Nervous system is divided into:

1. Central nervous system (Brain, Medulla, S.C)
2. Peripheral N.S.

Somatic nerves of voluntary nervous system which the efferent nerves are supplying the skeletal muscles.

Autonomic nerves of the involuntary nervous system i.e. efferent nerves supplying viscera, glands and smooth muscles.
Autonomic Nervous System

Parasympathetic Division
- Constricts pupil
- Stimulates tear glands
- Strong stimulation of salivaly flow
- Inhibits heart, dilates arterioles
- Constricts bronchi
- Stimulates stomach motility and secretion, stimulates pancreas
- Stimulates intestinal motility
- Contracts bladder
- Stimulates erection

Sympathetic Division
- Dilates pupil
- No effect on tear glands
- Weak stimulation of salivary flow
- Accelerates heart constricts arterioles
- Dilates bronchi
- Inhibits stomach motility and secretion, inhibits pancreas and adrenals
- Inhibits intestinal motility
- Relaxes bladder
- Stimulates ejaculation
Autonomic Nervous system
Syn: Involuntary N.S., Vegetative or Visceral nervous system.

-- It innervates: + Plain or involuntary or Smooth muscles

Exocrine glands
Visceral organs

Respiration, circulation, digestion, body temperature, metabolism, sweating, secretion of glands are regulated in a part and entirely by A.N.S and its control connections
Autonomic Nervous System consists of:
They are antagonistic in function on organs in a state of dynamic equilibrium.

Parasympathetic Nerves
Or
Craniofacial outflow
Or
Cholinergic

Sympathetic nerves
Or
Thoracolumbar Outflow
or
Adrenergic
Division of autonomic nervous system

Cranial (Brain) → Thoraco-lumber → Sacral region

Parasympathetic

Sympathetic

s.c.
Division of Autonomic nervous system

Parasympathetic
Cranioscral

Ganglia are inside organs

Cranio-Sacral

Sympathetic
Thoracolumbar Ganglia
(closed toss's)

Sacral

Brain

3rd

7th

9th

10th (Vagus Nerve)

S.C

2nd

3rd

4th

3rd

7th
Parasympathetic nerve
Parasympathetic outflow

Craniac
Sacral
Skeletal Muscle

1
Ach
somatic
N

2
Adrenal Medulla

3
Parasympathetic Ganglia

Viscera Ach
Smooth M Ach
Heart
Exocrine G Ach

Postganglionic fibers(nonmyelinated)

Preganglionic fiber(myelinated)

Central or nicotinic of acetylcholine
(1,2,3)

Peripheral action or muscurinic action of Acetylcholine

(1,2,3)
Sympathetic S.G. Postganglionic fiber Chromaffin granules
Preganglionic Ach (Adrenergic fiber)
(Cholinergic fiber)
Chromaffin granules at adrenergic nerve endings constitute S.m.
(Noradrenaline and adrenaline)
Sympathetic outflow

Sympathetic branches to sweat glands and BVs
(skin of face, an exception)

Preg.Fiber ACH Postganglionic fiber Adrenergic fiber
S.G. Chromaffin granules
Cholinergic Ach fiber
Autonomic fibers

Types of Autonomic fibers:

I Cholinergic fibers
Which secretes ACH

II Adrenergic fibers
which secretes
Adrenaline and
noradrenaline

A. Central C.F.
1. All autonomic preganglionic fibers
2. Splanchnic nerves to adrenal medulla
3. Somatic motor nerves to skeletal muscles

B. Peripheral C.F.
1. Parasympathetic postganglionic fibers
2. Postganglionic fibers of sympathetic branch supplying sweat glands & skin b. vs

They include all postganglionic fibers of sympathetic nervous system
Autonomic Receptors

These are areas or reactive chemical grouping on the surface of effector cells where the chemical transmitter (Acetylcholine or adrenaline or noradrenaline) when released at autonomic nerve endings combine and react specifically with it and a response is evoked from the effector cells.

These receptors are blocked by specific blockers (cholinergic or adrenergic blockers. (Lock and key)

B-Adrenergic cell receptors

- Adrenergic cell receptors @1

Cholinergic cell receptors

- Adrenergic cell receptors @1

B1

B2

B3
Autonomic Receptors

1. Cholinergic receptors

Central or nicotinic Receptors

- All autonomic ganglia
- Suprarenal medulla
- (modified sympathetic ganglia)
- Motor end plate of skeletal muscles

Sites

- smooth muscles
- Exocrine glands
- Heart (SAN&AVN) and other viscera
- Other organs supplied by postganglionic fibers e.g. sweat glands & BVs

Peripheral or muscarinic (m1, m2, m3, m4, m5)
2. Adrenergic receptors (Sites)  
(post-synaptic receptors)

@-adrenergic cell receptors:

@-1 Effector cells
(++) Smooth muscles of B.Vs

@-2 Presynaptic cells:
(--) release of NA
(--) Lipocytes
(--) Pancreas

B – Adrenergic cell receptors:

B1 (Effector cells):
(++) HEART

B2 (--) Smooth muscles
(--) blood vessels
(--) GIT
(++) Pancreas
(++) Lipocytes

B3:
(++) Lipocytes
Neurohumoral transmitters
Chemical transmitters or mediators
1. Cholinergic (Acetylcholine)
2. Adrenergic (Adrenaline & noradrenaline)

1. Acetylcholine

It is an ester of choline which is synthetized inside the nerve fiber within the mitochondria of cells, by combination of choline with an acetyl group by enzymatic transfer:

\[
\text{Acetate} + \text{Co-A} \rightarrow \text{Acetyl Co-A}
\]

\[
\text{Acetyl Co-A} + \text{choline} \rightarrow \text{Choline acetylase} \quad \text{Ach} + \text{Co-A}
\]

Acetylcholine is stored in inactive form in vesicles present in presynaptic membranes of cholinergic fibers.
Inactive Ach
Stored in viscles

Presynaptic membrane

Axon
Storage viscles

Active acetylcholine

Na+

K+

Na+

K+

Ca+

Synaptic cleft

Post synaptic membrane

Effector cells

Receptors

Neurohumoral transmission
Signal Transfer In The Synapse

1. Depolarization
   - Action potential
   - Ca^{2+} - channels
   - Ca^{2+}
   - Na^{+} - influx

2. Ca^{2+} - vesicle
   - Acetylcholine synthesis
   - Acetylcholine vesicle
   - Na^{+}

3. Exocytosis
   - Acetylcholine
   - Synaptic cleft

4. Ligand binding
   - Na^{+}

5. Na^{+} - influx
   - K^{+}

Preganglionic neuron
- Presynaptic terminal
- Acetylcholine esterase

Postganglionic neuron
- Action potential

Fig. 2-2
KMc
The acetyl group is obtained from acetyl coenzyme A, a part of the intermediary metabolism.

The coupling of choline with the acetyl group is catalyzed by the enzyme “Choline acetylase.”

