بسم الله الرحمن الرحيم

Autonomic Neurotransmission

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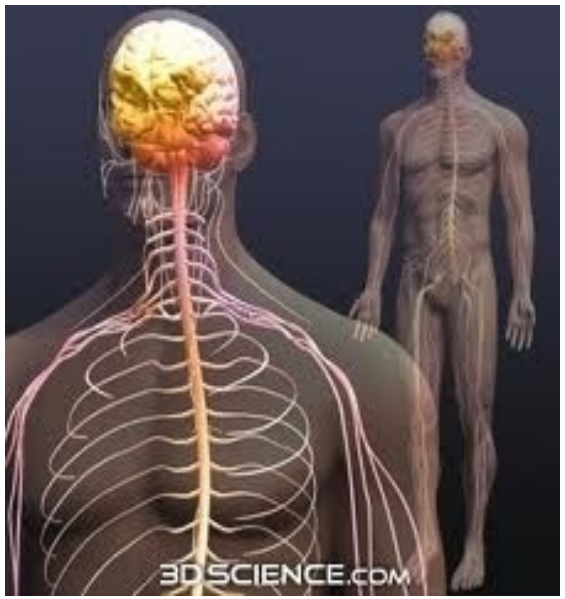


- The autonomic nervous system consist of:
  - *Sympathetic* ***(Adrenergic)- 1***
  - *Parasympathetic* ***(Cholinergic)-2***
  - *Enteric nervous system*

- **1 & 2 work in** an opposing manner

Restoring balance of involuntary functions

Maintaine homeostasis.

- **Sympathetic (adrenergic) activity** tends to predominate in stressful situations

And prepared the body for '**flight or fight**'

- **Parasympathetic (Cholinergic) activity** predominate during rest.

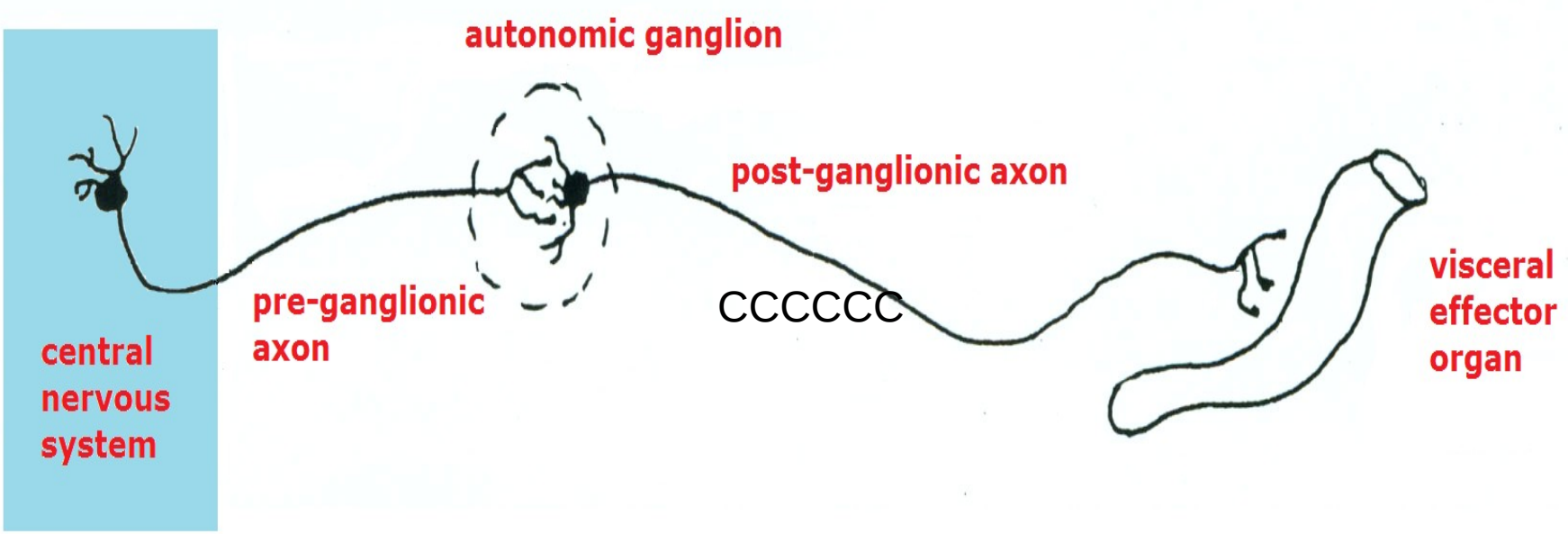
And participate in **tissue building reaction**

