INTRODUCTION TO THE AUTONOMIC NERVOUS SYSTEM (ANS)
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Learning Objectives:
1. Understand the role of the ANS in maintaining homeostasis by regulating cardiovascular, respiratory, gastrointestinal, endocrine, metabolic, etc. functions.
2. Understand the functional organization of the ANS and of its two branches, the sympathetic (SNS) and the parasympathetic nervous systems (PNS).
3. Understand the principle of chemical neurotransmission and its modulation.

I. DIFFERENT ROLES OF THE SOMATIC NERVOUS SYSTEM AND THE ANS

Nervous system: i) Somatic (voluntary control of skeletal muscle)  
ii) Autonomic (involuntary, visceral, vegetative)

The role of ANS is to regulate the activity of structures or organs not normally under voluntary control eg. respiration, circulation, digestion, body temperature, metabolism, sweating and secretions from certain glands.

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NERVOUS SYSTEM

- Central Nervous System
  - Peripheral Nervous System
    - Afferent Division
      - Somatic Voluntary
        - Sympathetic Nervous System
        - Parasympathetic Nervous System
      - Efferent Division
        - Autonomic Involuntary Visceral Vegetative

AUTONOMIC NERVOUS SYSTEM

- Sympathetic
  - Thoracolumbar T1-12, L1-3
  - “Flight or Fight”
    - ↑BP, ↑HR, ↓GIT

- Parasympathetic
  - Craniosacral
  - Cranial N. III, VII, IX, X
  - Sacral S2-3
  - “Feeding & Breeding”
    - ↓BP, ↓HR, ↑GIT

FUNCTIONS CONTROLLED

- Respiration
- Circulation
- Body Temperature
- Metabolism
- Sweating
- Secretions

CENTRAL INVOLVEMENT

- Hypothalamus - Integration, body temp & water balance
- Medulla - BP, respiration
- Cerebral cortex - somatic NS & ANS integration
II. ANATOMICAL DIVISIONS OF ANS (Figs. 1A,B)

It is important to remember that the division of the ANS into the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) is an anatomic classification and does not depend on the type of transmitter involved or whether the effect elicited is excitatory or inhibitory. An alternate classification can be based on the transmitter molecules released (e.g. acetylcholine or norepinephrine). Most organs receive reciprocal innervation by both divisions, although there are exceptions (e.g. peripheral vasculature only receives sympathetic innervation). Sympathetic and parasympathetic effects usually oppose one another, with one of the two dominating under resting conditions (e.g. dominant parasympathetic “tone” on the heart). This autonomic tone is very important for predicting the effects of autonomic drugs and is influenced by age, physical fitness or underlying disease. The SNS dominates during anger and stress situations and gives rise to the 'Flight or Fight' response (↑BP, ↑HR, ↓GI motility, relax bronchial SM). While the PNS is most important when the individual is resting or trying to conserve energy 'Feeding and Breeding' (↓HR, ↑GI motility, contract bronchial SM) see Table 1.

A. Sympathetic (thoracolumbar) Nervous System (SNS)
   a. T1-12; L1-3
   b. Location of ganglia (principally in the paravertebral and prevertebral ganglia)
   c. Preganglionic fibers (short); myelinated
   d. Postganglionic fibers (long); non-myelinated
   e. Type of activation; synchronized
   f. Types of receptors on effector organs (alpha-, beta-, dopamine-receptors)

B. Parasympathetic (craniosacral) Nervous System (PNS)
   a. Cranial nerves III, VII, IX, X; S2-3
   b. Location of ganglia (principally distributed diffusely in the walls of the innervated tissue)
   c. Preganglionic fibers (long); myelinated
   d. Postganglionic fibers (short); non-myelinated
   e. Type of activation; localized
   f. Types of receptors on effector organs (muscarinic & nicotinic)

III. FUNCTIONAL ORGANIZATION OF THE ANS

A. The elementary unit of ANS is the autonomic reflex arc, made up of sensory receptors, afferent neurons, central sites of integration, and efferent nerves.

B. Transmission of information between neurons or between a neuron and a target cell occurs through the synapse by the release of a specific neurotransmitter, and activation of specific receptors on the target cell by the transmitter.
Raynaud’s Syndrome: (Example of malfunction of ANS)
Excessive sympathetic tone in nerves supplying hands and feet. Minor cold, or even thought of cold, causes pronounced vasoconstriction that can be severe enough to cause necrosis of tissue. Three-phase color sequence (white to blue (↓O₂) to red (vessels reopen)

C. Receptor Subtypes in the Autonomic Nervous System

<table>
<thead>
<tr>
<th>Adrenoceptors</th>
<th>Cholinoceptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha α₁, α₂</td>
<td>Muscarinic M₁, M₂, M₃, M₄/M₅</td>
</tr>
<tr>
<td>Beta β₁, β₂, β₃</td>
<td>Nicotinic Nn, Nm</td>
</tr>
<tr>
<td>Dopamine D₁, D₂, D₃, D₄, D₅</td>
<td>Dopamine D₁, D₂, D₃, D₄, D₅</td>
</tr>
</tbody>
</table>

![Diagram of neurohumoral transmission](image-url)
FIG 1B. THE AUTONOMIC NERVOUS SYSTEM

SYMPATHETIC DIVISION

PARASYMPATHETIC DIVISION

Dr. Ishac

Introduction to the ANS
Table 1. Direct effects of autonomic nerve activity on some organ systems

<table>
<thead>
<tr>
<th>Organ</th>
<th>Sympathetic NS</th>
<th>Parasympathetic NS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Action</td>
<td>Receptor</td>
</tr>
<tr>
<td>Eye: Radial m.</td>
<td>Mydriasis</td>
<td>$\alpha_1$</td>
</tr>
<tr>
<td>Circular m.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciliary m.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart:</td>
<td>$\uparrow$HR, $\uparrow$force</td>
<td>$\beta_1$</td>
</tr>
<tr>
<td>Vascular muscle</td>
<td>Constrict</td>
<td>$\alpha_1$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial m.</td>
<td>Relax</td>
<td>$\beta_2$</td>
</tr>
<tr>
<td>Gl-tract</td>
<td>$\downarrow$ motility</td>
<td>$\alpha_1, \beta_2$</td>
</tr>
<tr>
<td>Sphincter m.</td>
<td>Contract</td>
<td>$\alpha_1$</td>
</tr>
<tr>
<td>Genitourinary m.</td>
<td>Relax</td>
<td>$\beta_2$</td>
</tr>
<tr>
<td>Penis</td>
<td>Ejaculation</td>
<td>$\alpha$</td>
</tr>
<tr>
<td>Uterus</td>
<td>Relax</td>
<td>$\beta_2$</td>
</tr>
<tr>
<td>Pilomotor</td>
<td>Contract</td>
<td>$\alpha$</td>
</tr>
<tr>
<td>Sweat glands</td>
<td>$\uparrow$secretion</td>
<td>$M_3$</td>
</tr>
<tr>
<td>Liver</td>
<td>$\uparrow$glucose</td>
<td>$\beta_2$</td>
</tr>
<tr>
<td>Kidney</td>
<td>$\uparrow$renin</td>
<td>$\beta_1$</td>
</tr>
<tr>
<td>Fat cell</td>
<td>Lipolysis</td>
<td>$\beta_3$</td>
</tr>
</tbody>
</table>

Specific receptor type: $\alpha$ = alpha, $\beta$ = beta, $M$ = muscarinic, $N$ = nicotinic

**Learning Resources:** Recommended Reading:


Additional Reading:

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 alpha2-adrenoceptors to inhibit further transmitter release and/or presynaptic beta2-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></th>
<th>MAO (important)</th>
<th>COMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location in cell</td>
<td>Outer mitochondrial membrane</td>
<td>Cytosol</td>
</tr>
<tr>
<td>Location in body</td>
<td>Symp. nerve, placenta (MAO&lt;sub&gt;A&lt;/sub&gt;) platelets (MAO&lt;sub&gt;B&lt;/sub&gt;) liver, kidney, brain (MAO&lt;sub&gt;A&lt;/sub&gt; + MAO&lt;sub&gt;B&lt;/sub&gt;)</td>
<td>Most tissues, not in sympathetic nerves</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>Minor effect</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
R&\text{CH}_2\text{NHR} &\rightarrow & R\text{CH}_2\text{OH} \\
R&\text{C}=\text{OH} &\rightarrow & R\text{CH}_2\text{OH} \\
R&\text{CO} &\rightarrow & R\text{CH}_2\text{OH} \\
\end{align*}
\]
V. ADRENERGIC RECEPTOR SUBTYPES

