Learning Objectives:

Understand the mechanism of action of drugs acting at different levels of the sympathetic nervous system:

a) at sites in the CNS to affect sympathetic “tone”

b) at sympathetic ganglia

c) at enzymes involved in the synthesis of epinephrine (EPI) & norepinephrine (NE)

d) at sites of catecholamine storage, release, uptake or metabolism at the postganglionic sympathetic nerve terminal

e) at pre- and post-synaptic adrenergic receptors

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

I. SYNTHESIS OF TRANSMITTER (Figs. 2A,B)

The amino acid tyrosine enters the neuron by active transport. In the cytosol, tyrosine is converted by the enzyme tyrosine hydroxylase to dihydroxyphenylalanine (DOPA), which is converted to dopamine (DA) by the enzyme DOPA decarboxylase. Dopamine is actively transported into storage vesicles where dopamine-β-hydroxylase converts dopamine to norepinephrine (NE). This is the end product in sympathetic nerve terminals. Rate-limiting step: Tyrosine hydroxylase. 50% of the dopamine synthesized is metabolized by monoamine oxidase (MAO) before entering the storage vesicle.

In the adrenal medulla, norepinephrine is converted to epinephrine (EPI) by the enzyme phenylethanolamine N-methyltransferase.

II. STORAGE OF TRANSMITTER

The active transport of dopamine into granular storage vesicles is necessary for the formation of NE because of the localization of dopamine-β-hydroxylase inside the vesicles. NE is stored in association with ATP (4:1). Vesicles “leaky” - NE must be pumped back.
Schematic diagram of a generalized noradrenergic junction.

1. Tyrosine (Tyr) is transported into nerve terminal (varicosity) by sodium-dependent carrier.
2. Tyr converted to dopamine, then transported into storage vesicle (inhibited by reserpine).
3. Dopamine is converted to NE by dopamine-β-hydroxylase. The conversion of NE to epinephrine occurs only in the adrenal medulla and some brain regions.
4. Transmitter release occurs when an action potential opens voltage-sensitive calcium channels and increases intracellular calcium. Release inhibited by guanethidine and bretylium.
5. Released NE can activate post- and presynaptic receptors.
6. Response terminated by neuronal uptake, extraneuronal uptake and diffusion out of the cleft.
7. Enzymatic inactivation by MAO (important) and COMT (Catechol-O-Methyl Transferase, not clinically important).

III. RELEASE OF TRANSMITTER AND AUTOREGULATION

Arrival of an action potential at the sympathetic neuron causes depolarization of the membrane of the varicosities. NE is released from the storage vesicles by an exocytotic process: the vesicular and neuronal membranes fuse, an opening forms and the contents of the vesicle are delivered into the synaptic cleft. Release of NE is regulated by feedback mechanisms 'autoreceptors'. Released NE can activate presynaptic α2-adrenoceptors to inhibit further transmitter release and/or presynaptic β2-adrenoceptors to enhance transmitter release (more important for circulating catecholamines eg. EPI).
IV. TERMINATION OF TRANSMITTER RESPONSE (Figs. 3,3B)

A. **Reuptake into the noradrenergic neuron:** (most important, 70-80%, neuronal uptake, uptake 1), followed by re-entry into the storage vesicles and/or enzymatic inactivation (MAO). This is the most important mechanism (NE > EPI. ISO not transported). Inhibited by cocaine, imipramine.

B. **Active transport into the effector cells** (10-20%, extraneuronal uptake, uptake 2) followed by enzymatic inactivation (EPI > NE).

C. **Passage into the circulation and enzymatic destruction in the liver** by MAO and COMT.

Relative proportion of the different mechanisms depends on:

i. Size of synaptic junction    ii. Density of innervation
iii. Neuronal release of transmitter (NE) iv. Circulating transmitter (EPI, NE)
Enzymatic metabolism of catecholamines

a. Monoamine Oxidase (MAO, outer mitochondrial membrane)
b. Catechol-O-Methyltransferase (COMT)

- Major urinary metabolites:
  3-methoxy-4-hydroxyphenylethylene glycol (MOPEG) and
  3-methoxy-4-hydroxymandelic acid (VMA)

- Inhibitors of MAO and COMT have little prompt effects

<table>
<thead>
<tr>
<th>MAO (important)</th>
<th>COMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location in cell</td>
<td>Outer mitochondrial membrane</td>
</tr>
<tr>
<td>Location in body</td>
<td>Symp. nerve, placenta (MAO_A)</td>
</tr>
<tr>
<td></td>
<td>platelets (MAO_B)</td>
</tr>
<tr>
<td></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 by tyramine-like drugs</td>
</tr>
</tbody>
</table>