- The synthesis of acetylcholine by choline acetylase is dependant upon the continued supply of choline and glucose, which is essential for synthesis of Coenzyme A. Choline is present in the extracellular site and cannot enter nerve axons.
- Choline is transported from extracellular site to intracellular particles by a specific choline transport mechanism (located in presynaptic membrane).
- The formed Ach is temporarily stored within the mitochondria (site of synthesis) and the main storage takes place within minute viscles formed by mitochondrial activity and scattered along the axon but found in the nerve terminals.
Acetylcholine is stored partly as a highly concentrated solution and partly adsorbed to vesicular membrane.

Acetylcholine is continuously released in small quantities from the vesicles even in absence of nerve impulses.

When the nerve fiber is stimulated, the contents of several vesicles are charged very rapidly due to increased permeabilities of the vesicular and axonal membranes.

The receptor site (cholinergic receptors) for Ach has an anionic site (to which the cationic head of Ach is attached) and an esteric site (to which the ester head of Ach is attached).

Cholinergic receptor

Anionic site

\[
\begin{array}{c}
\text{CH}_3 \\
\text{CH}_2 \\
\text{CH}_3 \\
\text{N} \\
\text{CH}_2 \\
\text{CH}_2 \\
\text{O} \\
\text{C} \sim \text{CH}_3
\end{array}
\]

cationic head of Ach

Esteric site

\[
\begin{array}{c}
\text{CH}_3 \\
\text{O} \\
\text{C} \sim \text{CH}_3
\end{array}
\]
esteric head of Ach
Acetylcholine is metabolized or hydrolyzed by choline-esterases at the site of Ach-release into Acetic acid + choline.

<table>
<thead>
<tr>
<th>1. Specificity</th>
<th>true choline-esterase</th>
<th>Pseudocholine-esterase</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Site</td>
<td>specific</td>
<td>non specific</td>
</tr>
<tr>
<td></td>
<td>Brain, neurons, ganglia</td>
<td>plasma, liver, pancreas</td>
</tr>
<tr>
<td></td>
<td>tissues, myoneural</td>
<td></td>
</tr>
<tr>
<td></td>
<td>junction, RBCs</td>
<td></td>
</tr>
<tr>
<td>3. Onset of action</td>
<td>Rapidly</td>
<td>slowly</td>
</tr>
<tr>
<td></td>
<td>in 3 months</td>
<td>in 3 weeks</td>
</tr>
<tr>
<td>4. Regeneration</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2- Adrenergic chemical transmitters (catecholamines)
   Adrenaline or epinephrine
   Noradrenaline or norepinephrine

PHENYLALANINE

+OH
hydroxylase enzyme

+OH
TYROSIN
Hydroxylase enzyme

-D02
DOPA
DOPA Decarboxylase enzyme

+OH
DOPAMINE
Dopamine B-Oxidae enzyme

+CH3
NORADRENALINE
N-methyltransferase

ADRENALINE

Stored in chromaffin cells in ad. medulla or granules at SNE
Synthesis and storage of catecholamines occur within chromaffin granules inside the adrenergic neurones (nearly all the noradrenaline contents of the adrenergically innervated organs and the chromaffin cells of adrenal medulla (mostly epinephrine *Catecholamine-ATP or calcium salt of catecholamine (bound forms) within the intracellular granules probably represents the reserve or stable pool of catecholamine storage (bound form) or stored in free form (mobile pools) * The mechanism of noradrenaline release is not known. They believe that after the nerve impulses Ach is released and combines with receptors on chromaffin cells (adrenal medulla) or those on nerve terminals (of the postsynaptic sympathetic nerves) with subsequent change in cell permeability, so calcium ions enter and causes mobilization of catecholamines from stores.
The released catecholamines produce their action on effector cells by direct combination either with \(-\)-receptors (\(-1\&\-2\)) or \(B\)-receptors (\(B1,B2,B3\))

Stimulation of \(-\)-receptors result in an excitatory effect on effector cells, whereas stimulation of \(B\)-receptors usually produce inhibitory effects. +There are certain exceptions to this rules, \(B1\)-receptors in heart is excitatory and increases renin production in kidneys. Both \(-\&\ B\) receptors in the intestine are inhibitory in character.

+ Stimulation of presynaptic \(-2\) receptors decrease the release of noradrenaline, stimulation of presynaptic \(B\)-receptors result in increase the release of noradrenaline
Synthesis of catecholamines

Phenylalanine

Tyrosin

DOPA

(1)

Dopamine

Granules

MOA

Bound-NE

Mobile-NE

Cytoplasmic NE

Neuronal NE

Deaminated metabolites

(2)

Deaminated NE

(3)

Neuronal Diffusion

(8)

Reuptake

NE @ B

(4)

Neuronal Reuptake

(7)

COMT

PJM

Na+

AP

Ca+

B
Catecholamines are mainly metabolized by 2 enzymes: Catechol ortho methyl transferase (COMT) and Mono amine-Oxidase (MAO).

Noradrenaline

1. Catechol ortho methyl transferase Enzyme (COMT)

2. Mitochondrial neuron enzyme, liver, A medullary cells

Metanephrine

- MOA
- Deamination and then oxidation by MOA

VANILLYMANDELIC ACID (Excreted in urine)

Adrenaline

• extraneural enzyme (cytoplasm)
**Mechanism of Neurohumoral transmission**

**AXONAL CONDUCTION** (Action potential, AP)

* It is the passage of an impulse along an axon or muscle fiber. At the rest the interior of the mammalian axon is approx. 70mv negative to exterior and K+ ions are highly concentrated in axoplasm as compared with the extracellular fluid. Na+ and Cl- ions are present in higher concentration in the extracellular than axoplasm. The resting axonal membrane is highly permeable to K+ but less permeable to Na+&Cl- ions.

# The concentration gradient of K+ is 30 – 50 fold higher in axoplasm than in extracellular fluid, but the concentration gradient of Na+ and Cl- are somewhat lower.

# The ionic gradient are maintained by an energy-dependent active transport or pump mechanism involving an ATPase activated by Na+ at inner and K+ at the outer surface of the membrane.
*In response to a stimulus above threshold level, NAP or nerve impulse is initiated at a local region of membrane by rapid deflection of the internal resting potential from negative value towards Zero or positive overshoot due to sudden selective increase in permeability of the membrane to Na+ which flow inward in the direction of their concentration gradients.