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

<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>
<tr>
<td>Alpha₂</td>
<td>Some vascular smooth muscle</td>
<td>Contraction</td>
</tr>
<tr>
<td>Nerve terminals (NE &amp; ACh)</td>
<td>Inhibit transmitter release</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>Aggregation</td>
<td></td>
</tr>
<tr>
<td>Fat cells</td>
<td>Inhibition of lipolysis</td>
<td></td>
</tr>
<tr>
<td>Beta₁</td>
<td>Heart</td>
<td>Increase force, rate, cond. velocity</td>
</tr>
<tr>
<td>Coronary blood vessels</td>
<td>Dilatation</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>Renin release</td>
<td></td>
</tr>
<tr>
<td>Beta₂</td>
<td>Bronchial smooth muscle</td>
<td>Relaxation</td>
</tr>
<tr>
<td>Intestinal smooth muscle</td>
<td>Relaxation</td>
<td></td>
</tr>
<tr>
<td>Uterine smooth muscle</td>
<td>Relaxation</td>
<td></td>
</tr>
<tr>
<td>Vascular smooth muscle</td>
<td>Relaxation</td>
<td></td>
</tr>
<tr>
<td>NA nerve terminals</td>
<td>Facilitation of release</td>
<td></td>
</tr>
<tr>
<td>Beta₃</td>
<td>Fat cells</td>
<td>Lipolysis</td>
</tr>
</tbody>
</table>

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>(\alpha_1)</td>
<td>Effector tissues: smooth muscle, glands</td>
<td>Gq</td>
<td>(\uparrow\text{Ca}^{2+}, \uparrow\text{IP}_3, \text{DAG})</td>
</tr>
<tr>
<td>(\alpha_2)</td>
<td>Nerve endings, some smooth muscle</td>
<td>Gi</td>
<td>(\downarrow\text{cAMP})</td>
</tr>
<tr>
<td>(\beta_1)</td>
<td>Heart, juxtaglomerular apparatus</td>
<td>Gs</td>
<td>(\uparrow\text{cAMP})</td>
</tr>
<tr>
<td>(\beta_2)</td>
<td>Smooth muscle, lung</td>
<td>Gs</td>
<td>(\uparrow\text{cAMP})</td>
</tr>
<tr>
<td>(\beta_3)</td>
<td>Adipose cells</td>
<td>Gs</td>
<td>(\uparrow\text{cAMP})</td>
</tr>
<tr>
<td>D₁, D₅</td>
<td>Vascular smooth muscle, brain, renal</td>
<td>Gs</td>
<td>(\uparrow\text{cAMP})</td>
</tr>
<tr>
<td>D₂, D₃, D₄</td>
<td>Brain, cardiovascular system</td>
<td>Gi</td>
<td>(\downarrow\text{cAMP})</td>
</tr>
</tbody>
</table>
Schematic representation of adrenergic receptors and their second messenger systems.
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.

\[
\text{OH} \quad \text{OH} \\
\text{3} \quad \text{2} \\
\text{1} \quad \text{2} \\
\text{5} \quad \text{6} \\
\text{4} \quad \text{CH2} \quad \text{CH2} \quad \text{NH2}
\]

Catechol Phenylethylamine

Modifications of the parent compound, phenylethylamine can drastically alter the behavior of the molecule as a ligand for the various receptor subtypes (alpha- or beta-receptors).

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 \rightarrow 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, \(\downarrow\) airway resistance
   - adverse effects: cardiovascular side effects (HR, BP), less by inhalation compared to oral administration

b. **Selective beta\(_1\)-agonists:** Dobutamine, Prenalteronol
   - cardiac stimulant, congestive heart failure (acute)
   - (tolerance/desensitization)
   - \(\uparrow\) 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 (\(\uparrow\)BP)

d. **Selective alpha\(_2\)-agonists:** Clonidine, guanfacine, \(\alpha\)-methyldopa (prodrug)
   - used in the treatment of hypertension, opiate withdrawal
   - central action (medulla oblongata) on postjunctional \(\alpha_2\)-receptors to decrease sympathetic outflow \(\rightarrow \downarrow\) 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 (i.e. not removed from synaptic junction).

a. **Cocaine**

b. **Tricyclic antidepressants** - imipramine, amitriptylline, clomipramine (tricycles 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, i.e. reduce effect of amphetamine)

[Diagram of NE re-uptake]

**Figure 6. Blockade of NE re-uptake**

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>
</thead>
<tbody>
<tr>
<td>Location in cell</td>
<td>mitochondria 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>Interations</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 (ie. 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: \( BP = CO \times TPR \)

- \( BP \) = blood pressure
- \( TPR \) = total peripheral arterial resistance
- \( CO \) = 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).

![Diagram of the sympathetic nervous system and its effects on cardiovascular parameters.](image)
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</th>
<th>BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha1 receptors</td>
<td>vasoconstriction</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Beta1 receptors</td>
<td>↑ heart rate</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Beta2 receptors</td>
<td>vasodilation</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>M2 receptors (vagus)</td>
<td>↓ heart rate</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>M receptors (vascular)</td>
<td>Vasodilation (NO)</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

**Note:**
1. Actions on alpha1 receptors are the most important in maintaining BP
2. Vascular M-receptors are least important in maintaining BP
3. Vascular alpha1-, 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></th>
<th>BP (mmHg)</th>
<th>HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (resting)</td>
<td>120 / 80</td>
<td>70</td>
</tr>
<tr>
<td>No tone*</td>
<td>60 / 40</td>
<td>75</td>
</tr>
</tbody>
</table>

* 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>Alpha1</td>
<td>++ + +</td>
<td>0</td>
<td>+ + + + + +</td>
</tr>
<tr>
<td>Beta1</td>
<td>+</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Beta2</td>
<td>+</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Vagus (M2)</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).

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 than 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

\[ \alpha_1, \beta_1, (\beta_2) \quad \alpha_1 \quad \beta_1, \beta_2, \alpha_1 \quad \beta_1, \beta_2 \]
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 alpha₁-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 alpha₂-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 pseudoephynlephrine. 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 β-adrenoceptors (ie. intrinsic β-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 β1-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 Anesthetic Action</th>
<th>Lipid Solubility</th>
<th>Elimination Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>β1</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>3–4 hours</td>
</tr>
<tr>
<td>Atenolol</td>
<td>β1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>6–9 hours</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>β1</td>
<td>No</td>
<td>Slight</td>
<td>Low</td>
<td>14–22 hours</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>β1</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>β1</td>
<td>Yes¹</td>
<td>No</td>
<td>Low</td>
<td>. . .</td>
</tr>
<tr>
<td>Esmolol</td>
<td>β1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>4–5 hours</td>
</tr>
<tr>
<td>Labetalol²</td>
<td>None</td>
<td>Yes¹</td>
<td>Yes</td>
<td>Moderate</td>
<td>5 hours</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>β1</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>3½–6 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>

¹Partial agonist effects at β2 receptors. ²Labetalol also causes α1-selective blockade. ³Bioavailability 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 of propranolol](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 $\rightarrow$ alpha-methyl-NE
      - Prodrug (ie. converted to alpha-methyl-NE)
      - alpha$_2$ action (alpha-methyl-NE)
      - antihypertensive, central action $\rightarrow$ ↓ sympathetic outflow
   b. Tyramine + MAO inhibition $\rightarrow$ octopamine
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)
Learning Objectives:

Understand the steps involved in cholinergic neurotransmission, and how drugs can interfere with these processes.

**Figure 1** Functional organization of the cholinergic nerve terminal

I. STEPS IN CHOLINERGIC NEUROTRANSMISSION

A. **Acetylcholine (ACh) synthesis:** Choline is transported into the nerve terminal and acetyl CoA produced by mitochondria is transported to the cytosol. The enzyme choline acetyltransferase synthesizes acetylcholine (Ach) from choline and acetyl CoA. Choline co-transports with Na⁺ and is the rate limiting step in the synthesis of Ach (inhibited by hemicholinium-3).

B. **ACh storage:** ACh is stored in vesicles. Nerve impulses cause a calcium-dependent quantal release of ACh. Botulinum toxin (food poisoning) is potent inhibitor of ACh release.

C. **ACh release:** Arrival of an action potential at the parasympathetic neuron causes depolarization of the membrane leading to an influx of Ca²⁺. ACh 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 (ACh, ATP, PG) are delivered into the synaptic cleft (1000-50,000 ACh/vesicle; 300,000 vesicles/terminal; need only 1000 ACh → mepp → action potential).
1. Choline is transported into nerve terminal (varicosity) by sodium-dependent carrier. Rate limiting step, inhibited by hemicholinium.
2. Ach is synthesized from choline and acetyl CoA by acetyltransferase
3. Ach transported to storage vesicle (inhibited by vesamicol)
4. Transmitter release occurs when an action potential opens voltage-sensitive calcium channels and increases intracellular calcium. Release inhibited by botulin
5. Released Ach can activate post- and presynaptic receptors
6. Response terminated by enzymatic degradation by acetylcholinesterase (inhibited by phosostigmine and other cholinesterase inhibitors))
7. Choline retaken up by nerve terminal