![Chemical structures](image)
V. ADRENERGIC RECEPTOR SUBTYPES

\[
\begin{align*}
\text{Alpha}_1: & \quad \text{EPI} \geq \text{NE} \gg \text{ISO} & \text{Beta}_1: & \quad \text{ISO} \geq \text{EPI} = \text{NE} \\
\text{Alpha}_2: & \quad \text{NE} > \text{EPI} \gg \text{ISO} & \text{Beta}_2: & \quad \text{ISO} \geq \text{EPI} \gg \text{NE} \\
& \quad \text{Beta}_3: & \quad \text{ISO} = \text{NE} > \text{EPI} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Tissue</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha₁</td>
<td>Most vascular smooth muscle</td>
<td>Contraction</td>
</tr>
<tr>
<td>Pupillary dilator muscle</td>
<td>Contraction (dilation)</td>
<td></td>
</tr>
<tr>
<td>Pilomotor smooth muscle</td>
<td>Erects hair</td>
<td></td>
</tr>
<tr>
<td>Vas deferens</td>
<td>Contraction</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>Glycogenolysis</td>
<td></td>
</tr>
<tr>
<td>Intestinal smooth muscle</td>
<td>Relaxation</td>
<td></td>
</tr>
<tr>
<td>Intestinal sphincters</td>
<td>Contraction</td>
<td></td>
</tr>
</tbody>
</table>

| Alpha₂  | Some vascular smooth muscle | Contraction |
| Nerve terminals (NE & ACh) | Inhibit transmitter release |
| Platelets | Aggregation |
| Fat cells | Inhibition of lipolysis |

| Beta₁  | Heart | Increase force, rate, cond. velocity |
| Coronary blood vessels | Dilatation |
| Kidney | Renin release |

| Beta₂  | Bronchial smooth muscle | Relaxation |
| Intestinal smooth muscle | Relaxation |
| Uterine smooth muscle | Relaxation |
| Vascular smooth muscle | Relaxation |
| NA nerve terminals | Facilitation of release |

| Beta₃  | Fat cells | Lipolysis |

VI. SECOND MESSENGER SYSTEMS FIGS. 4A,B

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>G Protein</th>
<th>Second Messenger</th>
</tr>
</thead>
<tbody>
<tr>
<td>α₁</td>
<td>Effector tissues: smooth muscle, glands</td>
<td>Gq</td>
<td>↑Ca²⁺, ↑IP₃, DAG</td>
</tr>
<tr>
<td>α₂</td>
<td>Nerve endings, some smooth muscle</td>
<td>Gi</td>
<td>↓cAMP</td>
</tr>
<tr>
<td>β₁</td>
<td>Heart, 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, D₅</td>
<td>Vascular smooth muscle, brain, renal</td>
<td>Gs</td>
<td>↑cAMP</td>
</tr>
<tr>
<td>D₂, D₃, D₄</td>
<td>Brain, cardiovascular system</td>
<td>Gi</td>
<td>↓cAMP</td>
</tr>
</tbody>
</table>
Schematic representation of adrenergic receptors and their second messenger systems.

**FIG. 4A**

**FIG. 4B**
VII. AGONISTS: SYMPATHOMIMETIC AGENTS

Sympathomimetic agents can be divided into three classes:

Directly acting: combine with alpha- and/or beta-adrenoceptors and hence activate them directly (eg. Epinephrine EPI; norepinephrine NE).

Indirectly acting: act by release (displacement) of NE from sympathetic nerve terminals; the released NE then activates the receptor (eg. tyramine, amphetamine).

Mixed acting: have both direct and indirect activity (eg. ephedrine).

A. Directly Acting Sympathomimetics

1. Catecholamines (CAs). The catecholamines may be thought of as being derived from the following 'parent compound': phenylethylamine. Most of the agonists, such as epinephrine (EPI), norepinephrine (NE), dopamine (DA), isoproterenol (ISO) and others have hydroxyl groups on the ring in the #3 or #4 positions.

   a. Norepinephrine (noradrenaline):
      - Activates: both alpha, beta_1, beta_3, beta_2 (weakest) receptors
      - Substrate for MAO & COMT, does not cross BBB

   b. Epinephrine (adrenaline):
      - Activates both alpha, beta_1, beta_2, beta_3 (weakest) receptors
      - Substrate for MAO & COMT, does not cross BBB
      - Drug of choice: Acute hypersensitivity reactions (anaphylaxis)

   c. Dopamine: - precursor of NE and EPI
      - Activates alpha_1, beta_1, dopamine receptors
      - Substrate for MAO & COMT, does not cross BBB
      - Drug of choice: Shock (septic), i.v. infusion, maintains renal blood flow (D_1-receptor → dilation)

   d. Isoproterenol (isoprenaline, synthetic, not endogenous):
      - Activates all beta receptors
      - Substrate for COMT, does not cross BBB
2. **Non-Catecholamines.** Most still retain phenylethylamine skeleton, benzene ring is sometimes substituted. Note these agents are generally not good substrates for COMT which requires both hydroxyl groups. Substitutions on the alpha carbon decreases MAO activity.