AUTONOMIC INNERVATION

Autonomic innervations consists of

1. **Preganglionic fibers (**Myelineted)
   - Form synaps with post ganglionic neuron

2. **Postganglionic neuron (**Nonmylinated)
   - **Postganglionic fibres** terminate in a receptor of organ.

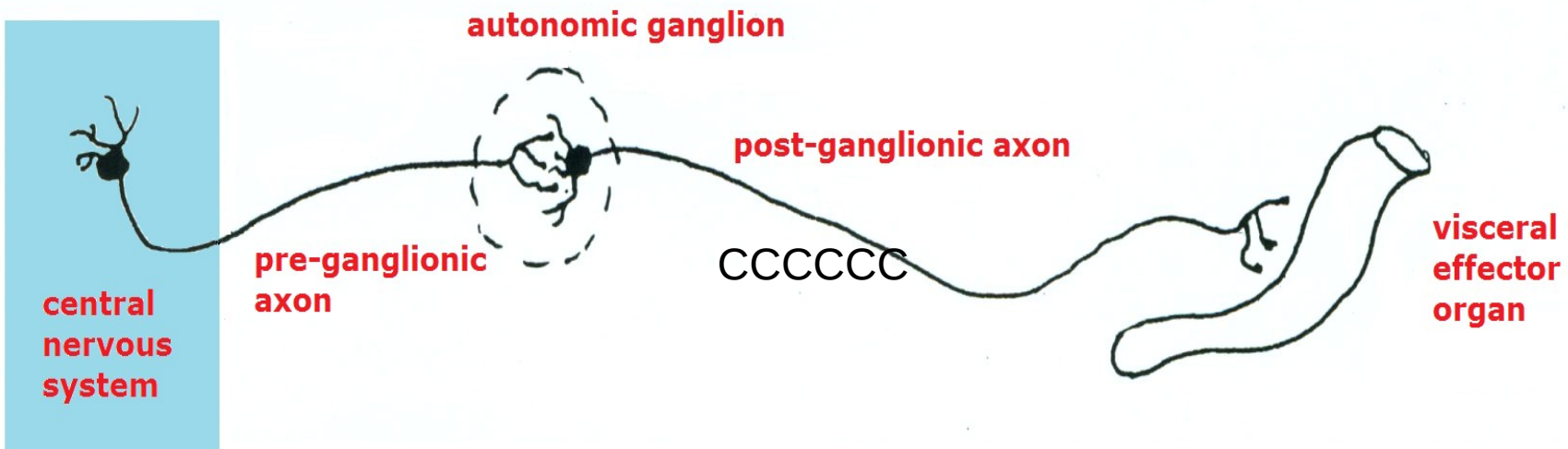