D. **ACh interaction with receptors:** Released ACh acts at muscarinic (parasympathetic) and nicotinic (ganglia, CNS, motor endplate) receptors. Muscarinic receptors (5 subtypes cloned to date) are G protein coupled, act via inhibition of adenylate cyclase or activation of phospholipase C. Nicotinic receptors are composed of multiple subunits, forming an ion channel. Pharmacologically distinct receptors in neuronal tissue (ganglia, CNS) and in motor endplate. Agonists and antagonists at different types of receptors are clinically used (see below). Certain snake venoms are potent inhibitors of nicotinic receptors in skeletal muscle.
1. **Muscarinic (7 transmembrane, glycoprotein)**
   - M₁ - (minor importance) autonomic ganglia, CNS
   - M₂ - heart
   - M₃ - smooth muscle, glands
   - M₄, M₅
   - similar to adrenoceptors and other G-protein coupled receptors in structure
   - M₁, M₃, M₅ $\uparrow$ IP₃
   - M₂, M₄ $\downarrow$ cAMP

2. **Nicotinic (ion channel, pentamer, 5 subunits)**
   - N₅ or N₁ - ganglia, adrenal medulla (α₂β₃, α₃β₂)
   - N₄ or N₂ - skeletal muscle (infant, α₂βδε; adult, α₂βδγ)
   - α-subunit contains Ach binding site

**E. Termination of ACh action:**
Ach released into the synaptic cleft is rapidly metabolized by acetylcholinesterase (AChE) to choline and acetate. The choline is then taken up by the nerve terminal for subsequent Ach synthesis. Butyrycholinesterase (pseudochoolinesterase) found in the circulation, liver, and other tissues can also metabolize Ach.
<table>
<thead>
<tr>
<th></th>
<th>Acetylcholinesterase</th>
<th>Butyrycholinesterase (Pseudocholinesterase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroeffector site</td>
<td>Yes</td>
<td>Little</td>
</tr>
<tr>
<td>Circulating</td>
<td>Little</td>
<td>Yes</td>
</tr>
<tr>
<td>Methacholine</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Physostigmine</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Neuromuscular junction</td>
<td>Yes</td>
<td>Little</td>
</tr>
</tbody>
</table>

II. MUSCARINIC EFFECTS ON ORGAN SYSTEMS (see Table 1)

A. Cardiovascular

- **Heart**: Decreased heart rate, decreased contractility and decreased conduction velocity in A-V node due to stimulation of M₂ receptors. Not clinically exploited, but important in the action of certain drugs (digitalis, quinidine), which potentiate muscarinic effects in heart.

- **Vasculature**: Vessels are not cholinergically innervated, but have muscarinic receptors on endothelial cells that mediate potent vasodilation via synthesis of nitric oxide (NO).

B. Other smooth muscle

- **GI-tract**: Increase tone in intestine, bladder, decreased tone in sphincters. E.g. clinical use: bethanecol in postoperative paralytic ileus, bladder dysfunction.

- **Lung**: Contraction of bronchial smooth muscle leads to an increase in air resistance. Also increases bronchial secretions.

- **Eye**: Contraction of sphincter muscle (miosis), contraction of ciliary muscle for near vision.

- **Exocrine glands**.

- **Increased sweating** (cholinergic sympathetic), increased salivation, increase in gastric acid secretion

Terminology

**Cycloplegia** – Paralysis of ciliary muscle (loss of accommodation, ability to focus)

**Miosis** – Contraction of pupil (leads to pinpoint pupil, i.e. Ach)

**Mydriatic** – Relaxation of pupil (leads to pupil dilation, i.e. atropine bella donna compound)
III. CLASSES OF CHOLINOCEPTOR-ACTIVATING DRUGS

CHOLINOCEPTOR STIMULANTS

Direct-acting (receptor agonists)

Muscarinic
Choline esters

Nicotinic
Alkaloids

Indirect-acting (cholinesterase inhibitors)

Reversible
Ganglionic
Edrophonium, carbamates

Irreversible
NMJ
Phosphates

A. Directly-Acting Parasympathomimetics

Directly acting parasympathomimetics: combine with muscarinic and/or nicotinic cholinoreceptors and hence activate the receptor directly.

1. Muscarinic receptor agonists.
   a. Choline esters
      - acetylcholine (both muscarinic and nicotinic)
      - methacholine
      - carbachol (direct/indirect; muscarinic & nicotinic)
      - bethanechol
   b. Alkaloids
      - muscarine (found in certain mushrooms)
      - pilocarpine (used in glaucoma, emergency drug of choice)
      - oxotremorine (synthetic) CNS action (basal ganglia)
   c. Uses
      - ophthalmic (Ach, brief miosis)
      - diagnostic for belladonna poisoning (methacholine)
      - urinary retention (bethanechol)
      - reverse GI depression ie. post-operative (bethanechol)
      - glaucoma (pilocarpine, emergency drug of choice)
d Adverse reactions:

- cardiac slowing (arrest)
- nausea, cramps
- bronchoconstriction, precipitate asthma
- involuntary defecation, urination
- tremor, CNS induced convulsions
- ↑ sweating, lacrimation, diarrhea
- emesis (vomiting)

SLUDE: Salivation, Lacrimation, Urination, Diarrhea, Emesis

2. Nicotinic receptor agonists (ganglionic stimulants)

- acetylcholine
- DMPP (experimental, not important)
- nicotine (alkaloid)
- lobeline

B. Indirectly-Acting Parasympathomimetics

Indirectly-acting parasympathomimetics: interact with acetylcholinesterase (true) and/or pseudocholinesterase (serum) to prevent the metabolism of Ach. Ach is normally metabolized by cholinesterase which has two sites: an anionic site that binds the quaternary amine and positions the Ach molecule, and an esteratic site which attacks the acyl carbon (Fig. 5A). Main target is acetylcholinesterase but also inhibit pseudocholinesterase.

Inhibitors of cholinesterase: Reversible inhibitors
Irreversible inhibitors

1. Reversible inhibitors (Fig. 5B).

a. Quarternary ammonium compounds

- edrophonium (competitive, water stable, 5-10 min action) diagnostic for myasthenia gravis (Tensilon test)
- ambenonium (4-8 hr action)

b. Carbamates

- physostigmine (tertiary amine, well absorbed, CNS activity, can give topically or orally, 0.5-2 hrs action)
- neostigmine (quaternary amine, no CNS activity, synthetic, some direct action, 0.5-2 hrs action)
- pyridostigmine (3-6 hrs action)
2. Irreversible inhibitors (Fig. 6).

a. Organophosphates (highly lipid soluble, >50,000 compounds)
   - Diisopropyl-fluorophosphate (Isoflurophate, DFP)
   - Echothiophate (Phospholine, poorly absorbed, no CNS action)
   - VX, sarin, suman (nerve gases)
   - malathion, parathion (pesticides, very lipid soluble)
     inactive (prodrugs), thiophosphates converted to active compounds,
     then inactive metabolites (birds/vertebrates) but not insects or fish
     Parathion more dangerous than malathion

b. ‘Aging’ (Fig. 6):
   - In time phosphorylation of acetylcholinesterase: becomes irreversible
   - Isoflurophate – ‘aging’ 30-45 min, nerve gases (secs)
   - If ‘aging’ has not occurred, AChE can be regenerated
   - AChE reactivator, pralidoxime (2-PAM).
3. **Actions and Clinical uses of Acetylcholinesterase Inhibitors:**

   **a. Eye:**
   - Miosis (sphincter contraction), accommodation block (ciliary muscle contraction)
   - Glaucoma, as maintenance therapy in chronic wide-angle or secondary glaucoma. Short acting (physostigmine) or long acting (echothiophate)
   - Combination with α-adrenergic agonist (acts by reducing vascular volume and secretion) or β-receptor antagonist (reduces secretion).
   - Non emergency treatment in acute narrow angle glaucoma (pilocarpine used)

   **b. GI tract.**
   - Increase in GI-tract motility
   - Neostigmine used to increase motility in paralytic ileus (post-operative) or atony of urinary bladder (bethanechol preferred).
c. **Neuromuscular junction.**
- Neostigmine is used to increase muscle strength in myasthenia gravis. Action due to both AChE inhibition and direct nicotinic receptor stimulation.
- Edrophonium (short acting) is used as diagnostic test to distinguish myasthenic weakness (improved) from cholinergic crisis (worsened). Also used to determine maintenance dose.

d. **Reverse toxicity by anticholinergic agents.**
- Physostigmine is preferred (CNS action)
- Toxicity caused by belladonna agents (atropine-like agents)
- Drugs that have anticholinergic side effects (e.g. tricyclic antidepressants).

4. **Toxicity and Treatment of Acetylcholinesterase inhibitors:**

a. **Symptoms resemble excessive muscarinic & nicotinic stimulation**

<table>
<thead>
<tr>
<th>Response</th>
<th>Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Sweating</td>
<td>Muscarinic</td>
</tr>
<tr>
<td>↑ Lacrimation, salivation</td>
<td>Muscarinic</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>Muscarinic</td>
</tr>
<tr>
<td>↑ Bronchosecretions, bronchoconstriction</td>
<td>Muscarinic</td>
</tr>
<tr>
<td>Paralysis (depolarizing block), fasciculations</td>
<td>Nicotinic</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Muscarinic</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Muscarinic</td>
</tr>
<tr>
<td>Hypotension/Hypertension</td>
<td>Nicotinic</td>
</tr>
<tr>
<td>Tremor</td>
<td>Muscarinic</td>
</tr>
</tbody>
</table>

**SLUDE**  Salivation, Lacrimation, Urination, Diarrhea, Emesis

b. **Treatment of poisoning by organophosphate AChE inhibitors**
- muscarinic antagonist atropine
- AChE reactivator (pralidoxime, 2-PAM)
- mechanical respiration.