*Repolarization of the membrane follows immediately and results from the rapid replacement of this change by one of increased permeability to K+. The transmembrane ionic currents produce local circuit currents around the axon (inactive region becomes activated and excitation of the next excitable portion of axonal membrane.
JUNCTIONAL TRANSMISSION
It is the passage of an impulse across a synaptic or neuro effector junction through the following steps:

1. The nerve action potential (AP) of innervated tissues or axonal conduction.
2. Release of chemical transmitter from nerve terminals (Exocytosis) either cholinergic (Ach) or adrenergic (adrenaline & noradrenaline),
3. Combination of the transmitter with post-junctional receptors resulting in increased ionic permeability or conductance of the membrane and produce post junctional potential or post synaptic potential (Excitatory post synaptic potential (EPSP)).
4. Enzymatic destruction of the transmitter or mediator e.g. Ach by cholinesterase and adrenaline or noradrenaline by MOA or COMT.
Two Types of Permeability change can occur:

1. **Depolarization**: Is result from the general increase in permeability to all types of ions (resulting in depolarization of membrane i.e. Excitatory post synaptic potential (EPSP)).

2. **Hyperpolarization**: The selective increase in permeability to only smaller ions (e.g. K+ & Cl-) resulting in stabilization or actual hyperpolarization of the membrane. Inhibition of post-synaptic potential (IPSP) •
Autonomic Drugs

These are drugs which act on the receptors of the cells innervated by autonomic nerves. They are classified:

<table>
<thead>
<tr>
<th>I. According to their action</th>
<th>II. According to Autonomic receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Stimulants</td>
<td>1. Cholinergic drugs</td>
</tr>
<tr>
<td>Which help the access of</td>
<td>2. Adrenergic drugs</td>
</tr>
<tr>
<td>chemical mediators to the</td>
<td></td>
</tr>
<tr>
<td>receptors</td>
<td></td>
</tr>
<tr>
<td>i.e Parasympathomimtics</td>
<td></td>
</tr>
<tr>
<td>Sympathomimtics.</td>
<td></td>
</tr>
<tr>
<td>2. Blocking agents (Inhibitors)</td>
<td>Which prevent the access of the chemical mediator to receptors e.g.</td>
</tr>
<tr>
<td></td>
<td>Parasympatholytics &amp; Sympatholytics</td>
</tr>
</tbody>
</table>
AUTONOMIC DRUGS

I. Cholinergic

A. Peripheral
   1. Parasympathomimetics (Stimulant)
      a) Choline-esters
         Acetylcholine
         Methacholine
         Carbacol
         Bethanocol
      b) Choline alkaloids
         Pilocarpine
         Arecoline
         Muscarine
      c) Anticholine-esterases
         1. Reversible
            Physostigmine
            Neostigmine
         2. Irreversible
            Organic phosphorous compounds

B. Central or nicotinic

II. Adrenergic

Peripheral

2. Parasympatholytic
   Parasympathetic blockers
   Muscarinic blockers
Cholinergic drugs

(A) Peripheral cholinergic drugs (drugs acting on post-ganglionic or peripheral cholinergic or muscarinic cell receptors.)

1. Parasympathomimetics (stimulants)
   a) Cholinesters.
      a.1 Acetylcholine, Ach, chemical transmitter of cholinergic nerves.

      **It has two action:**
      a.1.1 Nicotinic or central action:
         * It consists of the action of Ach on central cholinergic receptors in autonomic ganglia (Para and sympathetetic), Adrenal medulla and skeletal muscles.
         * It is like the action of nicotine which produces stimulation when given in small doses, whereas in large doses it produces inhibition.
         * Nicotinic action is blocked on the skeletal muscles by gallamine, tubcurarine (competitive blockers), suxamethonium and decamthonium (Persistant depoerization or hyperplerization) and on the ganglia by large dose of Ach, nicotine or leboline and also tetramethonium and hex or pentamethonium.
**a.1.2. Muscarinic action of Ach**

*It resembles the action of muscarine which stimulates the peripheral cholinergic receptors when given in small or large doses.*  
*The muscarinic action of Ach is blocked by belladona alkaloids (atropine, hyoscine and hyocyamine (parasympatholytics)).*

Ach is available as bromide and chloride (hydroscopic salt), easily soluble in water. It is destroyed in GIT.

*Its I.V. injection produces, flushed skin, increase sweating, lacrimation, salivation, constriction of eye pupils (miosis), increase bronchial secretion, GIT secretion, vomition, purgation (by increasing the intestinal motility and open of sphenictors, decrease in heart rate and conduction (-ve chronotropic activity), decrease in blood pressure (vasodilation of BVs).

Ach is unstable as a therapeutic agent but used as experimental standard agent it easily destroyed by ACHE enzymes.
Miosis (near vision) = contraction of circular muscle and ciliary muscle

Mydriasis (far vision) = contraction of radiated muscle and ciliary muscle

Sympathetic fiber
Radiated muscles @ 1 adrenergic cell receptors

Parasympathetic fiber
circular muscles cholinergic cell receptors

Mydriasis
CM
Miosis
Far Vision
Mydriasis (Dilatation of Eye pupile)

Near Vision
Miosis or constriction of eye pupile
Parasympathetic stimulation causes circular muscles to contract

Sympathetic stimulation causes radial muscles to contract
Cholinesters

ACH

N. CH2 - - CH2 – O – COCH3

Methacholine

N. CH2 - - CH2 – O – COCH3

carbacol

N. CH2 - - CH – O – CONH2

Bethanocol
a.2. Methacholine

It is a synthetic drug available as chloride salt, soluble in water. It results from the addition of a B-methyl group to Ach to slow the rate of destruction by ACHE so it is less readily hydrolyzed by ACHE (longer duration than Ach).

* Its effect entirely muscarinic and only nicotinic action affects the neuromuscular junction, thus increasing the muscular power in patients with myasthenia gravis in human practice. * It is partially absorbed from GIT.

* Its action is more pronounced on the circulatory system.
  (-ve chronotropic on heart, decrease B.p. due to vasodilation)

Uses: ..... Treatment of peripheral diseases (peripheral vasoconstriction) and thrombosis
       ..... Cases of Tachycardia.
a. 3. Carbacol (Carbaminocholine)

It is available as chloride salt which is soluble in water. It results from esterification of choline with carbamic acid.

* It is highly resistant to cholinesterase enzyme (has long life than Ach.)
* Its niconic action is more pronounced on ganglia.

It has a selective action on the smooth muscles of gastrointestinal tract and urinary bladder.

Uses:------- As Neuromuscular purgative

in cases of constipation

-------- As diuretic in case of urinary retention.

-------- As Ruminal tonic in cases of ruminal atony.
a.3. Bethanocol

It is not hydrolyzed by cholineasterase and has a prolonged but weak effect.

The main effect is upon the bladder and gastrointestinal tract.