a. **Selective beta\(_2\)-agonists:** Albuterol, ritodrine, terbutaline, metaproterenol
   - major use in the treatment of asthma (ie. Albuterol)
   - may be administered orally or by inhalation
     Oral: onset 1-2 hrs, 4-6 hrs duration
     Inhalation: onset 5-10 min, 3-4 hrs duration
   - premature labor, relax uterus, ritodrine
   - relax bronchial smooth muscle, ↓ airway resistance
   - adverse effects: cardiovascular side effects (HR, BP), less by inhalation compared to oral administration

b. **Selective beta\(_1\)-agonists:** Dobutamine, Prenalternol
   - cardiac stimulant, congestive heart failure (acute)
     (tolerance/desensitization)
   - ↑ force without significant HR or O\(_2\) increases

c. **Selective alpha\(_1\)-agonists:** Methoxamine, phenylephrine
   - limited clinical use
   - used in the treatment of hypotension or shock
   - phenylephrine also used as a nasal decongestant
   - adverse effects: cardiovascular side effects (↑BP)

d. **Selective alpha\(_2\)-agonists:** Clonidine, guanfacine, α-methyldopa (prodrug)
   - used in the treatment of hypertension, opiate withdrawal
   - central action (medulla oblongata) on postjunctional α\(_2\)-receptors to decrease sympathetic outflow → ↓ BP
   - adverse effects: dry mouth, impotence, sedation, rebound hypertension upon withdrawal

**Question:** How does Dobutamine, beta\(_1\) agonist, increase contractility but not HR?
**Answer:** The actions of dobutamine are complex. Racemic dobutamine has 2 isomers (-) and (+). (-)-dobutamine is thought to have alpha\(_1\)-agonist action, whereas the (+)-dobutamine is thought to have alpha-antagonist activity which could block the effects of the (-)-isomer. (+)-Dobutamine is more potent (10x) than (-)-isomer on beta-receptors. Dobutamine has more prominent effects on iontropic (force) than heart rate compared to isoproterenol. The reason for the selectivity is still unclear. It may be in part due to the fact that peripheral resistance is relatively unchanged (ISO BP is decreased). Alternately, cardiac alpha\(_1\)-receptors (yes they are also present) may contribute to the inotropic effect.
B. Indirectly Acting Sympathomimetics:

1. Displacement of Transmitter:

Act by release (displacement) of NE from sympathetic nerve terminals; the released NE then activates the receptor(s). Compete with NE for uptake 1 (Fig. 5A). Commonly cause tachyphylaxis (Fig 5B).

a. **Amphetamine, methamphetamine** (greater CNS activity), **Methylphenidate** (Ritalin)

- powerful CNS stimulant, performance enhancer, physical and mental (abuse)
- ↑alertness, mood, self-confidence, concentration
- depression of appetite (?), tolerance (tachyphylaxis)
- toxicity: cardiovascular, restlessness, tremor, insomnia
- tolerance and psychological dependence develops

b. **Ephedrine** (mixed action)

- direct action (alpha- and beta-receptors)
- indirect action to release norepinephrine

c. **Tyramine**

- Not a drug, found in food sources eg. beer, red wine, aged cheeses.
- Interaction with MAO inhibitors
- Can precipitate a hypertensive crisis (↑BP, ↑HR)

**Question:** What is the difference between Tachyphylaxis and Tolerance?

**Answer:** Tachyphylaxis means rapidly diminishing response. It is common with the amphetamine type compounds. These compounds cause displacement of transmitter (NE) from the storage vesicles. There appears to be a limited amount of transmitter available for this type of release. When these stores are depleted the response to these agents is also reduced. This diminished response can occur within hours/days, dose to dose. Whereas tolerance is a long term reduction (adaptation) in response ie. Develops over weeks/months.
2. Inhibition of NE reuptake (Fig. 6)

Inhibition of the neuronal uptake (70-80%) mechanism can:
- prevent the action of indirectly acting agents (e.g. amphetamine)
- inhibit the actions of agents that require neuronal uptake to gain access into the varicosity (e.g. guanethidine, not major effect)
- potentiate the effects of NE (ie. not removed from synaptic junction).

a. Cocaine

b. Tricyclic antidepressants - imipramine, amitriptylline, clomipramine (tricyclics have significant muscarinic- and α-adrenoceptor blocking activity at high doses (overdose)

c. Atomoxetine (used for ADHD)

d. Guanethidine (competes with agents for neuronal uptake, not a major action of guanethidine, ie reduce effect of amphetamine)

![Figure 6. Blockade of NE re-uptake](image)

3. Inhibition of Metabolic Degradation of CAs (Figs. 3,3B).

a. Inhibition of COMT

Minor clinical importance
- pyragallol (experimental, toxic)
- tropolone (used in Parkinsons D. to decrease L-Dopa metabolism, associated with fatal liver failure)
b. Inhibition of MAO (Tranylcypromine, Pargyline, Phenelzine, Isocarboxazid)

- NE will accumulate in nerve terminal
- interaction with tyramine-like drugs (Fig. 7)

Two isozymes present:
- MAO-A (clorgyline, antidepressant)
- MAO-B (selegiline, Deprenyl, Parkinson’s Disease.)