**Question:** Why does toxicity to acetylcholinesterase inhibitors include hypotension and hypertension?
**Answer:** In the presence of AchE inhibitors the action of Ach is prolonged at all sites (i.e. ganglia, neuroeffector & NMJ). The increased ganglionic stimulation leads to an increased sympathetic stimulation to the vascular smooth muscle leading to vasconstriction via alpha1-receptors (hypertension). However if the Ach concentration becomes too high then Ach begins to act like succinylcholine, resulting in a depolarizing blockade in the ganglia (i.e. it resembles the actions of a ganglionic blocker). This then causes the BP to fall (hypotension).
IV. **ANTAGONISTS: PARASYMPATHOLYTIC AGENTS**

Antimuscarinic  
Block ACh in parasympathetic effector junctions (muscarinic receptors)

Antinicotinic  
block ACh in ganglia (both parasympathetic and sympathetic, N_N or N_1-receptors)

Antinicotinic  
block ACh in neuromuscular junctions (skeletal muscle relaxants, N_M or N_2- receptors)

A. **Anticholinergic Effects on Organ Systems:**

1. **Heart:**
   - Removal of vagal tone causes tachycardia, increase in A-V nodal conduction due to block of M_2 receptors on target cells.

2. **Vasculature**
   - No effect due to lack of cholinergic innervation, although toxic doses cause pronounced vasodilation

3. **Smooth muscle**
   - GI, urinary tract: relaxation, reduced secretion and motility
   - Lung: cause bronchial relaxation and ↓ bronchial secretions
   - Eye: mydriatic (sphincter relaxation), cycloplegic (ciliary muscle relaxation for far vision), diagnostic tool to dilate pupil (homatropine)

4. **Secretions**
   - Antisecretory activity. Dry mouth, dry skin, decreased gastric acid secretion. May worsen pre-existing dry mouth and dry eyes in elderly.
   - Used as preoperative to reduce salivation, respiratory tract secretion.

5. **CNS**
   - CNS effects prominent in belladonna toxicity (“mad as a hatter, red as a beet, blind as a bat, hot as hell, dry as a bone”).
   - Scopolamine skin patch used in motion sickness.

**Question:** Why do antimuscarinic agents cause hypotension in high concentrations?  
**Answer:** The muscarinic and nicotinic receptors although different recognize the same transmitter (ie. Ach). Therefore the receptive site for Ach is very similar. Atropine will block muscarinic receptors, and at high toxic doses can inhibit ganglionic nicotinic receptors to cause a fall in BP. The muscarinic receptors in the vasculature are not innervated and thus do not receive any activity, hence blocking these has no effect. However, atropine does have a non-receptor, direct vasodilator effect at high toxic doses (Red as a beet). The other terms for atropine toxicity are 'Hot as hell' referring to decreased sweat secretion and CNS changes in thermoregulation; 'Mad as a hatter': CNS delium; 'Dry as a bone': decreased saliva and 'Blind as a bat': cycloplegia (blurred vision).
B. Antimuscarinic Agents:

Inhibition of the action of Ach on muscarinic receptors can unmask nicotinic effects or unmask sympathetic tone ie. injected antimuscarinic can lead to increase in heart rate.

1. **Belladonna alkaloids (well absorbed, CNS effects)**
   - atropine (deadly nightshade, 7-10d)
   - homatropine (1-3 d)
   - scopolamine (3-7 d)

2. **Synthetic antimuscarinics**
   - ipratropium (quaternary amine)
   - pirenzepine (tri-cyclic, M1-selective)
   - benztropine (Parkinson’s Disease)
   - gycopyrolate (quaternary amine)
   - propantheline (Probanthine, quaternary amine)

C. Clinical Uses of Antimuscarinic Agents:

1. respiratory (decrease bronchial secretion)
2. asthma (ipratropium)
3. ophthalmologic (mydriasis, cycloplegia)
4. Parkinson’s disease (benztropine)
5. cardiovascular (prevent HR changes with AchE inhibition)
6. motion sickness (scopolamine)
7. GI disorders: peptic ulcers (pirenzepine), diarrhea
8. cholinergic poisoning eg. pesticides, mushrooms

D. Toxicity and Treatment of Antimuscarinic Agents

Toxicity is an extension of their antimuscarinic effects: ie. dry mouth, mydriasis, tachycardia, hot flushed skin, agitation and delirium. Also side-effect of ‘therapeutic’ action: ie. mydriasis when used for motion sickness. High concentrations may cause ganglionic-blockade leading to hypotension.

Treatment of antimuscarinic poisoning: cholinesterase inhibitor eg. neostigmine or physostigmine. For reversal of hypotension may use sympathomimetics such as phenylephrine or methoxamine.

E. Other Parasympatholytics

1. Hemicholinium: inhibit the uptake of choline (↓ synthesis of Ach)
2. Botulinus toxin: prevent release of Ach
   Used to treat facial muscle spasms, Strabimus, facial wrinkles
V. PHARMACOLOGY OF THE EYE

A. Mechanism of action of drugs used in the treatment of glaucoma.

Glaucoma is caused by a number of eye conditions, which in most cases is associated with an increase in intraocular pressure. In open-angle (wide-angle or chronic) glaucoma this is due to decreased outflow (most common) or increased secretions. Whereas in narrow-angle (acute) glaucoma, dilation of the pupil causes decreased outflow. Usually this is surgically corrected. Elevated pressure is caused by a backup of fluid in the anterior chamber and over time, causes damage to the optic nerve leading to blindness. Outflow of aqueous humor occurs through the Trabecular meshwork. Approximately 3 million in USA have glaucoma and only 50% are diagnosed..

1. Increased intraocular pressure (IOP): Untreated → blindness
   a. Open-angle (wide, chronic) – usually treated with beta-blockers, PGs
   b. Closed-angle (narrow-angle) – dilated iris can occlude outflow, (surgical removal of part of iris (iridectomy))
   c. Pilocarpine: ‘drug of choice’ for rapid reduction in IOP
B. Agents used in the Treatment of Glaucoma

<table>
<thead>
<tr>
<th>Agents</th>
<th>Mechanism Description</th>
<th>Side-Effects</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Blockers: Timolol, betaxolol, carteolol</td>
<td>↓ secretion from ciliary epithelium</td>
<td></td>
<td>Topical</td>
</tr>
<tr>
<td>Prostaglandins (PGF2α) Latanoprost</td>
<td>↑ Outflow</td>
<td>redness, pupil darkening</td>
<td>Tropical</td>
</tr>
<tr>
<td>Cholinomimetics</td>
<td>Ciliary muscle contraction → opening of trabecular meshwork → ↑ outflow</td>
<td>miosis, cycloplegia</td>
<td>Topical</td>
</tr>
<tr>
<td>Pilocarpine, physostigmine, echothiophate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Beta-blockers like Timolol and Prostaglandins like latanoprost are the most commonly used for chronic glaucoma.

For acute glaucoma treatment: Pilocarpine (DOC) → rapid ↓ pressure in wide- and narrow-angle.

**Question:** What causes cycloplegia?

**Answer:** Cycloplegia is loss of accommodation or loss of the ability to focus. Contraction or relaxation of the ciliary m. alters the shape of the lens and hence the ability to focus. To function normally the ciliary m. needs to be able to both relax and contract. This is why both muscarinic blockers (like atropine) and muscarinic agonists (like pilocarpine) as well as AchE inhibitors can cause cycloplegia. Likewise ganglionic blockers can also cause cycloplegia because they interfere with the parasympathetic transmission to the ciliary m. Note the absence of sympathetic innervation to the ciliary m. hence the lack of effect on cycloplegia.
C. Horner’s Syndrome

1. destruction of sympathetic fibers on affected side
2. ptosis, miosis, anhydrosis
3. diagnosis: cocaine will not dilate “Horner’s pupil”, but fully dilate the normal contralateral pupil

D. Effects of pharmacological agents on the pupil

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Drug*</th>
<th>Pupillary Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Alpha-agonist</td>
<td>Dilation (mydriasis)</td>
</tr>
<tr>
<td>Normal</td>
<td>Alpha-blocker</td>
<td>Constriction (miosis)</td>
</tr>
<tr>
<td>Normal</td>
<td>Muscarinic agonist</td>
<td>Constriction (miosis), Cyclopegia</td>
</tr>
<tr>
<td>Normal</td>
<td>Muscarinic blocker</td>
<td>Dilation (mydriasis), Cyclopegia</td>
</tr>
<tr>
<td>Normal</td>
<td>Cocaine</td>
<td>Dilation</td>
</tr>
<tr>
<td>Normal</td>
<td>Hydroxyamphetamine</td>
<td>Dilation</td>
</tr>
<tr>
<td>Normal</td>
<td>Opioids</td>
<td>Miosis (pinpoint pupils)</td>
</tr>
<tr>
<td>Horner’s syndrome</td>
<td>Cocaine</td>
<td>No dilation</td>
</tr>
<tr>
<td>Preganglionic Horner’s</td>
<td>Hydroxyamphetamine</td>
<td>Dilation</td>
</tr>
<tr>
<td>Postganglionic Horner’s</td>
<td>Hydroxyamphetamine</td>
<td>No dilation</td>
</tr>
</tbody>
</table>

Figure 8. Innervation of the iris muscle
THE AUTONOMIC GANGLIA
Edward JN Ishac, Ph.D.
Associate Professor, Pharmacology and Toxicology
Smith 742, 828-2127, e-mail: eishac@vcu.edu

Learning Objectives:
1. Understand steps involved in ganglionic neurotransmission
2. Understand the role the autonomic ganglia plays in the regulation of homeostasis.