Uses: ------ Post operative urine retention.
        ------ Paralytic ileus and dilation of stomach.
## Comparison between members of cholinesters

<table>
<thead>
<tr>
<th></th>
<th>ACH</th>
<th>Methacholine</th>
<th>Carbacol</th>
<th>Bethnocol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>True ACHE</strong></td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>PseudoACHE</strong></td>
<td>+</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>Muscarinic</strong></td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Nicotinic</strong></td>
<td>+++</td>
<td>--</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td><strong>Selectivity</strong></td>
<td>all</td>
<td>Cardio-vascular</td>
<td>Smooth muscles</td>
<td>GIT &amp; Bladder</td>
</tr>
<tr>
<td><strong>Oral Absor</strong></td>
<td>Nil</td>
<td>incomplete</td>
<td>incomplete</td>
<td>complete</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>I.V.</td>
<td>S/C</td>
<td>S/C&amp; oral</td>
<td>S/C&amp;oral</td>
</tr>
</tbody>
</table>
b. Choline alkaloids
Muscarine, pilocarpine, arecoline

b.1. Muscarine
*It is obtained from the fungus *aminata muscaria.*
*Its action is on all receptors innervated by peripheral cholinergic nerves. It is not used in the clinical practice.

b.2 Pilocarpine
*It is alkaloid obtained from the leaves of shrub pilocarpus. It is Available as pilocarpine nitrate, soluble in water.
--- It has only a muscarinic action.
---- It has a specific action on glands (increase secretions and the eye pupile (miosis).
--- It increases the sweat glands secretion (diaphoretic effect).
Uses: It is used alternatively with physostigmine for treatment of glucoma and alternatively with atropine to breakdown the adheision between iris (cornea) and lens.
b. 3. Arecoline

It is an alkaloid obtained from seeds of areca nuts and is available as arecoline hydrochloride. It has both muscarinic and nicotinic action. Uses: It is commonly used in Vet. Practice as anthelmintic for tape worms and round worms (Vermifuge).
C. Anticholinesterases

Cholinesterase Inhibitors.

Cholinesterases are true and pseudo

Anionic site (-)  Esteric side (+)

CH₃ CH₃

O N CH₂ - CH₂ - ---- O -

CH₃ C - CH₃

Cationic head of ACH  Esteric head of ACH

Ach → esterified Ach (Each)
EAch → choline + Acetylated enzyme
Acetylated enzyme + H₂ = Acetic acid
Anticholinesterases: Reversible and irreversible
These are drugs which inhibit the cholinesterase enzyme leading to the accumulation of ACH

A. REVERSIBLE:
Drugs inhibit AchE reversibly. They are shortly acting in the transficacion sequence of Ach but a carbamylated rather an acetylated enzyme is formed which is only slowly hydrolzed to regenerate the enzyme. They can prolong the nicotinic and muscarinic action of Ach.

1. NEOSTIGMINE(PROSTIGMINE):
It is a synthetic quaternary ammonium compound available as bromide salt (given orally) or methyl sulphate (i.m.)
It acts by attaching the anionic and esteric sides of Ach produces a reversible carbamylated enzyme.
It is a strong inhibitor and it produces its muscarinic action mainly on GIT, Urinary smooth m., genital tract and circular muscle of eye (miosis).
Its nicotinic action is mainly on skeletal muscle endplate (twitches) by a direct effect on cholinergic cell receptors.

**Therapeutic Uses:**

1. Paralytic ileum
2. Postoperative paralysis of urinary bladder
3. GLUCOMA
4. Cases of myasthenia gravis (skeletal muscle paralysis) usually associated with atropine to prevent its muscarinic action.
5. Used in cases of tubucurarine or gallamine poisoning as antidote.
2. Physostigmine (Eserine)

It is an alkaloid obtained from the dried seeds of calabash beans. It is available as physostigmine salicylate easily soluble in water. It inhibits ACHE (Ach), thus prolong the muscarinic action of Ach (mainly on eye, miosis, secretion, and cardiovascular system and nicotinic action (skeletal muscle twitches, but not directly as neostigmine).

Large doses produce a stimulation of CNS (Convulsions, tremors) followed by coma and death occurs due to respiratory failure.

Therapeutic use:
1. Glaucoma as eye drops to reduce intraocular pressure.
2. Used alternatively with atropine to breakdown the adhesion between iris and lens.
3. Used in case of atropine poisoning to prevent the central and peripheral action of atropine.
4. Used in cases of myasthenia gravis.
b. Irreversible Anticholine-Esterases

These are irreversible ACHE inhibitors reach to form a stable phosphorylated enzyme. Almost there is no regeneration of cholinesterase by hydrolysis and the pharmacological effects persists untile new enzyme is synthetized

E.g. Organic phosphorous compounds:
Malathion, parathion, volaton, neguvon, diazenon, Diptriex,
Toxicity of organic phosphorous compounds (insecticides)

1. Muscarinic symptoms
2. Nicotinic symptoms
3. CNS symptoms

Anionic site

Esteric site

Phosphorylated enzyme

Irreversible inhibition
1. Muscarinic symptoms (as parasympathomimtics):
   Salivation, miosis, Asthma vomition, diarrhoea, abdominal pain, urination difficult respiration, decrease in Bp

2. Nicotinic Symptoms:
   Stimulation of skeletal muscle activity (Twitches) followed by Paralysis

3. CNS Symptoms:
   Insomnia, restlessness, tremors, convulsions, coma, collapse, Death due to respiratory failure.
Treatment of acute toxicity of organic phosphorous compounds

1. Administration of the specific reversible competitive antidote ((ATROPINE SULPHATE)) to overcome and control the muscarinic symptoms by blocking the cholinergic cell receptors (muscarinic), Parasympatholytics present in smooth muscles, exocrine glands and heart.

Atropine is given i.m. continuously until the muscarinic symptoms completely disappeared.
2. Administration of cholinesterase Reactivators (Oximes)

++ These are drugs which induce a specific reactivation of the enzyme ACHE which previously inhibited by cholinesterases inhibitors.

The oximes react directly with the alkylphosphorylated enzyme to free the active (Esteric unite) of ACHE.

++ They are active only for few hours.

++ Members of OXIMES: PRALDOXIME CHLORIDE of 2-PAM and OBIDOXIME HCL.

++ OXIMES are active only within the 12 hours following occurrence of the symptoms, later became ineffective due to complete inactivation of the enzyme.

They are given as 1 gm/100 cc of saline by i.v. administration.
3. Symptomatic treatment

1. Administration of anticonvulsants e.g., Barbiturates.
2. The use of respiratory stimulants (Carbogen).
3. The use of cardiovascular stimulants and bronchodilators.
4. The use of gastric lavage and fluid therapy in dog and cat.
Miosis (near vision) = contraction of circular muscle and ciliary muscle
Mydriasis (far vision) = contraction of radiated muscle and ciliary muscle

Sympathetic fiber

Radiated muscles @1 adrenergic cell receptors

parasympathetic fiber

circular muscles cholinergic cell receptors

Mydriasis
CM
Miosis
AUTONOMIC DRUGS

I. Cholinergic

A. Peripheral
   1. Parasympathomimetics (Stimulant)
      a) Choline-esters
         Acetylcholine
         Methacholine
         Carbacol
         Bethanocol
      b) Choline alkaloids
         Pilocarpine
         Arecoline
         Muscarine
      c) Anticholine-esterases
         1. Reversible
            Physiostigmine
            Neostigmine
         2. Irreversible
            Organic phosphorous compounds

B. Central or nicotinic

II. Adrenergic

Peripheral

2. Parasympatholytic
   Parasympathetic blockers
   Muscarinic blockers
Parasympatholytics, parasympatholytic drugs, Muscarinic Receptors Blocking agents.