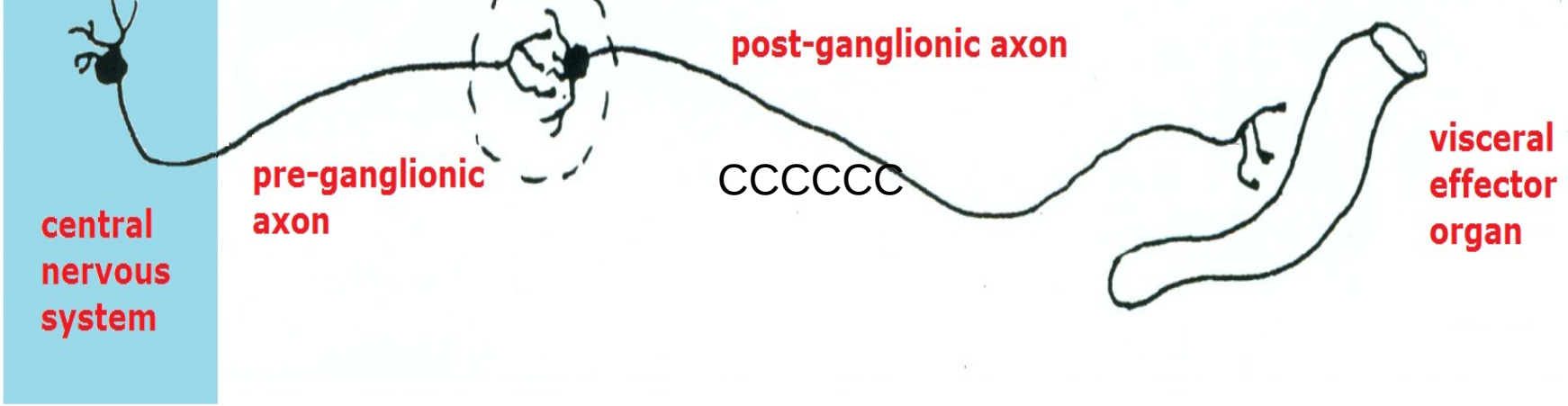
Important terminology

- **Synapse**: Structure that is formed by closed apposition of a neuron either with another neuron or with effector cell.

Function:

- It transmit impulses from one neuron to another neuron.





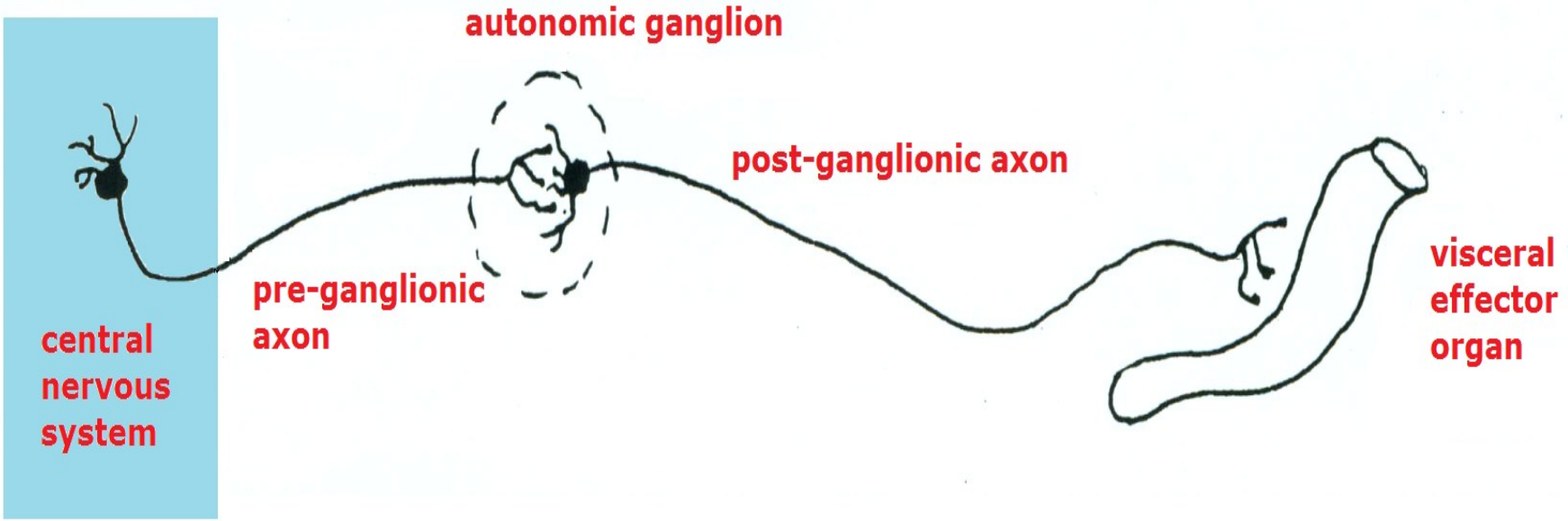
Ganglion:

- The synapse between preganglionic and postganglionic fiberes is called as **Ganglion**.

- While the postganglionic fiberes and the receptors is termed as **neuroeffector junction** (eg. Neuromuscular junction)

- **Transmission**: Passage of an impulse across a synapse is carried out by the process of transmission.

- **Conduction**: Passage of impulses from preganglionic and post ganglionic fiberes is called as conduction.



Sympathetic (Adrenergic) nervous system

- Neurons convey impulses from their origin in the CNS

To effector organs and tissues.

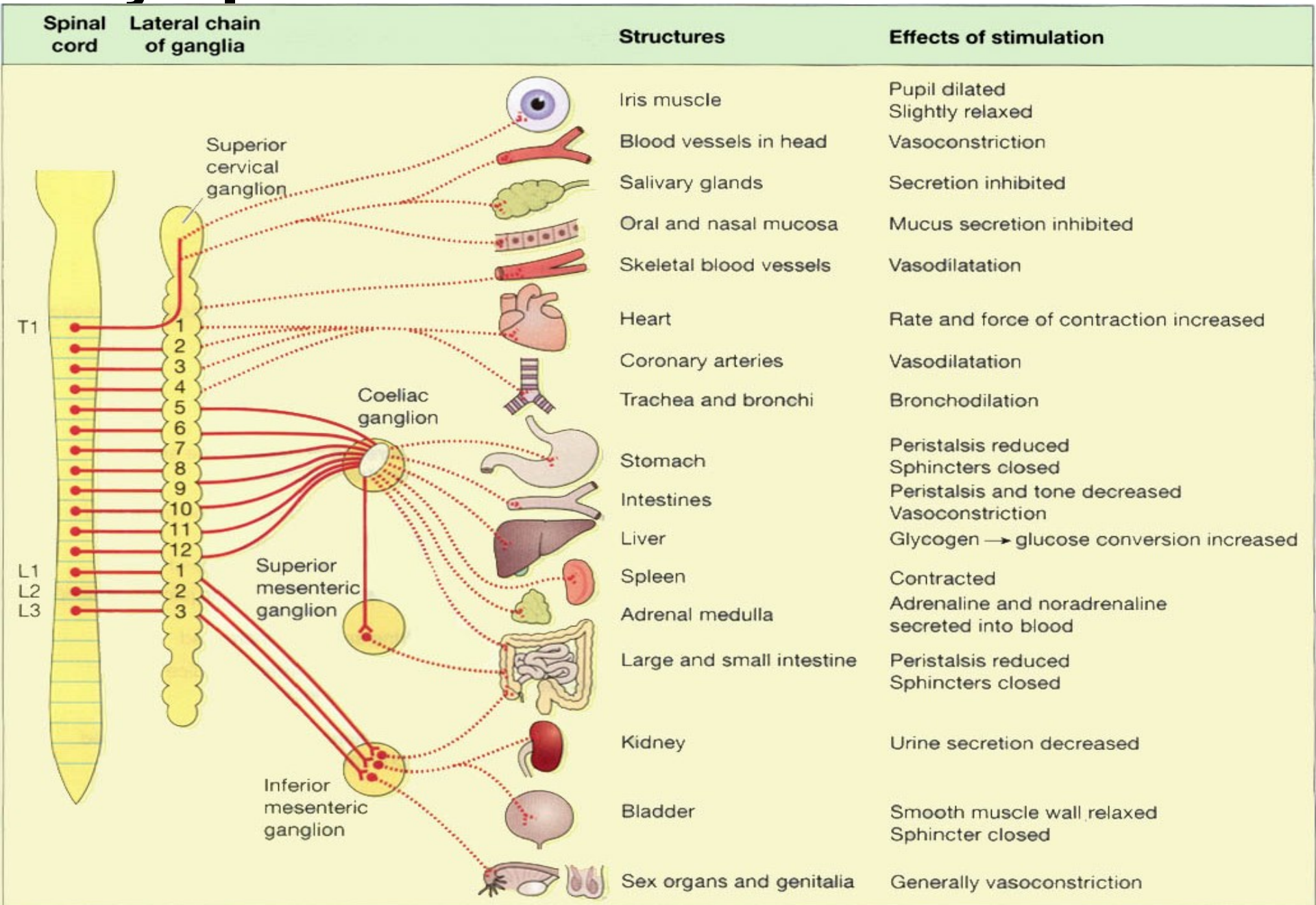
Distribution of Sympathetic Nervous System