I. STRUCTURE AND PHYSIOLOGY OF THE AUTONOMIC GANGLION

The ganglionic nicotinic receptor (sympathetic and parasympathetic) is a pentamer composed of 2 distinct subunits ($\alpha, \beta$), $\alpha$ chains contain the Ach binding sites. Binding of Ach to receptor leads to opening of ion channel (inward Na$^+$, outward K$^+$).
II. GANGLIONIC STIMULANTS (clinically not important)

A. Nicotine
   • active ingredient in tobacco (0.3-20mg)
   • fatal dose (40mg)
   • metabolized & excreted rapidly
   • slight increase in heart rate
   • some rise in blood pressure
   • modest increase in respiratory rate

Others:

   Lobeline (tobacco)
   Acetylcholine, DMPP (experimental, not important)

B. Insecticides and rodenticide
   • nicotine is often the effective agent
   • persistent stimulation

C. Toxicity
   • CNS stimulation: convulsions, headache
   • NMJ paralysis: depolarizing blockade
   • hypertension, hypotension, cardiac arrhythmias
   • vomiting, diarrhea
   • increase secretions, salivation

D. Treatment
   • vomiting induced for oral ingestion (insecticides)
   • treatment symptom-directed
      a. muscarinic excess: anticholinergic (atropine)
      b. NMJ blockade: mechanical respiration
      c. CNS stimulation: anticonvulsant (diazepam)
III. GANGLIONIC BLOCKING AGENTS

Not important clinically

A. Mecamylamine (effective orally, CNS effects)

B. Trimethapan (inactive orally)
   • used in hypertensive emergencies of central origin
   • controlled hypotension during surgery
   • short duration of action

C. Nicotine - depolarizing blocker (never used as such)

D. Toxicity is extension of their ganglionic blocking activity
   • hypotension, postural hypotension

E. Treatment
   • pressor agent to counter hypotension actions

IV. PREDOMINANT AUTONOMIC NERVOUS SYSTEM ON VARIOUS EFFECTOR SITES

<table>
<thead>
<tr>
<th>Site</th>
<th>Predominant ANS</th>
<th>Effect of Ganglionic Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterioles</td>
<td>Sympathetic</td>
<td>vasodilation, hypotension</td>
</tr>
<tr>
<td>Veins</td>
<td>Sympathetic</td>
<td>vasodilation, ↓venous return, ↓CO</td>
</tr>
<tr>
<td>Heart</td>
<td>Parasympathetic</td>
<td>tachycardia</td>
</tr>
<tr>
<td>Iris</td>
<td>Parasympathetic</td>
<td>mydriasis (dilation)</td>
</tr>
<tr>
<td>Ciliary muscle.</td>
<td>Parasympathetic</td>
<td>cycloplegia (loss of accommodation)</td>
</tr>
<tr>
<td>GI tract</td>
<td>Parasympathetic</td>
<td>↓tone, ↓motility, constipation</td>
</tr>
<tr>
<td>Urinary</td>
<td>Parasympathetic</td>
<td>urinary retention</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>Parasympathetic</td>
<td>xerostomia (dry mouth)</td>
</tr>
<tr>
<td>Sweat glands</td>
<td>Sympathetic</td>
<td>anhidrosis (low sweating)</td>
</tr>
</tbody>
</table>
Learning Objectives:

1. Understand the physiology of the neuromuscular junction and the structure and function of nicotinic receptor
2. Understand the mechanisms by which competitive and depolarizing neuromuscular blockers cause paralysis.

I. NEUROMUSCULAR NICOTINIC RECEPTORS.

History: first receptor to be isolated, cloned. High concentration of receptors in electric eel, potent long lasting blocker: \( \alpha \)-bungarotoxin. Five receptor subunits forming ion channel. Different subunit isoforms and composition define pharmacological differences among receptors in skeletal muscle, ganglia and CNS.

Active zones contain “docking” sites, quantal release of ACh \((10^4 \text{ molecules})\) causes miniature end plate potential (MEPP), which summate to EPP, trigger action potential in muscle.

ACh receptors are located on the ends of folds. Acetylcholinesterase (AChE) is located in folds. Binding of ACh to receptor leads to opening of ion channel (inward \( \text{Na}^+ \), outward \( \text{K}^+ \)).

![Figure 1. The motor endplate](image-url)
II. CLASSIFICATION OF NEUROMUSCULAR BLOCKING AGENTS
See Tables 1, 2, 3 at end for characteristics of individual NMJ Blocking Agents

A. Non-depolarizing (competitive) blocking agents (ie. Tubocurarine)
B. Depolarizing blocking agents (ie. Succinylcholine)

**Acetylcholine:** The binding of Ach to the NMJ N-receptor leads to membrane depolarization and opening of the ‘ion-channel’ allowing the outflow of K+ and inflow of N+ ions. Ach is rapidly metabolized by acetylcholinesterase and the membrane repolarizes leading to closure of the ‘ion-channel’. The triggered muscle action potential travels over the muscle surface and T-tubules to cause the release of calcium from the endoplasmic reticulum and subsequent muscle contraction.

**Depolarizing Drugs:** *Succinylcholine* is the only therapeutically useful neuromuscular blocker that acts as a depolarizing agent. It is effectively a more stable agonist than ACh, undergoing slow inactivation and hence having a much more prolonged duration of action than ACh. Initially, it causes persistent depolarization of the muscle end plate (synaptic target), yielding fasciculations. [This stage is referred to as phase I]. Maintained depolarization will block the ability of ACh to trigger muscle action potentials. With time, succinylcholine will desensitize the muscle nicotinic receptors, resulting in repolarization of the muscle, but the end plate remains blocked, most likely due to succinylcholine blocking the ion channel of the muscle nicotinic receptor. [Sometimes called ‘desensitization block’; this stage is referred to as phase II, clinically not important]. NMJ blockade cannot be reversed by increasing ACh concentration.

**Nondepolarizing Drugs:** The remaining NMJ blockers all act as basic competitive blockers, such as Tubocurarine for ACh at the muscle nicotinic receptors. NMJ blockade can be reversed by increasing ACh concentration (ie with AChE inhibitors). Relaxed, flaccid paralysis.
A. Competitive (nondepolarizing) Neuromuscular Blocking Agents:

- Compete with Ach for binding to receptor
- Muscle can still be stimulated directly
- Given intravenously, not well absorbed orally
- Flaccid, relaxed paralysis.
- Paralysis: small, rapidly moving muscles (eyes, fingers); then limbs, neck; last in respiratory muscles (recovery in reverse order)
- Some ganglionic blocking effect and histamine release, resulting in hypotension and tachycardia, bronchospasm. Vecuronium is devoid of these secondary effects.
- Neuromuscular block reversible by inhibitors of acetylcholinesterase e.g. neostigmine

1. Tubocurarine (curare: South America arrow poison)
   - dimethyltubocarine (metocarine)
     - no effect on nerve transmission
     - in its presence muscle can still be stimulated
     - long onset, 4-6min; long-acting, 80-120min
     - can cause bronchospasm due to histamine release from mast cells
     - can block ganglionic receptors at high concentrations which can lead to hypotension

2. Pancuronium
   - more potent than tubocurarine (x5)
   - less histamine release than curare
   - lack of ganglionic blockade

3. Others:
   - Gallamine: no histamine release, no ganglion block, muscarinic block
   - Mivacurium: fast onset, 2-4min; short acting, 12-18min; some histamine release, good substitute for succinylcholine
   - Rocuronium: fast onset, 1-2min, short-intermediate, 30-40min, hypersensitivity, good substitute for succinylcholine
   - Atracurium, Vecuronium, Alcuronium
4. **Adverse effects and treatment**
   - apnea (loss of breathing)
   - ganglionic blockade (tubocurarine)
   - histamine release leads to bronchospasm (tubocurarine)
   - hypotension due to ganglionic block and secondary due to histamine release (tubocurarine)
   - no significant CNS effects
   - treatment of toxicity with AChE inhibitors (neostigmine)

![Figure 3](image)

**B. Depolarizing Neuromuscular Blocking Agents**

1. **Succinylcholine**
   - Initial depolarization (agonist, transient fasciculations) followed by paralysis.
   - Rapid onset, 1-2min
   - Brief duration (5-10min), due to breakdown by pseudocholinesterase 1/10,000 atypical pseudocholinesterase → long lasting inhibition.
   - Less effects at ganglia or on histamine release.