<table>
<thead>
<tr>
<th>MAO</th>
<th>COMT</th>
</tr>
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<tbody>
<tr>
<td>Location in cell</td>
<td>mitochondrial membrane</td>
</tr>
<tr>
<td>Location in body</td>
<td>symp. nerve, placenta (MAO_A)</td>
</tr>
<tr>
<td></td>
<td>platelets (MAO_B)</td>
</tr>
<tr>
<td></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 by tyramine-like drugs</td>
</tr>
<tr>
<td>Inhibitors</td>
<td>tranylcypromine (non-selective)</td>
</tr>
<tr>
<td></td>
<td>clorgyline (MAO_A-selective)</td>
</tr>
<tr>
<td></td>
<td>selegiline (MAO_B-selective)</td>
</tr>
<tr>
<td>Clinical use of inhibitors</td>
<td>mental depression (non-selective or MAO_A-selective)</td>
</tr>
<tr>
<td></td>
<td>Parkinson’s disease (MAO_B-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>
</tr>
</tbody>
</table>

**Interaction Between Tyramine and Monoamine Oxidase Inhibition**

Tyramine is normally rapidly metabolized by MAO. However in the presence of MAO inhibitors such as tranylcypromine (non-selective) or clorgyline (MAO_A-selective), more NE is synthesized by the normal pathway and some NE is now produced from tyramine (this normally does not occur because of the action of MAO). This leads to increased content of NE in the storage vesicles. If an individual then consumes food rich in tyramine (e.g., aged cheese, red wine), then this tyramine is not metabolized by MAO and acts like amphetamine to cause displacement of NE. Since the vesicles have a large amount of transmitter, a large release occurs. The released NE causes a hypertensive crisis (↑BP, ↑HR).

Note: MAO_B-selective inhibitors are less likely to precipitate this reaction.
C. Therapeutic uses of Sympathomimetic Drugs

1. Asthma (major use)
   - bronchodilation with ↓airway resistance
   - beta2-selective agents eg. albuterol, terbutaline

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

3. Allergic Reactions (anaphylaxis)
   - acute hypersensitivity reactions (food, bee sting, drug allergy)
   - bronchospasm & hypotension due to histamine release
   - epinephrine (im) physiological antagonist: drug of choice

4. Hypotension (acute)
   - due to antihypertensive agents, spinal anesthesia, hemorrhage
   - α-receptor agonists: phenylephrine, methoxamine, metaraminol

5. Hypertension (chronic)
   - decrease sympathetic outflow from CNS
   - centrally acting α2-receptor agonists: clonidine, α-methyl-dopa

6. Shock (need to treat cause)
   - blood loss, cardiac failure, septic shock, cardiac obstruction
   - inadequate perfusion, requires immediate attention to maintain BP
   - dopamine iv (drug of choice), norepinephrine, epinephrine

7. Congestive Heart Failure
   - ↑cardiac performance without ↑demand on heart
   - dobutamine iv (not EPI or ISO)

8. Cardiac Heart Block & Cardiac Arrest
   - stimulate cardiac β1-receptors
   - epinephrine or isoproterenol

9. Ophthalmic
   - dilate the pupil (phenylephrine)
   - glaucoma
     - α1-receptor agonists eg. epinephrine (↑ outflow)
     - α2-receptor agonists eg. clonidine (↓ secretion)
     - β-receptor blockers eg. timolol (↓ secretion, most important)
10. **Premature Labor**
   - suppress uterine contractions: ritodrine, terbutaline (not FDA approved, cheaper & longer acting)

11. **Attention Deficit Hyperactivity Disorder (ADHD):**
   - Amphetamine-like agents ie. methylphenidate
   - NE-uptake inhibition: atomoxetine

12. **Other:**
   - Obesity (amphetamine-like agents)
   - Nacrolepsy (amphetamine-like agents)

D. **Toxic Effects of Sympathomimetic Agents**
   - Generally extensions of their receptor-mediated effects
   - Adverse cardiovascular effects can include:
     - excessive rise in blood pressure with pressor agents, which can give rise to cerebral hemorrhage
     - excessive myocardial stimulation can accompany the actions of beta-adrenoceptor agonists
   - CNS stimulation:
     - restlessness, dizziness, insomnia etc with sympathomimetics which can pass into the CNS eg. amphetamine.
   - - $\alpha_2$-receptor agonists
     - dry mouth, sedation, impotence,
E. Cardiovascular Effects Of Sympathomimetics

1. Sympathomimetics have prominent effects on the cardiovascular system. It is extremely important to keep in mind that autonomic function is under the control of the CNS; and that there are reflexes involved which may over ride any direct drug actions.

General hemodynamics: $BP = CO \times TPR$

$BP = \text{blood pressure}$ $TPR = \text{total peripheral arterial resistance}$

$CO = \text{cardiac output}$ $CO = \text{stroke volume} \times \text{heart rate}$

Integration: in order to maintain homeostasis and the appropriate coordinated autonomic state, the individual afferent and efferent components of the sympathetic and parasympathetic nervous systems are integrated within the CNS (Figs 8A,B).

![FIG. 8A](image)

Sites of action of the major classes of antihypertensive drugs.
2. The Baroreceptor Reflex Arc (response)

The baroreceptor reflex is the body's rapid response system for dealing with changes in blood pressure.