These are drugs which compete with ACH for the same cholinergic receptor at peripheral but not central cholinergic nerves. They differ from nicotine and curare which are also depressant of the parasympathetic but act as blocking agents at the preganglionic cholinergic nerves.

Classification

1. Natural alkaloids
   - Atropine (atropa belladonna)
   - Hyoscine (hyocymus nigra)
   - Hyocyamine (datura stramonium)

2. Synthetic esters
   - Homotropine
   - Eucatropine
   - Methylscopolamine
   - Hyoscine butyl bromide
   - Buscopan (Buscopan)
Inactive Ach
Stored in viscles

Presynaptic membrane

Axon

Storage viscles

Active acetylcholine

Synaptic cleft

Post synaptic membrane

Neurohumoral transmission

Effector cells

Receptors

Ca+

K+

Na+

K+

Na+
Signal Transfer In The Synapse

1. Depolarization
   - Action potential

2. Ca$^{2+}$-channels
   - Ca$^{2+}$

3. Exocytosis
   - Acetylcholine vesicle
   - Acetylcholine

4. Ligand binding
   - Na$^{+}$

5. Na$^{+}$-influx
   - Action potential

6. Acetylcholine esterase

Preganglionic neuron

Postganglionic neuron

Fig. 2-2
Blocking of peripheral cholinergic cell receptors in smooth muscles, exocrine glands and heart by atropine

Competitive blocking

Ach

Atropine

Ch-R
Cholinergic receptors blockers

- Preganglionic Ganglia
- Skeletal M
- Adrenal medulla

- central Cholinergic receptors
  - Blocked by Gallamine, tubocurarine

- peripheral Cholinergic receptors
  - Blocked by Atropine

- ++ chronotropic
  - Smooth M.
  - Exocrine glands
  - Viscera
  - Heart
ATROPINE

Source and chemistry: It is an alkaloide obtained from atropa belladonna and Datura stramonium. It is ester of tropic acid and tropine.

Pharmacokinetics:
* It is absorbed orally and from the site of injections except intact skin. It is highly distributed allover the body and metabolized in the liver and excreted in urine. Rabbits exhibit natural tolerance to atropine (has atropinase enzyme).

Pharmacological Actions:
++ Atropine blocks the muscarinic receptors (Peripheral CH R) by competing with ACH. It does not affect its release, Large dose affect the nicotinic action. Inhibition of muscarinic action of ACH produces effects similar to those produced by SYMPATHOMIMITICS.
Autonomic supply of heart

Bradycardia
Tachycardia

Cholinergic Fibers
SAN
AVN
B of H
P.F.

Adrenergic fibers

Cholinergic Fibers

Ach

Adrenaline

B1

B1

B1

--- Decrease rate
-- Decrease cond.

++ Increase rate
++ Increase Conductivity
++ Increase Contractility
++ Action on exocrine glands: It reduces all secretions (Salivary, bronchial, GIT secretion (anitvomiting, antidiarrhoeal) decrease Sweat gland secretion.

++ Action on cardiovascular system:
Atropine stimulates the heart rate by blocking Cholingeric cell receptors in S.A.N and A.V.N. (- x - = ++). This lead to TACHYCARDIA (positive chronotropic effect). Atropine has a specific antagonistic effect against Vagal stimulation or digitalis toxicity as they cause bradychardia.

Action on eye:
It causes mydriasis (dilatation of eye pupile) by blocking cholinergic receptors in circular muscle of IRIS leads to relaxation. It causes relaxation of ciliary smooth muscle.

Action on Smooth muscles (spasmolytic)
It relaxes smooth muscles of bronchial M (bronchodilator or antiasthmatic) GIT (Antivomiting or antiemetic, intestinal spasmolytic or antispasmodic) it relaxes smooth M of urinary bladder and ureter (urinary sedative or antispasmodic)
Miosis (near vision) = contraction of circular muscle and ciliary muscle
Mydriasis (far vision) = contraction of radiated muscle and ciliary muscle

Diagram:
- Sympathetic fiber
- Parasympathetic fiber
- Radiated muscles
- Circular muscles
- Adrenergic cell receptors
- Cholinergic cell receptors

Legend:
- Mydriasis
- CM
- Miosis
Parasympathetic stimulation causes circular muscles to contract

Sympathetic stimulation causes radial muscles to contract
Far Vision
Mydriasis (Dilatation of Eye pupil)

Near Vision
Miosis or constriction of eye pupil
**Action on CNS:** Large doses of atropine have a stimulant effect upon the brain producing excitation, restlessness, convulsions following by depression. Atropine increases the rate and depth of respiration by direct stimulation of respiratory center in medulla (respiratory Stimulants).

**Therapeutic uses:**
1. Ophthalmic examination of eye.
2. Used alternatively with Physiostigmine to prevent adhesion between cornea and lens.
3. Used before the administration of neostigmine for treating of myasthenia gravis to prevent the muscarinic action of neostigmine.
4. Used as pre-anaesthetic medication to prevent excessive salivation and bronchial secretion due to the irritating effect of volatile general anaesthetic agents (ETHER), and therefore prevent Asphyxia, counteract the vagal effect on heart or depressent action of anaesthetic drugs on heart (Bradycardia). It has a medullary stimulant to maintain respiration during anaesthesia.
5. Used in cases of vomition (peripheral antiemetic drug), diarrhoea, intestinal spasomic colic, urinary coloic biliary colic and bronchial asthma.

6. Specific antidote in cases of organic phosphorous compound poisoning, neostigmine poisoning, pilocarpine poisoning, and digitalis poisoning. It overcomes vegetal stimulation by digitalis.

ATROPINE POISONING

Atropine toxicity may occur after frequent administration. Deaths is rare because atropine has a wide safety margin.

SYMPTOMS: mouth dryness, dilatation of eye pupil, tachycardia, urine retention, constipation, muscular incoordination and respiratory failure.

TREATMENT: 1. Administration of methacholine or pilocarpine at different intervals until the mouth becomes moisten.
2. Administration of respiratory stimulants.
3. Cold fomentation to overcome atropine fever.
HYOSCINE (SCOPOLAMINE)
** It is an alkaloides obtained from the flowers : Solanaceous plant
It is differe than atropine in that it is a C.N.S depressant (sedative, hypnotic).

It has more prominent effect on the eye and secretory glands than atropine.
Atropine is more active on heart (Tachycardia), GIT and bronchial muscle and also more longer in duration of action than hyoscine.