Persistent action induces depolarization, fasciculations (stimulation then paralysis)
Phase 1 block: - depolarization (potentiated by AChE inhibitors)
Phase 2 block: - desensitization (membrane repolarizes, hyposensitive to Ach)

![Figure 4](image)
3. **Adverse effects**

a. similar to competitive blockers

b. use of AChE inhibitors will not reverse NMJ blockade

c. **Malignant hyperthermia** (more likely with halothane)
   65% mortality, treat immediately with dantrolene (drug of choice, inhibits calcium release)

d. **Hyperkalemia** $\rightarrow$ cardiac arrest
   (more common in trauma and burn patients, develops slowly in 4-6 days)

e. **Prolonged paralysis** due to atypical or low circulating pseudocholinesterase

f. **Rocurarium** (liver metabolism) or **Mivacurium** are often used as substitutes when succinylcholine is not suitable

---

**Malignant Hyperthermia:** is a life-threatening disease, also referred to as a syndrome, which occurs when a person with malignant hyperthermia (MH) susceptibility trait is exposed to triggering factors, which include succinylcholine and most inhalational anesthetics (though not Nitrous Oxide). Classic Malignant Hyperthermia is characterized by hypermetabolism, (increased oxygen consumption and increased carbon dioxide production), increased calcium release, muscle rigidity, muscle injury, and increased sympathetic nervous system activity. Hypermetabolism reflected by elevated carbon dioxide production precedes the increase in body temperature. Halothane and Caffeine contracture tests used to examine patients suspected of being MH susceptible. Prompt administration of Dantrolene (DOC) required for treatment.

**Prolonged paralysis:** Succinylcholine is metabolized by plasma (pseudo) cholinesterase. Metabolism is normally complete within 5-10 minutes. Some patients lack this enzyme or have an altered enzyme that does not metabolize succinylcholine as rapidly. These patients may remain paralysed for many hours after a standard dose of succinylcholine, and must be kept anaesthetized and ventilated until the succinylcholine has been eliminated by other slower methods (ie. excretion).

**Hyperkalemia:** can occur in some patients after succinylcholine administration and can be severe and fatal. Up-regulation of ACh N-receptors can occur after burn injury, severe muscle trauma, upper or lower motor neuron denervation (e.g., stroke or spinal cord injury). The increased receptors can lead to excessive increase in plasma K+ levels due to membrane depolarization following succinylcholine administration. Develops in 4-6 days.

**Question:** Atypical pseudocholinesterase would cause problems with succinylcholine, does it increase the effects of non-depolarizing drugs such as mivacurium that are AchE metabolized.

**Answer:** Yes, if plasma cholinesterase activity is low (ie atypical pseudocholinesterase), then the actions of competitive NMJ blockers that are metabolized by AchE would also be prolonged. However unlike succinylcholine, the NMJ-blockade with the competitive NMJ blockers can be reversed with cholinesterase inhibitors such as neostigmine. This is not possible with succinylcholine, it would only make the blockade deeper. Rocurarium (liver metabolism) can be used as a substitute when use of succinylcholine is not advised.
C. Clinical Uses of Neuromuscular Blocking Agents

1. Muscle relaxation in surgery
   
a. Muscle relaxation decreases depth of anesthesia needed (decreases risk of respiratory and cardiovascular depression)

   Note synergism with certain agents necessitates dose reduction
   - calcium channel blockers (↓ Ach release)
   - aminoglycoside antibiotics (↓ Ach release & stabilize membrane)
   - certain general anesthetics eg. halothane (stabilize membrane)

b. Orthopedics: dislocations, alignment of fractures

c. Facilitate intubation in mechanical artificial ventilation

d. Facilitation of laryngoscopy, bronchoscopy, esophagoscopy

2. Prevent trauma during electroshock therapy

3. Diagnostic (tubocurarine: myasthenia gravis ie. makes it worse, not recommended)

D. Direct Acting Neuromuscular Relaxant

- dantrolene (Dantrium) inhibits calcium release from SR
- significant liver toxicity, muscle weakness
- used to treat malignant hyperthermia (DOC, drug of choice)
- used in stroke, cerebral palsy, multiple sclerosis, muscle spasticity/rigidity

Other agents used as muscle relaxants (e.g. benzodiazepines) will be discussed in the CNS portion of the course.
### Table 1. Autonomic Effects of Neuromuscular Blocking Drugs

<table>
<thead>
<tr>
<th></th>
<th>Ganglia</th>
<th>Muscarinic</th>
<th>Histamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Succinylcholine</strong></td>
<td>Stimulates</td>
<td>Stimulates</td>
<td>Slight release</td>
</tr>
<tr>
<td><strong>Tubocurarine</strong></td>
<td>Moderate block</td>
<td>None</td>
<td>Moderate release</td>
</tr>
<tr>
<td><strong>Metaocurine</strong></td>
<td>Blocks weakly</td>
<td>None</td>
<td>Slight release</td>
</tr>
<tr>
<td><strong>Gallamine</strong></td>
<td>None</td>
<td>Blocks strongly</td>
<td>None</td>
</tr>
<tr>
<td><strong>Pancuronium</strong></td>
<td>None</td>
<td>Blocks weakly</td>
<td>None</td>
</tr>
<tr>
<td><strong>Vecuronium</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Atracurium</strong></td>
<td>None</td>
<td>None</td>
<td>Slight release</td>
</tr>
<tr>
<td><strong>Rocuronium</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Mivacurium</strong></td>
<td>None</td>
<td>None</td>
<td>Slight release</td>
</tr>
</tbody>
</table>

### Table 2. Comparison of Competitive (d-Tubocurarine) and Depolarizing (Succinylcholine) Agents

<table>
<thead>
<tr>
<th></th>
<th>Phase I</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addition of succinylcholine</td>
<td>Antagonistic</td>
<td>Additive</td>
</tr>
<tr>
<td>Addition of tubocurarine</td>
<td>Additive</td>
<td>Antagonistic</td>
</tr>
<tr>
<td>Effect of neostigmine</td>
<td>Antagonistic</td>
<td>Augmented</td>
</tr>
<tr>
<td>Initial effect on striated</td>
<td>None</td>
<td>Fasciculations</td>
</tr>
<tr>
<td>Response to tetanic stimulation</td>
<td>Unsustained</td>
<td>Sustained</td>
</tr>
</tbody>
</table>