1. Pressure sensors in the carotid sinus and aortic arch respond to stretch caused by blood pressure changes.
2. Higher pressure causes increased signal firing and lower pressure leads to decreased firing.
3. Integration of the signal occurs in the nucleus tractus solitarius of the medulla oblongata in the brain.
4. If the BP is decreased the baroreflex will initiate responses to increase cardiac output and cause vasoconstriction.
5. If the BP is increased the baroreflex will initiate responses to decrease cardiac output and cause vasodilatation.

The baroreceptor reflex is concerned with changes in BP (either up or down), and not by changes in HR or pulse pressure. The strength of the reflex depends on the rate of change in BP (increase or decrease).

**Question:** What is the difference in the baroreflex response to therapeutic/high doses of EPI and NE?

High EPI will cause an increase in BP as the alpha1-mediated constriction dominates over the beta2-mediated vasodilation. Because of the significant increase in BP the baroreflex has been activated. It will try to lower BP by decreasing HR. However since EPI is such a potent beta1-agonist, the baroreflex evoked is weaker than EPI's direct action on the heart. Therefore we still see the tachycardia although it has been reduced by the reflex.

In contrast, in the case of NE, the reflex evoked is stronger than the direct effect of NE on the heart so we see an increase in BP with reflex bradycardia.
3. **Direct effects of activation of ANS receptors**

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Effect</th>
<th>TPR Effect</th>
<th>BP Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha&lt;sub&gt;1&lt;/sub&gt;</td>
<td>vasoconstriction</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Beta&lt;sub&gt;1&lt;/sub&gt;</td>
<td>↑ heart rate</td>
<td>↑ CO</td>
<td>↑ BP</td>
</tr>
<tr>
<td>Beta&lt;sub&gt;2&lt;/sub&gt;</td>
<td>vasodilation</td>
<td>↓ TPR</td>
<td>↓ BP</td>
</tr>
<tr>
<td>M&lt;sub&gt;2&lt;/sub&gt; receptors (vagus)</td>
<td>↓ heart rate</td>
<td>↓ CO</td>
<td>↓ BP</td>
</tr>
<tr>
<td>M receptors (vascular)</td>
<td>Vasodilation (NO)</td>
<td>↓ TPR</td>
<td>↓ BP</td>
</tr>
</tbody>
</table>

**Note:**
1. Actions on alpha<sub>1</sub> receptors are the most important in maintaining BP.
2. Vascular M-receptors are least important in maintaining BP.
3. Vascular alpha<sub>1</sub>- and cardiac M- and beta1-receptors respond to reflex activation.
4. Vascular beta2-receptors respond to circulating EPI, NE (ie. stress).
5. Vascular beta2- and M-receptors are non-innervated.

4. **Influence of sympathetic & parasympathetic tone (basal activity) on BP & HR**

<table>
<thead>
<tr>
<th>Normal (resting)</th>
<th>BP (mmHg)</th>
<th>HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 / 80</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>

| No tone*         | 60 / 40   | 75       |

* Central and circulation hormone actions removed.

**Note:** Athletic individuals have lower HR due to higher vagal tone, ie. Lance Armstrong (resting HR 32 bpm).

**Influence of BP change on ANS tone**

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Resting</th>
<th>After ↑ BP</th>
<th>After ↓ BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha&lt;sub&gt;1&lt;/sub&gt;</td>
<td>++++</td>
<td>0</td>
<td>++++</td>
</tr>
<tr>
<td>Beta&lt;sub&gt;1&lt;/sub&gt;</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>*Beta&lt;sub&gt;2&lt;/sub&gt;</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Vagus (M&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>++</td>
<td>+++</td>
<td>0</td>
</tr>
</tbody>
</table>

* Non-innervated, respond to circulation epinephrine (EPI).

**Note:** Vascular M receptors have no major role in BP regulation (Ach is not a circulating hormone.)
5. **Cardiovascular Effects of Catecholamines in Humans**

Figure 8C. Cardiovascular effects of low to moderate infusions of NE, ISO and EPI in humans. Heart rate is given in beats/min, blood pressure in mmHg, and peripheral resistance in arbitrary units. Dotted line in the BP record is the calculated mean arterial blood pressure (MAP).

![Diagram](image)

**Norepinephrine (NE):** At low dose NE is acting mainly at alpha1- and beta1-receptors with little effect on beta2-receptors. The action of NE on the vascular alpha1-receptors causes a large increase in peripheral resistance and hence an increase in BP. It also directly acts on beta1-receptors to increase HR. Together these lead to an increase in BP. However since there is an increase in BP, the baroreflex has been activated and attempts to lower the BP by decreasing HR (reflex). In the case of NE the reflex-mediated decrease in HR (via M-receptors, vagus N.) is stronger that the direct-mediated increase in HR (via beta1-receptors). The final net response as depicted is an increase in BP associated with reflex bradycardia (↓HR).

**Isoproterenol (ISO):** At low dose ISO is acting equally at beta1- and beta2-receptors with no alpha-receptor activity. Action on the beta1-receptors increases HR, CO and hence increases BP. This is seen as an increase in systolic BP. Whereas action on beta2-receptors decreases peripheral resistance (TPR) and hence decreases BP. This is seen as a decrease in diastolic BP. Although the pulse pressure has increased, there is little change in mean arterial BP and thus no activation of the baroreflex response.