HYOSCIAMINE
It is an alkaloide obtained from Datura stramonium.
It has more activity on smooth muscles than atropine. It has the same activity as atropine but somewhat less stimulating activity on C.N.S.
It is used with drastic purgative (sever irritant purgative) to counteract gripping.
4. SYNTHETIC AND SEMISYNTHETIC ATROPINE SUBSTITUTES

a) HOMOTROPINE and EUCATROPINE HCL
   It is synthetic compound used mainly for eye examination due to its short duration (24 hours). As compared with atropine (7 – 10 days).

b) Methscopolamine bromide.
   It devoides the central depressant effect of hyoscine. Used specifically for treatment of peptic ulcers, renal colic, cystitis and GIT spasm.
   e.g. HYOSCINE butyl bromide (Buscopan)

c) Antihistaminic atropine substitutes
   e.g. Ipratropine (Atrovent) used as bronchodilator and not decrease bronchial secretion

d) Emeproronum (Cetiprin) Used in cases of urinary incontinence
ADRENERGIC DRUGS

SYMPATHOMIMITICS
(STIMULANTS)

SYMPATHOLYTICS

**Sympathomimetics**

**Catecholamines**
- Direct
  - Adrenaline (@, B)
  - Noradrenaline (@)
  - Isoprenaline (B1B2B3)
  - Dopamine (Dopaminergic Cell receptors)

**Non catecolamines**
(Direct + indirect)
- @ + B)
  - Ephedrine
  - Amphetamine
  - Methylamphetamine
  - Salbutamol
  - Mephentramine
  - Hydroxyamphetamine
  - Metaramine
  - Phenylphrine
Synthesis of catecholamines

Phenylalanine $\rightarrow$ Tyrosin $\rightarrow$ DOPA $\rightarrow$ Dopamine $\rightarrow$ Mobile-NE $\rightarrow$ Mobile-NE $\rightarrow$ Bound-NE $\rightarrow$ MOA $\rightarrow$ Deaminated metabolites $\rightarrow$ Cytoplasmic NE $\rightarrow$ Neuronal Reuptake $\rightarrow$ Diffusion $\rightarrow$ Compartments $\rightarrow$ COMT $\rightarrow$ PJM

- (1) $\rightarrow$ (2) $\rightarrow$ (3) $\rightarrow$ (4) $\rightarrow$ (5) $\rightarrow$ (6) $\rightarrow$ (7) $\rightarrow$ (8) $\rightarrow$ (9)

- Na$^+$ $\rightarrow$ AP $\rightarrow$ Ca$^+$ $\rightarrow$ AP $\rightarrow$ Ca$^+$ $\rightarrow$ AP

- Phenylalanine $\rightarrow$ Tyrosin $\rightarrow$ DOPA $\rightarrow$ Dopamine $\rightarrow$ Granules $\rightarrow$ Deaminated metabolites $\rightarrow$ Cytoplasmic NE $\rightarrow$ Neuronal Reuptake $\rightarrow$ Diffusion $\rightarrow$ Compartments $\rightarrow$ COMT $\rightarrow$ PJM

- Synthesis of catecholamines involves the conversion of Phenylalanine to Tyrosin, then to DOPA, Dopamine, and finally to NE through a series of enzymatic reactions and cellular transport processes.
<table>
<thead>
<tr>
<th>Receptors</th>
<th>TYPE OF ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>@1</td>
<td><strong>Excitatory</strong></td>
</tr>
<tr>
<td>@2</td>
<td><strong>Inhibitory (preganglionic)</strong></td>
</tr>
<tr>
<td></td>
<td>(--) noradrenaline release</td>
</tr>
<tr>
<td></td>
<td>(--) lypolysis, (--) insulin release</td>
</tr>
<tr>
<td>B1</td>
<td><strong>Excitatory (+++ heart) renen release(+++)</strong></td>
</tr>
<tr>
<td>B2</td>
<td><strong>Inhibitory Smooth muscle(---) lypolysis (++)</strong>, <strong>Insulin release (++)</strong></td>
</tr>
<tr>
<td>B3 fat cell</td>
<td><strong>Lipolysis.(+++)</strong></td>
</tr>
</tbody>
</table>
## The effects on various tissue of stimulation of @ and B-adrenergic cell receptors

<table>
<thead>
<tr>
<th>Tissue</th>
<th>@-effects</th>
<th>B-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Eye</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiated m</td>
<td>contraction (Mydriasis, @1)</td>
<td>relaxation (far vision)</td>
</tr>
<tr>
<td>Cilary muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2. Heart</strong></td>
<td>General Excitation (B1)</td>
<td></td>
</tr>
<tr>
<td>S.A.N</td>
<td>Increase in heart rate</td>
<td>Increase contractility</td>
</tr>
<tr>
<td>atrium</td>
<td></td>
<td>Increase conduction.</td>
</tr>
<tr>
<td>A.V.N</td>
<td></td>
<td>General Excitation (B1)</td>
</tr>
<tr>
<td>Ventricle</td>
<td></td>
<td>Increase contractility</td>
</tr>
<tr>
<td></td>
<td>++force ++output (TACHYCARDIA)</td>
<td></td>
</tr>
<tr>
<td><strong>Blood vessels</strong></td>
<td>vasoconstriction</td>
<td>vasodilatation (B2)</td>
</tr>
<tr>
<td>Coronary</td>
<td>@1 skin &amp; mm</td>
<td>coronary, skeletal muscle</td>
</tr>
<tr>
<td>Cutaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skeletal</td>
<td>Vasodilatation (@2</td>
<td></td>
</tr>
<tr>
<td>Sp, renal genital</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: @ and B refers to different types of adrenergic receptors.*
Autonomic supply of heart

Bradycardia                        Tachycardia

Cholinergic Fibers

SAN

AVN

B of H

P.F.

Adrenaline

Adrenergic fibers

++ Increase rate
++ Increase Conductivity
++ Increase Contractility

--- Decrease rate
-- Decrease cond.