- It consist of thoracolumbar outflow.

Location:

- The cell of the **preganglionic sympathetic fibres** extend from 8th cervical to the 2nd or 3rd lumbar segment.

Sympathetic distribution



- The **sympathetic ganglia** are of five types:
  - Paravertibral
  - Prevertibral
  - Terminal
  - Intermediate
  - Adrenal medulla

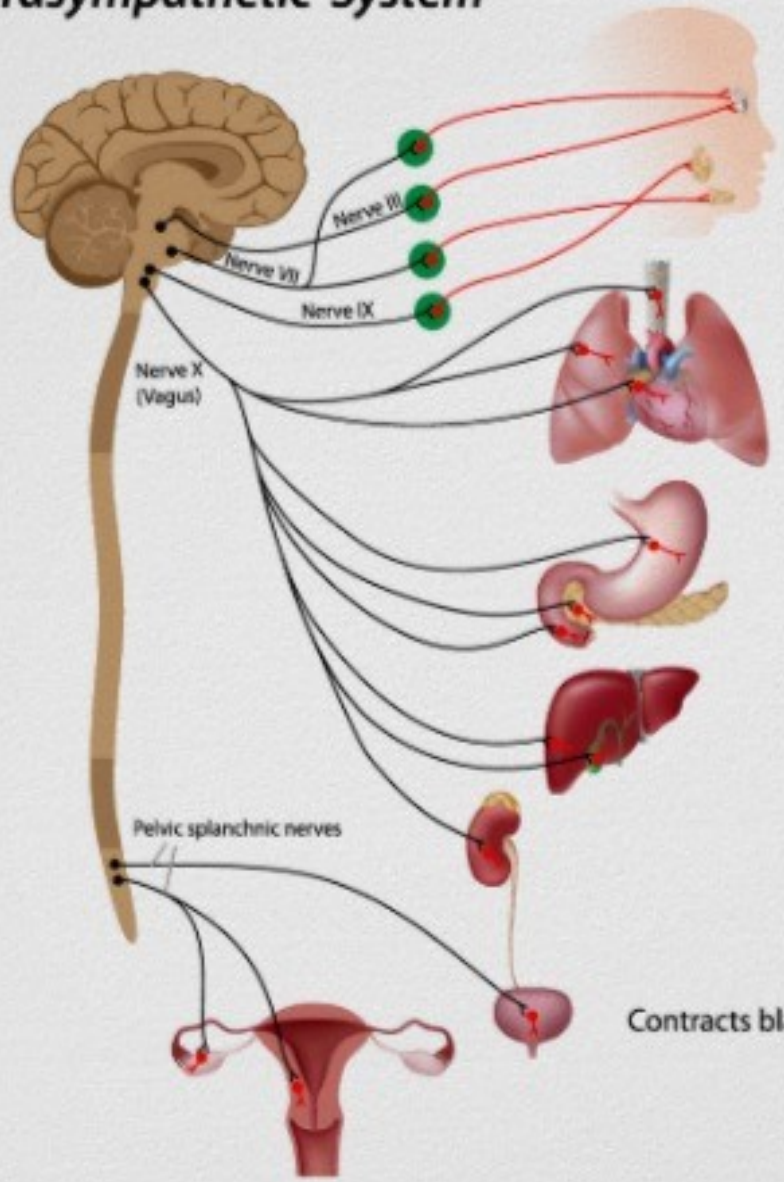
Distribution of Parasympathetic nervous system