**Epinephrine (EPI):** At low dose EPI is acting mainly at beta-receptors with a little alpha-receptor activity. At low doses EPI acts on the beta1-receptors to increase CO and hence BP. Some vasoconstriction (alpha1-action) to increase TPR and hence BP. These two actions are the cause of the increase in systolic BP. Finally vasodilatation via an action on beta2-receptors to decrease TPR and hence decrease BP. The overall effect on peripheral resistance at low dose is a fall in TPR (beta2-effect is greater than alpha1-effect). Although the pulse pressure has increased, there is little change in mean arterial BP and thus no activation of the baroreflex response.
6. Agonist Actions on BP & HR (high doses)

Phenylephrine (PE): PE acts mainly at alpha-receptors with little or no effect on beta-receptors. Action of PE on the vascular alpha1-receptors causes a large increase in peripheral resistance and hence an increase in BP. Since there is a large increase in BP, the baroreflex has been activated and attempts to lower the BP by decreasing HR (reflex). PE has no direct action on the heart.

Epinephrine (EPI): At moderate/high/therapeutic doses EPI acts on alpha1-, beta1-receptors and beta2-receptors. EPI will cause an increase in BP as the alpha1-mediated constriction dominates over the beta2-mediated vasodilation. Because of the significant increase in BP the baroreflex has been activated. It will try to lower BP by decreasing HR. However since EPI is such a potent beta1-agonist, the baroreflex evoked is weaker than EPI's direct action on the heart. Therefore we still see the tachycardia although it has been reduced by the reflex.

Isoproterenol (ISO): ISO is acting equally at beta1- and beta2-receptors. Action on the beta1-receptors increases HR, CO and hence tends to increase BP. Whereas action on beta2-receptors decreases peripheral resistance (TPR) and hence decreases BP. The decrease in TPR dominates over the increase in HR and thus BP decreases. Since there is a large decrease in BP, the baroreflex has been activated and attempts to raise the BP by increasing HR. Thus in this example the direct action of the drug and the reflex response are working in the same direction for HR.

Phentolamine: Alone, an alpha-blocker such as phentolamine causes a fall in BP and reflex tachycardia. Phentolamine blocks the endogenous action of released NE on alpha1-receptors to decrease TPR and thus decrease BP. Since there is a decrease in BP, the baroreflex has been activated and attempts to raise the BP by increasing HR.

Epinephrine reversal describes the response seen to EPI in the presence of an alpha-blocker. The normal response to EPI alone is an increase in BP and HR (see above). However in the presence of an alpha-blocker, EPI can now only activate the beta-receptors to cause a fall in BP with an increase in HR (as per ISO above).
8. Cardiovascular Effects of Various Agents Figure 8F

α1, β1, (β2)  α1  β1, β2, α1  β1, β2

Control

NE  PE  Lo EPI  Hi EPI  Lo ISO  Hi ISO

Phentolamine

Propranolol

Atropine

Phentolamine  Mecamylamine  Guanethidine  Atropine  Propranolol  Acetylcholine

BP

HR
VIII. ANTAGONISTS: SYMPATHOLYTIC AGENTS

Adrenergic receptor antagonists:

Drugs that have high affinity but no (or low negative or positive) intrinsic activity. Competitive vs. irreversible antagonists.

Factors that can determine the effect of antagonists in vivo:

- Absence or presence of intrinsic activity
- Preexisting “tone” at receptor.
- Net effect at pre- vs. postsynaptic receptors.
- Selectivity for receptor subtype.
- Compensatory reflex adjustments.

Sympatholytics – Receptor Blockade

A. Alpha-Adrenoceptor Antagonists

Clinical applications:

- hypertensive crisis
- pheochromocytoma
- excess side effects in ADHD
- tyramine intake in patients on MAO inhibitors
- chronic hypertension
- benign prostrate hypertrophy

Pheochromocytoma: Is a tumor that develops in the adrenal gland. That causes increased synthesis, storage and release of norepinephrine and epinephrine resulting in increased BP and HR. Most commonly occurs in people between ages 40 and 60. Most of the time, a pheochromocytoma is noncancerous (benign), and treatment can return blood pressure to normal.
1. **Phenoxybenzamine (non-competitive)**
   - irreversible alpha$_1$-blocker, forms covalent bond
   - also some block of ACh, histamine, serotonin receptors
   - also can inhibit neuronal and extraneuronal uptake
   - therapy: primary hypertension, pheochromocytoma (acute & chronic)
   - toxicity: impotence

2. **Phentolamine and Tolazoline (competitive)**
   - non selective $\alpha_1 = \alpha_2$ antagonist activity
   - cardiovascular: vasodilation, reflex tachycardia
   - enhance NA release due to presynaptic alpha$_2$-blockade

3. **Prazosin, Terazosin and doxazosin (competitive)**
   - selective $\alpha_1 - > \alpha_2$-receptors (1000 fold)
   - cardiovascular effects: reduced peripheral resistance
     lowered vascular return, generally no reflex tachycardia
   - first pass effect
   - therapy: primary hypertension, benign prostrate hypertrophy (BPH)