### Table 3. Onset, Duration and Elimination of Neuromuscular Blocking Drugs

<table>
<thead>
<tr>
<th></th>
<th>Onset (min)</th>
<th>Duration (min)</th>
<th>Mode of elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Succinylcholine</strong></td>
<td>1-2</td>
<td>6-8</td>
<td>Hydrolysis by AChE</td>
</tr>
<tr>
<td><strong>Tubocurarine</strong></td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td><strong>Metaocurine</strong></td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney</td>
</tr>
<tr>
<td><strong>Gallamine</strong></td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney</td>
</tr>
<tr>
<td><strong>Pancuronium</strong></td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td><strong>Vecuronium</strong></td>
<td>2-4</td>
<td>30-40</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td><strong>Atracurium</strong></td>
<td>2-4</td>
<td>30-40</td>
<td>Hydrolysis by AchE</td>
</tr>
<tr>
<td><strong>Pipecuronium</strong></td>
<td>2-4</td>
<td>80-100</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td><strong>Rocuronium</strong></td>
<td>1-2</td>
<td>30-40</td>
<td>Liver</td>
</tr>
<tr>
<td><strong>Mivacurium</strong></td>
<td>2-4</td>
<td>12-18</td>
<td>Hydrolysis by AChE</td>
</tr>
</tbody>
</table>
1. **Tissues / Organs:** - receptors present, tissue / organ response
2. **Transmitters:** - synthesis, storage, release, regulation (NE, Ach)
3. **Eye:** - miosis, mydriasis, cycloplegia, Glaucoma: wide- vs narrow-angle, Horner’s S.
4. **Drugs:** - receptor selectivity, mechanism of action, 2nd messenger
5. **Can predict:** - clinical application, side effects, toxicity, treatment of toxicity
6. **General:** - learn drugs by drug classes, important adverse reactions, not dosage
7. **Key diagrams:** - ANS structures, NE & Ach neurons, eye anatomy
8. **ANS Excess / Deficiency**
   - Cholinergic excess: salivation, lacrimation, urination, diarrhea, emesis (sludge), miosis (ie AchE inh)
   - Cholinergic deficiency: ↓GI motility, mydriasis, cycloplegia, ↓secretions, delirium (ie. Atropine toxicity)
   - Sympathetic excess: ↑BP, ↑HR, pupil dilation (mydriasis), ↓GI motility (ie. Tyr-MAOI or pheochroma.)
   - Sympathetic deficiency: ↓BP, ↓tissue perfusion, pupil constriction (miosis) (ie. ganglia blockade)
9. **Terminology:**
   i. clammy: → parasympathetic (PNS) excess (↑secretions)
   ii. wheezy: → PNS excess, ie difficulty in breathing (↑bronchial resistance)
   iii. flushed: → PNS deficiency ie. vasodilatation, thermoregulation (atropine toxicity)
   iv. cramps: → muscle contraction ie. abdominal cramps (↑PNS activity)
   v. palpitations: → SNS excess → increase HR, BP (ie. pheochromocytoma, MAOI-tyramine interaction)
10. **Drugs of Choice (DOC):**
    | Agent            | Therapeutic use                                      | Notes                                                                 |
    |------------------|------------------------------------------------------|----------------------------------------------------------------------|
    | Epinephrine      | Acute hypersensitivity reaction ie. bee attack, food or drug reaction | α- β-agonist, physiologically counters the effects of released histamine (ie. bronchospasm, ↓BP) |
    | Dopamine         | Shock ie. septic                                      | Pressor agent (α1-receptors) to maintain BP but dilates renal vessels (D1-receptors), NE → renal vasoconstriction |
    | Timolol, Latanoprost | Glaucoma (chronic)                                   | β-blocker, ↓secretion, least side effects, 2/d PGF2α analogue, ↑outflow, redness, dark pigment, 1/d |
    | α-blocker or Labelol, Carvedilol | Hypertensive (HT) crisis ie. Tyramine-MAOI effect, ADHD Rx excess, pheochromocytoma | Labelol, Carvedilol (α- β-blockers) can reduce both BP & HR, or α-blocker (ie. phenoxybenzamine or phenolamine only reduce BP). Note: in HT crisis can give β-blocker only after α-blocker, never before |
    | β-Blocks (Propranolol) A-M β1-selective | Hypertension, angina, CHF, arrhythmias, tremor, migraine, hyperthyroidism, panic stress | Differ in selectivity (β- vs β1-), LA-action, partial agonist activity (ISA). CI: heart failure (unstable CHF, depression, bradycardia, bronchospasm), asthma, diabetes, Raynaud D |
    | Pilocarpine      | Emergency glaucoma                                    | M-agonist causes rapid ↑outflow, both wide-, narrow-angle              |
    | Physostigmine    | Reverse atropine toxicity                             | Reversible AchE inhibitor, can cross CNS                                |
    | Pralidoxime      | Regenerate AchE enzyme                                | 2-PAM, use before ‘aging’ occurs, only organophosphates               |
    | Atropine         | Reverse AchE inhibition                              | Reverse toxic effects of AchE inhibitors ie. neostigmine, physostigmine, or organophosphates |
    | Dantrolene       | Malignant hyperthermia                               | Inhibits calcium release from SR                                        |
11. **Prototype, common Drugs:** ie. propranolol, metoprolol, atenolol, tubocurarine, succinylcholine, etc
12. **Cardiovascular Responses**
    Moderate/high doses (typical) for NE (↑BP, ↓HR reflex), EPI (↑BP, ↑HR), ISO (↓BP, ↑HR)
    Epinephrine reversal (EPI response in presence of α-blocker ie. phentolamine)
    Norepinephrine in presence of atropine (↑BP, ↑HR)
13. **Neuromuscular Agents**
    Succinylcholine: - depolarizing (only agent), cannot reverse, short-acting, fasciculations atypical pseudo-AchE, malignant hyperthermia, hyperkalemia
    Tubocurarine: - non-depolarizing, competitive, reversible, long-acting, relaxed paralysis
    Rocuronium: fast onset, 30-40min duration
    Mivacurium: fast onset, short duration
### Cardiovascular System

\[ BP = CO \times TPR, \quad CO = SV \times HR \]

#### Sympathetic NS

<table>
<thead>
<tr>
<th>Organ</th>
<th>Action</th>
<th>Receptor</th>
<th>Action</th>
<th>Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye: Radial m.</td>
<td>Mydriasis</td>
<td>( \alpha_1 )</td>
<td>Miosis</td>
<td>( M_2, M_3 )</td>
</tr>
<tr>
<td>Circular m.</td>
<td>Contract</td>
<td>( \alpha_1 )</td>
<td>Relax</td>
<td>( M_3 (NO) )</td>
</tr>
<tr>
<td>Ciliary m.</td>
<td>Miosis</td>
<td>( \alpha_1 )</td>
<td>Contract</td>
<td>( M_3 )</td>
</tr>
<tr>
<td>Heart</td>
<td>↑HR, ↑force</td>
<td>( \beta_1 )</td>
<td>↓HR</td>
<td>( M_2 )</td>
</tr>
<tr>
<td>Vascular muscle</td>
<td>Constrict</td>
<td>( \alpha_1 )</td>
<td>Relax</td>
<td>( M_3 (NO) )</td>
</tr>
<tr>
<td>Bronchial m.</td>
<td>Relax</td>
<td>( \beta_2 )</td>
<td>Contract</td>
<td>( M_3 )</td>
</tr>
<tr>
<td>GI-tract</td>
<td>↓motility</td>
<td>( \alpha_1, \beta_2 )</td>
<td>↑motility</td>
<td>( M_3 )</td>
</tr>
<tr>
<td>Sphincter m.</td>
<td>Contract</td>
<td>( \alpha_1 )</td>
<td>Relax</td>
<td>( M_3 )</td>
</tr>
<tr>
<td>Genitourinary m.</td>
<td>Relax</td>
<td>( \beta_2 )</td>
<td>Contract</td>
<td>( M_3 )</td>
</tr>
</tbody>
</table>

#### Parasympathetic NS

<table>
<thead>
<tr>
<th>Organ</th>
<th>Action</th>
<th>Receptor</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye</td>
<td>Miosis</td>
<td>( M_2, M_3 )</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>↓HR</td>
<td>( \alpha_1 )</td>
<td>↓HR (reflex)</td>
</tr>
<tr>
<td>Vascular muscle</td>
<td>Constrict</td>
<td>( \beta_1 )</td>
<td>( M_3 (NO) )</td>
</tr>
<tr>
<td>Bronchial m.</td>
<td>Relax</td>
<td>( \beta_2 )</td>
<td>( M_2 )</td>
</tr>
<tr>
<td>GI-tract</td>
<td>↑motility</td>
<td>( \alpha_1, \beta_2 )</td>
<td>( M_3 )</td>
</tr>
<tr>
<td>Sphincter m.</td>
<td>Contract</td>
<td>( \alpha_1 )</td>
<td>( M_3 )</td>
</tr>
<tr>
<td>Genitourinary m.</td>
<td>Relax</td>
<td>( \beta_2 )</td>
<td>( M_3 )</td>
</tr>
</tbody>
</table>

#### Cardiovascular Drug Effects

<table>
<thead>
<tr>
<th>Circuit</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine, PE</td>
<td>↑BP, ↓HR (reflex)</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>BP (o/-), ↑HR, ↑PP</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>↑BP, ↑HR, ↑PP</td>
</tr>
<tr>
<td>Mecamylamine</td>
<td>↓BP, ↓HR (o/+), ↑HR</td>
</tr>
<tr>
<td>Propranolol</td>
<td>BP (o/-), ↓HR</td>
</tr>
<tr>
<td>Atropine</td>
<td>BP (o/-), ↓HR</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>↓BP, ↑HR (reflex), ↑PP</td>
</tr>
</tbody>
</table>

#### Messengers

<table>
<thead>
<tr>
<th>Messenger</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>↑BP, ↑HR, ↑PP</td>
</tr>
<tr>
<td>Mecamylamine</td>
<td>↓BP, ↓HR (o/+), ↑HR</td>
</tr>
<tr>
<td>Propranolol</td>
<td>BP (o/-), ↓HR</td>
</tr>
<tr>
<td>Atropine</td>
<td>BP (o/-), ↓HR</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>↓BP, ↑HR (reflex), ↑PP</td>
</tr>
</tbody>
</table>

---

**Diagram:**
- Sympathetic and parasympathetic nervous system interactions with various organs.
- Diagrams of neurotransmitter pathways, including monoamines and receptors.