Ach
Effect of catecholamines on blood pressure

Blood Pressure % vs. Time

- Adrenaline @1&B2
- Noradrenaline @1
- Isoprenaline B2
<table>
<thead>
<tr>
<th>Organs</th>
<th>@-effect</th>
<th>B-effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Bronchiols</td>
<td></td>
<td>Relaxation B2</td>
</tr>
<tr>
<td>Smooth M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exocrine g</td>
<td>Viscid secretion</td>
<td></td>
</tr>
<tr>
<td>4. GIT</td>
<td></td>
<td>Relaxation (B2)</td>
</tr>
<tr>
<td>S.M.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sphenictor</td>
<td>Contraction (@1)</td>
<td></td>
</tr>
<tr>
<td>Glands</td>
<td>Decrease secretion (@1)</td>
<td></td>
</tr>
<tr>
<td>Gall B &amp; ducts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Urinary bladder</td>
<td></td>
<td>Relaxation (B2)</td>
</tr>
<tr>
<td>Muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sphinctor</td>
<td>contraction (@1)</td>
<td></td>
</tr>
<tr>
<td>6. Adrenergic terminal</td>
<td>decrease release of noadrenaline (@2)</td>
<td></td>
</tr>
<tr>
<td>7. Splenic capsule</td>
<td>contraction @1</td>
<td>realxation (B2)</td>
</tr>
<tr>
<td>8. Genitalia</td>
<td>Ejaculation @</td>
<td></td>
</tr>
<tr>
<td>Organs</td>
<td>@ effect</td>
<td>B-effect</td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>9. Pancrease</td>
<td>Decrease in secretion @2 (--- insuline)</td>
<td>increase in secretion B2 (++ insuline)</td>
</tr>
<tr>
<td>10. Sweat gland</td>
<td>++ secretion (cholinergic)</td>
<td>decrease secretion B2 (horse)</td>
</tr>
<tr>
<td>11. Salivary gland</td>
<td>scant, viscous secretion(@1)</td>
<td></td>
</tr>
<tr>
<td>12. Piloerector muscle</td>
<td>Contraction (@)</td>
<td></td>
</tr>
<tr>
<td>13. Kidney (renin release)</td>
<td>@2 Decrease</td>
<td>Increase secretion(B1)</td>
</tr>
<tr>
<td>14. Uterus</td>
<td>contraction(@1)</td>
<td>Relaxation(B)</td>
</tr>
<tr>
<td>15. Metabolism (liver)</td>
<td>Glucogenisis(+)</td>
<td>Glycogenlysis(B2)</td>
</tr>
<tr>
<td>16. Fat cells (hepatocytes)</td>
<td>decrease in lypolysis(+)</td>
<td>increase in lypolysis (B2&amp;B3)</td>
</tr>
<tr>
<td>17. Platlets</td>
<td>decrease aggregatioin@2</td>
<td>B2 Hypokalaemia</td>
</tr>
<tr>
<td>18. Vo;untry Muscle</td>
<td></td>
<td>Muscle tremors</td>
</tr>
</tbody>
</table>
Adrenergic drugs
(A) Sympathomimetics
  1. Catecholamines

1. Adrenaline or epinephrine:

Pharmacological actions:

1. On the heart:

   Adrenaline acts on B1 receptors in heart (excitatory), results in increase
   heart rate (positive chronotropic effect), conduction and contractile
   force of ventricles and ateria (+ve inotropic effects) i.e
   Tachycardia, improves the cardiac output. This leads to subsequent rise in
   blood pressure. This rise in blood pressure is followed by sudden fall
   in B.p. due to stimulation of vagal receptors in carotid sinus and
   aortic arch.

USES:
1. Cardiac arrest by a direct intracardiac injection (emergency) or S/c or I.m
Contraindications: cardiac shock during chloroform anaesthesia to prevent ventricular fibrillation.

2. Action on blood vessels (@&B):
   - It causes vasoconstriction of cutaneous B.vs (skin), cerebral, pulmonary, hepatic, m.m., and salivary B.vs, (action on @1 overcomes action on B2). This increases B.p. for a short time due to rapid breakdown or metabolism.
   - It causes vasodilations of skeletal muscle B.vs. and abdominal visceral B.Vs, and coronary B.vs, ( B2 overcomes @1)

Uses:
Adrenaline solution 1:2000 and 1:20000 used topically to control bleeding from arterioles and capillaries in cases of skin haemorrhages, nasal haemorrhages (epistaxis) and with local Anaesthetics (procaine) to prevent bleeding after tooth extraction (as adrenaline produces vasoconstrictions and prevent systemic absorption of procaine.)
Effect of catecholamines on blood pressure

- Blood Pressure %
- Time

- Noradrenaline @1
- Adrenaline @1&B2
- Isoprenaline B2
Adrenaline

Noradrenaline

isoprenaline
3. Action on bronchioles:
Adrenaline acts on B2-receptors and causes relaxation of bronchial smooth muscles (bronchodilator or antiasthmatic).

Adrenaline also decrease the congestion of m.m. of respiratory Tract.
USES: Used against allergic bronchial asthma induced by histamine (physiological antagonism).

4. Action on C.N.S.:
Slight stimulation, insomnia, and tremors (anxiety).

5. Other actions:
Adrenaline inhibits smooth muscles of GIT and urinary bladder (B2) and constricts the sphinctores (@1).
Effect of adrenaline on bronchi

Bronchial Asthma

Bronchiodiating effect Of adrenaline

Bronchiols Smooth m And glands

B2
B. It relaxes uterine muscles of rabbits, bitche and non pregnant cat.

C. Adrenaline accelerates glycogenolysis in liver and skeletal muscles, therefore it is contraindicated to be used in diabetic patients, but may be used in cases of hypoglycemia.

D. It contracts the wall of spleen (@1) and increases the No. of Circulated R.B.Cs.

E. It causes an increase in the basal metabolic rate.

F. It causes mydriasis (dilatation of eye pupile (@1 radiated s.m. pf iris,))
Parasympathetic stimulation causes circular muscles to contract

Sympathetic stimulation causes radial muscles to contract

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**Far Vision**

Mydriasis (Dilatation of Eye pupil)

**Near Vision**

Miosis or constriction of eye pupil
b. Noradrenaline (norepinephrine)

-----It is one of catecholamines.
--- It is synthetized from dopa and dopamine and stored in the chromaffine granules at sympathetic nerve endings and chromaffine cells in adrenal medulla.

---- It acts only on α1 adrenergic cell receptors (α1 agonist). Therefore, it causes vasoconstrictions of the peripheral blood vessels and rise of blood pressure, i.e., steady rise in systolic and diastolic blood pressure but has no effect on cardiac output.
C. Isoprenaline (synthetic catecholamine)

It acts only on B – adrenergic cell receptors

- **B1** Excitatory
- **B2** Inhibitroy

It induces positive inotropic and chronotropic effects on the heart (B1), (induces Tachycardia)

It dilates the coronary blood vessels (antagonize s angina pectoris), and skeletal B.Vs. (B2).

It relaxes smooth muscle of bronchi and bronchiols (bronchodilators or antiasthmatic effect)

Uses:
1. in cases of bradycardia (heart failure)
2. Bronchial asthma especially patients with hypertension.
d.Salbutamol (B2 agonists)
Selective B2 agonists

It is one of selective B2 agonists has a selective effects on smooth muscle of bronchi, vasculature and uterus. It is more powerful than isoprenaline with long duration as it is not sensitive to the action of COMT and MAO so it can be used without side effect on heart (cardio-intoxication).