4. **Toxicity**
   - postural hypotension (very marked) all agents
   - reflex tachycardia, arrhythmias, myocardial infarction
   - ↓ plasma lipids
   - impotence (significant with phenoxybenzamine)
   - headache, dizziness, nausea, drowsiness

5. **Yohimbine (competitive)**
   - selective alpha2-antagonist, was used for impotence but removed from the market (available OTC), not important

**Question:** With Prazosin and Terazosin, why is there no reflex tachycardia?
**Answer:** Phentolamine (non-selective, alpha1- and alpha2-blocker) causes a fall in BP with reflex tachycardia. Whereas Prazosin and Terazosin are selective alpha1-blockers. It is thought that since they leave the presynaptic alpha2-receptors operational, this prevents the reflex tachycardia.

**Question:** Why does vasoconstriction lead to nasal decongestion?
**Answer:** When someone has a runny/stuffy nose such as with a cold. Fluid is leaking from the nasal vascular vessels. PE or other vasoconstrictors will decrease this and are commonly found as the active ingredient in nasal decongestions. Usually the forms are pseudoephedrine or pseudophenylephrine. Pseudoephedrine should not be used by someone taking MAOI agents, as this can cause a hypertensive crisis (similar to tyramine response).
B. Beta-Adrenoceptor Antagonists.

Therapeutically a much more useful class of drugs than alpha-adrenoceptor antagonists. Beta-adrenoceptor antagonists vary in respect to:

- relative affinity (selectivity) for beta1- and beta2-adrenoceptors
- ability to act as agonists at beta-adrenoceptors (ie. intrinsic beta-activity, partial agonists activity, ISA)
- ability to stabilize membranes (local anaesthetic activity)
- lipid solubility (least important)

General features of beta-blocking agents:
- End in -olol (exceptions: Sotalol, Labetalol & Carvedilol)
- Agents beginning with A-M are beta1-selective (exceptions: Carteolol, Labetalol & Carvedilol).

Properties of several beta-receptor blocking drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selectivity</th>
<th>Partial Agonist Activity</th>
<th>Local Anaesthetic Action</th>
<th>Lipid Solubility</th>
<th>Elimination Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>beta1</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>3–4 hours</td>
</tr>
<tr>
<td>Atenolol</td>
<td>beta1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>6–9 hours</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>beta1</td>
<td>No</td>
<td>Slight</td>
<td>Low</td>
<td>14–22 hours</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>beta1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>9–12 hours</td>
</tr>
<tr>
<td>Carteolol</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>Low</td>
<td>6 hours</td>
</tr>
<tr>
<td>Celiprolol</td>
<td>beta1</td>
<td>Yes(^1)</td>
<td>No</td>
<td>. . .</td>
<td>4–5 hours</td>
</tr>
<tr>
<td>Esmolol</td>
<td>beta1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>10 minutes</td>
</tr>
<tr>
<td>Labetalol(^2)</td>
<td>None</td>
<td>Yes(^1)</td>
<td>Yes</td>
<td>Moderate</td>
<td>5 hours</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>beta1</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>3–4 hours</td>
</tr>
<tr>
<td>Nadolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>14–24 hours</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>High</td>
<td>5 hours</td>
</tr>
<tr>
<td>Pindolol</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>3–4 hours</td>
</tr>
<tr>
<td>Propranolol</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td>High</td>
<td>3(\frac{1}{2})–6 hours</td>
</tr>
<tr>
<td>Sotalol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>12 hours</td>
</tr>
<tr>
<td>Timolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
<td>4–5 hours</td>
</tr>
</tbody>
</table>

\(^1\) Partial agonist effects at beta2 receptors. \(^2\) Labetalol also causes alpha-selective blockade. \(^3\) Bioavailability is dose-dependent.

Question: What does ISA mean?
Answer: ISA refers to Intrinsic sympathomimetic activity (ie. Partial agonist action). This means that the agent in addition to being a beta-receptor antagonist, also has some partial agonist activity (ie. Pindolol). This feature was developed to decrease the downside of the beta-blockers (ie. supersensitivity effects as well as negative effects with asthma and diabetes).
1. **Clinical uses:**
   
a. **Hypertension**
   
   Hemodynamic effects of propranolol in patients with essential hypertension.

   ![Graph showing hemodynamic effects](image)

   Beta-blockers, together with diuretics, calcium channel blocker and Angiotensin Converting Enzyme (ACE) inhibitors are considered ‘first-line’ treatment for uncomplicated essential hypertension. The usual hemodynamic effect of a β-blocker in a hypertensive patient is shown in the figure below (gradual reduction of total peripheral resistance (TPR) in spite of long-term decrease in cardiac output). Mechanism unclear, but possibilities include action in CNS to reduce sympathetic tone, block of presynaptic β-receptors to reduce NE release, decrease in renin release. Both non-selective and β₁-selective drugs are effective.

b. **Arrhythmia**
   
   Mechanism: blockade of catecholamine-induced increases in conductivity and automaticity in heart.
   