---

**Key Terms:**
- BP: Blood Pressure
- CO: Cardiac Output
- TPR: Total Peripheral Resistance
- SV: Stroke Volume
- HR: Heart Rate
<table>
<thead>
<tr>
<th>Agent (trade name®)</th>
<th>Therapeutic Use</th>
<th>Notes</th>
<th>E. Ishac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine (Levarterenol)</td>
<td>Hypotension, pressor agent</td>
<td>α / β; β₁ (β₂) neuronal, non-circulating, I: MAOI, TCA</td>
<td></td>
</tr>
<tr>
<td>Epinephrine (generic)</td>
<td>Allergic reactions, shock, CPR</td>
<td>α / β; β₁ (β₂) adrenal medulla, circulate; I: maoi, TCA</td>
<td></td>
</tr>
<tr>
<td>Dopamine (Intropin)</td>
<td>Renal vasodilation during shock</td>
<td>α₁ / β₁ / D, precursor to NE, I: MAOI</td>
<td></td>
</tr>
<tr>
<td>Isoproterenol (Isuprel)</td>
<td>Asthma, cardiac stimulant</td>
<td>β, synthetic, not endogenous; BP(α, →) HR↑</td>
<td></td>
</tr>
<tr>
<td>Phenylephrine (Neosynephrine)</td>
<td>Nasal decongestant, hypertension</td>
<td>Not commonly used for hypotension; S: CV, reflex bradycardia</td>
<td></td>
</tr>
<tr>
<td>Methoxamine (Vasoxyl)</td>
<td>Hypotension, pressor agent</td>
<td>α, orally active; NE or DA better choice</td>
<td></td>
</tr>
<tr>
<td>Metaraminol (Aramine)</td>
<td>Hypotension, pressor agent</td>
<td>β₁; iv infusion, tolerance, desensitization</td>
<td></td>
</tr>
<tr>
<td>Clonidine (Catapres)</td>
<td>Hypertension</td>
<td>α₂, CNS sympathetic outflow, inhibit NE release, rebound HT; S: dry mouth, sedation, impotence. α-methyl-dopa is metabolized to α-methyl-NE (α₂-agonist, positive Coombs test)</td>
<td></td>
</tr>
<tr>
<td>Guanfacine (Tenex)</td>
<td>Opioid withdrawal (clonidine)</td>
<td>α₁, no LA-action, no ISA, very short acting</td>
<td></td>
</tr>
<tr>
<td>α-methyl-dopa (Aldomet)</td>
<td>Hypertension</td>
<td>α₁, irreversible, S: PHX</td>
<td></td>
</tr>
<tr>
<td>Dobutamine (Dobutrex)</td>
<td>CHF, cardiac stimulant</td>
<td>β₁; iv infusion, tolerance, desensitization</td>
<td></td>
</tr>
<tr>
<td>Prenalterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol (Proventil, Ventolin)</td>
<td>Asthma - bronchodilator</td>
<td>β₂-selective, Oral 1-2 hrs onset → 4-6 hrs duration, Inhalation 5-10 min onset → 3-4 hrs duration; S: cardiovascular; less via inhalation</td>
<td></td>
</tr>
<tr>
<td>Ritodrine (Yutopar)</td>
<td>Premature labor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metaproterenol (Alupent)</td>
<td>Asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terbutaline (Brethaire)</td>
<td>Asthma, (premature labor)</td>
<td>Note: Terbutaline not FDA approved for premature labor (cheaper, longer lasting than Ritodrine)</td>
<td></td>
</tr>
</tbody>
</table>

### Miscellaneous Adrenergic Agents

<table>
<thead>
<tr>
<th>Agent (trade name®)</th>
<th>Therapeutic Use</th>
<th>Notes</th>
<th>E. Ishac</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Dopa (Dopar, Larodopa)</td>
<td>Parkinson's disease</td>
<td>precursor to DA, cross to CNS → DA</td>
<td></td>
</tr>
<tr>
<td>Ephedrine (Vatrolol, Efedron)</td>
<td>Nasal decongestant, red eyes</td>
<td>α₁, also indirect to release NE; I: MAOI, TCA</td>
<td></td>
</tr>
<tr>
<td>Amphetamine (Dexedrine)</td>
<td>Narcolepsy, hyperactivity, [obesity]</td>
<td>Displaces NE, CNS stimulant, requires uptake1, can cause tolerance, tachyphylaxis</td>
<td></td>
</tr>
<tr>
<td>Methylyphenidate (Ritalin)</td>
<td>Hyperactivity disorder (ADHD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tyramine</td>
<td>None, [high] in red wine &amp; cheese</td>
<td>Interaction with MAO inhibitors, → hypertension</td>
<td></td>
</tr>
</tbody>
</table>

### Adrenergic Antagonists

<table>
<thead>
<tr>
<th>Agent (trade name®)</th>
<th>Therapeutic Use</th>
<th>Notes</th>
<th>E. Ishac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenoxymethamine (Dibenzyline)</td>
<td>Pheochromocytoma, acute, chronic HT</td>
<td>α₁, irreversible, S: PHT</td>
<td></td>
</tr>
<tr>
<td>Phentolamine (Regitine)</td>
<td>Pheochromocytoma, acute HT</td>
<td>α, competitive, S: PHT, reflex tachycardia</td>
<td></td>
</tr>
<tr>
<td>Tolazoline (Priscoline)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prazosin (Minipres)</td>
<td>Hypertension (HT), benign prostate hypertrophy</td>
<td>α₁, competitive; no reflex tachycardia S: 1⁴th pass effect, PHT, nausea, drowsiness</td>
<td></td>
</tr>
<tr>
<td>Terazosin (Hytrin), Doxazosin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yohimbine (Yohimex)</td>
<td>[Impotence]</td>
<td>α₂, currently not used as such, available OTC</td>
<td></td>
</tr>
<tr>
<td>Propranolol (Inderal)</td>
<td>Hypertension, angina, arrhythmias, tremor, migraine, hyperthyroidism (propranolol), panic stress</td>
<td>β₁, non-selective, LA-action, no ISA; Useful group, CI: heart failure (unstable CHF, depression, bradycardia or brochospasm), asthma, diabetes, Raynaud D</td>
<td></td>
</tr>
<tr>
<td>Note: β₁-blockers end in –olol, those that begin with A-M are β₂-selective</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pindolol (Visken)</td>
<td>Hypertension, angina, arrhythmias</td>
<td>β₁, LA-action, ISA, angina commonly</td>
<td></td>
</tr>
<tr>
<td>Timolol (Blocadren)</td>
<td>Glaucoma, decrease secretion; (HT)</td>
<td>β₁, no LA-action, no ISA, glaucoma commonly</td>
<td></td>
</tr>
<tr>
<td>Sotalol (Betapace)</td>
<td>Arrhythmias</td>
<td>β₁, no LA-action, no ISA, also K+ channel block</td>
<td></td>
</tr>
<tr>
<td>Metoprolol (Lopressor)</td>
<td>Hypertension, angina, arrhythmias, CHF</td>
<td>β₁, LA-action, no ISA, arrhythmia commonly</td>
<td></td>
</tr>
<tr>
<td>Atenolol (Tenormin)</td>
<td>Hypertension, angina</td>
<td>β₁, no LA-action, no ISA</td>
<td></td>
</tr>
<tr>
<td>Esmolol (Brevablate)</td>
<td>Arrhythmias, [angina]</td>
<td>β₁, no LA-action, no ISA, very short acting</td>
<td></td>
</tr>
<tr>
<td>Labetalol (Normodyne)</td>
<td>Hypertensive crisis, hypertension, CHF</td>
<td>β &amp; α₁-blocker, some β₂-agonist action</td>
<td></td>
</tr>
<tr>
<td>Carvedilol (Coreg)</td>
<td></td>
<td>β &amp; α₂-blocker</td>
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</tr>
</tbody>
</table>

### Miscellaneous Adrenergic Agents

<table>
<thead>
<tr>
<th>Agent (trade name®)</th>
<th>Therapeutic Use</th>
<th>Notes</th>
<th>E. Ishac</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-methyl-p-tyrosine (Metyrosine)</td>
<td>Pheochromocytoma (diffuse)</td>
<td>inhibit tyrosine hydroxylase (rate limiting step)</td>
<td></td>
</tr>
<tr>
<td>Cocaine (generic)</td>
<td>Drug of abuse, local anaesthetic</td>
<td>inhibit neuronal uptake, cross CNS; I: CA's, amph.</td>
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</tr>
<tr>
<td>Atiomoxetine (Strattera)</td>
<td>Attention deficient hyperactivity (ADHD)</td>
<td>inhibit NE neuronal uptake, FDA approved 2003</td>
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</tr>
<tr>
<td>Imipramine (tricyclic's) (Janitmine)</td>
<td>Depression, inhibit neuronal uptake; at toxic doses can block muscarinic, alpha, and histamine receptors</td>
<td>S: dry mouth, blurred vision, decrease urination; T: severe anticholinergic effect, respiratory depression, PHT (alpha-block)</td>
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<tr>
<td>Amitriptyline (Amitri, Elavil)</td>
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<tr>
<td>Pargyline, Phenelzine (MAOa)</td>
<td>Depression: non-selective, accumulation of NE, TCAs or SSRIs preferred</td>
<td>MAO inhibitors have important interaction with tyramine → HT crisis, S: agitation, tremor, insomnia,</td>
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<tr>
<td>Tranflcyclpromine (Parnate)</td>
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<tr>
<td>Clorgiline (MAOa)</td>
<td>Depression</td>
<td>found in nerve terminals, liver, kidney, CNS</td>
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</tr>
</tbody>
</table>
### Prostaglandins
- Latanoprost (PGF2α analogue) (Xalatan)
  - Glaucoma
  - ↓ outflow. S: brown pupil, red eyes (inflammation)

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### Diuretics
- Acetazolamide, Methazolamide
  - Glaucoma, mountain sickness
  - Oral, ↓ secretion due to lack of HCO₃⁻
- Dorzolamide, Brinzolamide
  - Topical, ↓ secretion due to lack of HCO₃⁻

### Prostaglandins
- Latanoprost (PGF2α analogue) (Xalatan)
  - Glaucoma
  - ↓ outflow. S: brown pupil, red eyes (inflammation)