Uses: acute and chronic bronchial asthma (Spray)
<table>
<thead>
<tr>
<th>Catecholamines</th>
<th>non-catecholamines</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Not absorbed from GIT</td>
<td>absorbed from GIT</td>
</tr>
<tr>
<td>2. Destroyed by MAO</td>
<td>Inhibit MOA</td>
</tr>
<tr>
<td>3. Rapid onset of action and short duration</td>
<td>slow onset of action and long duration</td>
</tr>
<tr>
<td>4. Can pass blood and brain barriers</td>
<td>can pass brain barriers</td>
</tr>
<tr>
<td>5. Low CNS excitation</td>
<td>potent CNS excitation</td>
</tr>
</tbody>
</table>
Mechanism of action of ephedrine and amphetamine as sympathomimetics

- Ephedrine
- Amphetamine

- Sympathetic Nerve fiber
- AD Noradrenergic transmitters

- Effector cells
- MOA
- B

- Direct
- Indirect
2. Non-catecholamines
A. Ephedrine

--- It is one of non-catecholamines, alkaloid obtained from Epdera plant. It is also prepared synthetically.

---- It stimulates α and β adrenergic cell receptors by a direct effect and indirect by causing release of adrenaline and noradrenaline.

--- It has a prolonged effect than adrenaline and noradrenaline by inhibiting MONO-AMINOXIDASE enzyme (MOA).

--- It stimulates CNS but less than amphetamine.

USES:
1. Hypotension during volatile anaesthesia, bradycardia.
3. Bronchial asthma.
4. As Mydriatic (3 – 5 %)
5. Before spinal anaesthesia (local anaesthesia).
2. Amphetamine (Benzedrine)

--- It is a synthetic non-catecholamine and can be taken orally.
--- It can resist the action of Monoaminoxidase, so its action is more prolonged than catecholamines.
--- Its mechanism of action by acting directly on α and β adrenergic cell receptors and indirectly by causing release of adrenaline and nor–adrenaline.
--- It has a prominent effect on CNS as a cerebral stimulant (improve cerebral activity, decrease cerebral fatigue and increase mental activity.
--- It is also increases basal metabolic rate and overcomes OBACITY.
--- Large doses cause insomonia, restlessness, CNS excitation.
3. Mephentramine (Wayamine)

--- It has prominent effect on B-receptors and weak effect on @-receptors.
--- It increases the blood pressure due to the increase in cardiac output, dilate the coronary B.Vs., renal Bevis, splanchnic B.Vs. but does not stimulate the C.N.S.

4. Hydroxyamphetamine : (like amphetamine)

5. Matraminal:
   It resemble noradrenaline in pharmacological action, increases blood pressure by causing vasoconstriction of peripheral B.Vs.
   It has no effect on C.N.S.
6. Phenylephrine & methoxamine

----It resemble noradrenaline, act only as α1 agonist

Uses:
1. used in cases of sever hypotention
2. Nasal epistaxis and nasal congestion
3. as mydriatic agent

N.B. Methoxamine resists MOA and COMT so it is considered as one of prolonged hypertensive agents
Sympatholytics

Classified Into:

1. Adrenergic receptors blockers
   A. &-adrenergic Blockers
e.g.: dibenamine, dibenzyline
   Ergot alkaloides, Tolazoline, Phentolamine
   B. -adrenergic Blockers
   Dichloroisoprenrenol, Pronethalol, proranolol (inderal)

2. Antidrenergic drugs:
   A. Drugs interfering with the release of catecholamines (Guanethidine)
   B. Drugs interfering with the store of catecholamines (Reserpine)
   C. Drugs interfering with the synthesis of catecholamines
e.g. alphamethyldopa, alpha methyl tyrosine
Sympatholytics
These are drugs which selectively inhibit the adrenergic nerves and structures innervated by them.

1. Dibenamine and dibenzyline:
   ---- They produce a prolonged α-adrenergic blocking effect lasting 3–5 days after a single administration.
   --- Small doses block the α-adrenergic cell receptors but large doses inhibit the stimulation of adrenergic nerves.
   ---- It produces moistness, marked hypotension and stimulates CNS.

USES:
1. Used in cases of hypertension.
2. Peripheral vascular diseases (Thrombosis).
2. Ergot alkaloides

--- Ergot is a parasitic fungus grows on rye and rarely in other plants.
Ergot alkaloides are: ERGOTAMINE, ERGOTOXINE and ERGOMETRINE.

----Ergotamine and ergotoxine in small doses block the @1 adrenergic cell receptors and cause lowering in Bp.
---Large doses cause a direct contracile response of the smooth muscles of peripheral B.Vs. And rise of Bp.
Uses: Used in cases of MIGARIN (cerberal vasodilatation) with caffeine.

ERGOMETRINE Acts specifically on the uterine smooth muscles causes contraction and acts as uterine stimulants.
Uses: AS abortifacient, uterine bleeding, uterine inertia
3. Imidazoline derivatives
Tolazoline and Phentolamine (Regitin).

+++ They are moderate Alpha-adrenergic blockers
+++ They cause vasodilation of coronary B.Vs. as they cause stimulation of heart.
+++ They stimulate GIT motility like parasympathomimetics.

Uses: In cases of hyperetention

4. Dibenzazapine series (AZAPTIN)
+++ It is active as tolazolone.
5. Yohambine

++ It is an alkaloide obtained from tree yohambine.
++ It blocks adrenergic cell receptors, so causes vasodilation.
++ It has antidiuretic effect by the releasing antidiuretic hormone.
++ It has a prominent effect as aphrodisiac.
B. B-adrenergic blockers
Dichloroisoprenternol, pronetrhalol, propranolol (Inderal)

They block B-receptors particularly in cardiac tissues causing decrease in heart rate, conduction, and contractility (Bradycardia).

Inderal is used mainly in hypertension via blocking B1 and B1. It inhibits also metabolic actions of adrenaline in muscles and liver (Glycogenolysis and Lipolysis).

It is also antagonises the release of renin or Hypertensine from the kidney.
These are drugs which interfere with the release or store or synthesis of the chemical transmitters (adrenaline & noradrenaline).  

1. GUANETHIDINE (ismelin) and Bretylium.

They act by replacing the noradrenaline in Chromaffine granules of the sympathetic nerve endings and decrease the uptake of noradrenaline by the granules. They decrease the NORAD and actually cause the release of guanethidine (false transmitters).

Uses: severe hypertension, Glucoma
2. Rawofila alkaloides (Reserpine)

++ Reserpine inhibits noradrenaline uptake by C.granules and decreases its store.
++ It inhibits ATP-Mg+ dependent uptake mechanism of granular membrane.
Uses Hypertension.

3. Alpha-methyl dopa:
It inhibit the synthesis of noradrenaline by inhibiting B-decarboxylase enzyme responsible for formation of dopamine and noradrenaline in C.granules and chromaffin cells in adrenal medulla (FALSE TRANSMISSION)
Mechanism of action of alpha methyl dopa (Aldomet)

PHENYLALANINE

+OH

TYROSIN

Hydroxylase enzyme

DOPA

DOPA Decarboxylase enzyme

A M

DOPAMINE

Dopamine B-Oxidae enzyme

A M

NORADRENALINE (false transmitter)

A M

ADRENALINE

N-methyltransferase

Stored in chromaffin cells in ad.medulla or granules at SNE