   β₁-blockers with membrane stabilizing properties better eg. metoprolol

c. **Angina**
   
   β-blockers block catecholamine effects on heart. They reduce O₂ demand more than O₂ supply. Exercise tolerance is increased in patients with angina.
   
   β₁-selective blocker better eg. atenolol
   
   Note: ‘rebound’ angina upon abrupt cessation of treatment, less rebound with pindolol (non-selective, partial agonist)

d. **Glaucoma (major use):** ↓ aqueous humor formation (timolol)

e. **Heart failure (Congestive, CHF):** (Metoprolol, Labetalol & Carvediolol)
   
   Decrease load and O₂ demand of heart
   
   MERIT-HF: Use of Metoprolol in CHF  JAMA 2000, 283, p1295-1302
   
   Mortality ↓ 34%, Hospitalization ↓ 29%, Felt better ↑ 25
   
   **Caution:** β-blockers can precipitate latent heart failure by removing compensatory increase in sympathetic effects on heart
   
   **Contraindicated:** unstable CHF, significant bronchospasm, bradycardia or depression
f. Other Clinical Uses.

- Tremor of peripheral origin (β2-receptors in skeletal muscle)
- Migraine prophylaxis (mechanism unknown).
- Hyperthyroidism: block of cardiac manifestations due to β-receptor supersensitivity (propranolol).
- Panic attacks, stage fright (propranolol)

g. Untoward effects, contraindications:

- Depression
- Supersensitivity: blockade of beta-receptors can cause receptor up-regulation, if discontinued should be gradual (rebound hypertension)
- Asthma. Asthma precipitated by blockade of pulmonary β2-receptors. β1-selective agents are preferred in patients with asthma.
- Diabetes. Compensatory hyperglycemic effect of EPI during hypoglycemia is prevented by block of β2-receptors in liver. β1-selective agents preferred.
- Elderly: Effectiveness is decreased with age. Despite decreased sensitivity to the chronotropic effects of β blockade, there may be increased myocardial sensitivity to the negative inotropic effect during exercise. The elderly are at increased risk of orthostatic hypotension, reduced peripheral circulation, and mental status changes with β blockers. than in younger adults.
- May precipitate Raynaud’s Syndrome (decreased peripheral circulation)

h. Labetalol, Carvedilol

- Used for chronic hypertension, CHF, hypertensive crisis (better than α-receptor blocker, can decrease both BP & HR effects)
- competitive antagonist at both α- and β-adrenoceptors
- β1 = β2 activity > α-activity (some intrinsic β-adrenoceptor activity)
- can cause postural hypotension due to α-receptor block

Question: Why are non-selective beta blockers not recommended for individuals with diabetes?
Answer: Beta2-receptors are present in liver cells, activation of these receptors leads to glycogen breakdown to glucose. In diabetes there is compromised glucose handling. Blockade of the beta2-receptors in diabetes would prolong the recovery from a hypoglycemia episode and mask the symptoms of hypoglycemia (ie. anxiety, tremors, palpitations). Therefore it is preferred to use a beta1-selective agent to minimize this effect.

Question: Why shouldn't propranolol be given first to a patient with pheochromocytoma?
Answer: The main problem with pheochromocytoma is the high BP not the tachycardia. If a beta-blocker is given alone, you allow the alpha1-activity of the catecholamines to act unopposed. This would increase the BP still further. Beta-blockers can safely be given after the BP has been stabilized with an alpha-blocker.

Exception: Labetalol (beta- and alpha-blocker) can be given alone to treat the crisis.
C. Agents that Decrease the Quantity of NE in Nerve Terminals.

1. Direct inhibition of synthesis (Figs. 2A,10)
   - Alpha-methyl-p-tyrosine (inhibits tyrosine hydroxylase) treatment of pheochromocytoma (long-term, diffuse tumor)

2. False transmitters (Fig. 10)
   a. Alpha-methyl-DOPA → alpha-methyl-NE
      - Prodrug (ie. converted to alpha-methyl-NE)
      - alpha2 action (alpha-methyl-NE)
      - antihypertensive, central action → ↓ sympathetic outflow
   b. Tyramine + MAO inhibition → octopamine

\[
\text{FIG. 10} \quad \text{BIOSYNTHESIS OF "FALSE" NEUROTRANSMITTERS}
\]
3. **Inhibition of intraneuronal storage of CAs** (FIGS. 11A,B)

Reserpine: "leaky" vesicle (also depletes 5-HT stores) and inhibits transport of NE from cytosol to vesicle. Leads to gradual depletion of NE stores.

Inhibition of Vesicular Storage of NE  
Consequences of Reserpine Treatment

Major side effects include: lethargy, diarrhea, depression (very long lasting).

4. **Prevention of normal transmitter release** (Fig. 12)
   - Used in the treatment of hypertension and arrhythmias.
   - Side effects include: diarrhea, nasal congestion, impotence, postural hypotension.
   - Competes with TCA’s for uptake process.

   a. Bretylium (local anesthetic action, arrhythmias, premedication)
   b. Guanethidine (reuptake inhibitor, inhibits release)