-receptors

D1, D5-receptors

Inhibit Alpha2-receptors

D2, D3, D4-receptors

M2, M4-receptors

Adrenergic

Alpha1-receptors

Cholinergic

M1

M3

M5

G-Protein coupled receptors

Hepatocyte

Vasculature

Catecholamines

Non-Catecholamines - Beta agonists

A. Norepinephrine (limited use, pressor agent, shock)
   - Activates: both alpha, beta1, beta2 (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)
   - 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

- 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, prenalterol
  - 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), guanfacine
  
  Uses: hypertension (CNS action)
  
  **Side effects**: impotence, dry mouth, rebound HT

Dopamine Agonists

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

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

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

- **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

Crystal Meth Drug Abuse

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.

After 1.5 years of drug use
Indirectly-acting Sympathomimetics (cont.)

- 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)

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)

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<td></td>
<td>platelets (MAO&lt;sub&gt;3&lt;/sub&gt;)</td>
</tr>
<tr>
<td></td>
<td>liver, kidney, brain (MAO&lt;sub&gt;, MAO&lt;sub&gt;B&lt;/sub&gt;&lt;/sub&gt;)</td>
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<td><strong>Effect of inhibition on NE levels</strong></td>
<td>Increases NE level in symp. neuron, potentiates release by tyramine-like drugs</td>
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<td><strong>Inhibitors</strong></td>
<td>Pargyline, tranylcypromine (non-selective)</td>
</tr>
<tr>
<td></td>
<td>Clorgyline (MAO&lt;sub&gt;, MAO&lt;sub&gt;B&lt;/sub&gt;&lt;/sub&gt;-selective)</td>
</tr>
<tr>
<td></td>
<td>Selegiline (MAO&lt;sub&gt;, MAO&lt;sub&gt;B&lt;/sub&gt;&lt;/sub&gt;-selective)</td>
</tr>
<tr>
<td><strong>Clinical use of inhibitors</strong></td>
<td>Depression (non-selective or MAO&lt;sub&gt;B&lt;/sub&gt;-selective)</td>
</tr>
<tr>
<td></td>
<td>Parkinson’s disease (MAO&lt;sub&gt;, MAO&lt;sub&gt;B&lt;/sub&gt;&lt;/sub&gt;-selective)</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>MAO inhibitors potentiate effects of tyramine (due mainly to blocking metabolism of tyramine by MAO in liver)</td>
</tr>
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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 options:
    
    - MAO inhibitors:
      
      - Dopamine agonists: bromocriptine, pramipexole
    
    - L-Dopa
    
    - Anticholinergics: benztropine
    
    - Decarboxylase inhibitor: carbidopa
    
    - Amantadine: inhibit D-uptake, M-rec, NMDA-block, release dopamine

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<th>MAOI and Tyramine Crisis</th>
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<tr>
<td>Blood pressure, Heart rate</td>
<td>Treatment: α-blocker or labetolol (α-, β-blocker)</td>
</tr>
<tr>
<td>Normally dietary tyramine is metabolized by MAO</td>
<td></td>
</tr>
<tr>
<td>With MAO inhibition, octopamine is produced and stored in vesicles with NE</td>
<td></td>
</tr>
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<td>Aged cheese, red wine are rich in tyramine</td>
<td></td>
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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
- bronchodilation with ↓airway resistance
- β2-selective agents eg. albuterol
- bronchodilation
- β2-selective agonists
- inhalation vs oral
- less side effects
- Ritodrine
- premature labor

Therapeutic uses: Sympathomimetics 2
- Hypertension
  - Chronic: centrally acting α2-receptor agonists (clonidine, α-methyl-dopa)
  - Acute: fenoldopam (D1A-agonist)
- Shock (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
  - dobutamine (acute)
- Cardiac Heart Block & Cardiac Arrest
  - epinephrine or isoproterenol
Therapeutic uses: Sympathomimetics

- 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 Contractions
  - suppress premature labor
  - ritodrine, terbutaline (not FDA approved)

- Hyperactivity Disorder (ADHD)
  - amphetamines, methylphenidate (ritalin)
  - NE uptake inhibition: atomoxetine

- Others: [obesity], narcolepsy: - amphetamines

Parkinson's Disease

- General population 1:1000, over 60 1:75
- Tremor, stiffness, or clumsiness, usually involving one side, difficulty walking, fatigue, depression
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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