- The **parasympathetic nervous system** serve two important functions:

  1.It carries the afferent impulses from viscera which **refluxly** modify autonomic functions

  2.It supply motor fibers to the smooth muscle, gland, heart and viscera through its **craniosacral out flow.**

Parasympathetic System



Constricts pupils

Stimulates flow of saliva

Constricts bronchi

Slows heartbeat

Stimulates peristalsis and secretion

Stimulates bile release

Contracts bladder

Enteric Nervous System

- It consist of collection of highly organized neurons situated in the wall of the GIT.

- It include:

  1. Myenteric plexus (Auerbach's plexus)
  2. Submucosal Plexus (Meissner plexus)

- Enteric nervous system control
  - GI Motility
  - Secretions
  - Mucosal blood flow

- Stimulation of ENS lead to release of putative transmitter ----

- Responsible for relaxation or stimulation of smooth muscles.

Putative transmitter

- **Inhibitory transmitters:**
  - Peptide eg. VIP
  - Nucleotide eg. ATP
  - Nitric oxide (NO)

- **Excitatory transmitters:**

  - Substance P

Neurohumoral Transmission

- Transmission of impulses across the synapse with the help of neurotransmitter is called as **Neurohumoral transmission**.

- Classical Neurotransmitters ARE:

  - Ach

  - NA

  - Dopamine (DA)

  - Gamma Amino butyric acid (GABA)

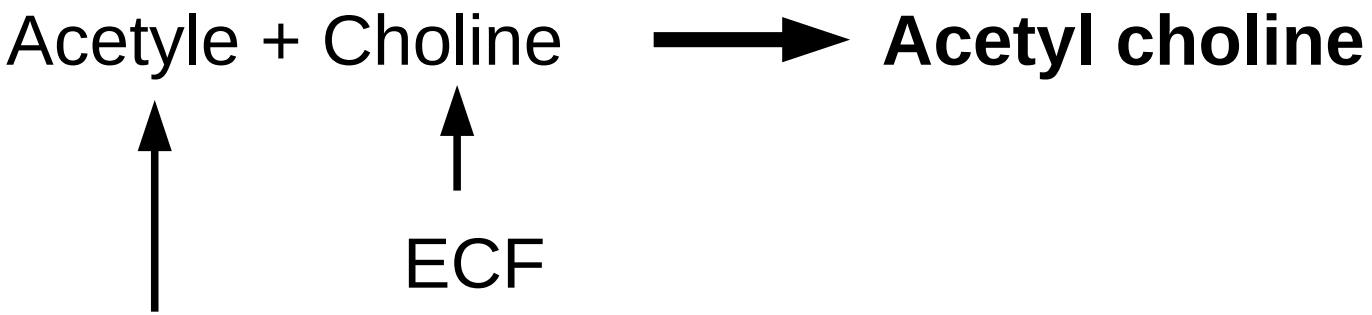
  - 5-hydroxy tryptamine (5-HT)

Acetyl Choline

- **Ach:**

  - Extremely potent Pcological Substance

  - Synthesize inside the nerve fibers



Acetyl coenzyme A (synthesize in mitochondria of axone terminal)

- Ach → Stored in synaptic vesicle

  ↘ Released by exocytosis

- Coupling of choline with acetyl gp is catalysed by choline acetyl transferase----- Synthesis.

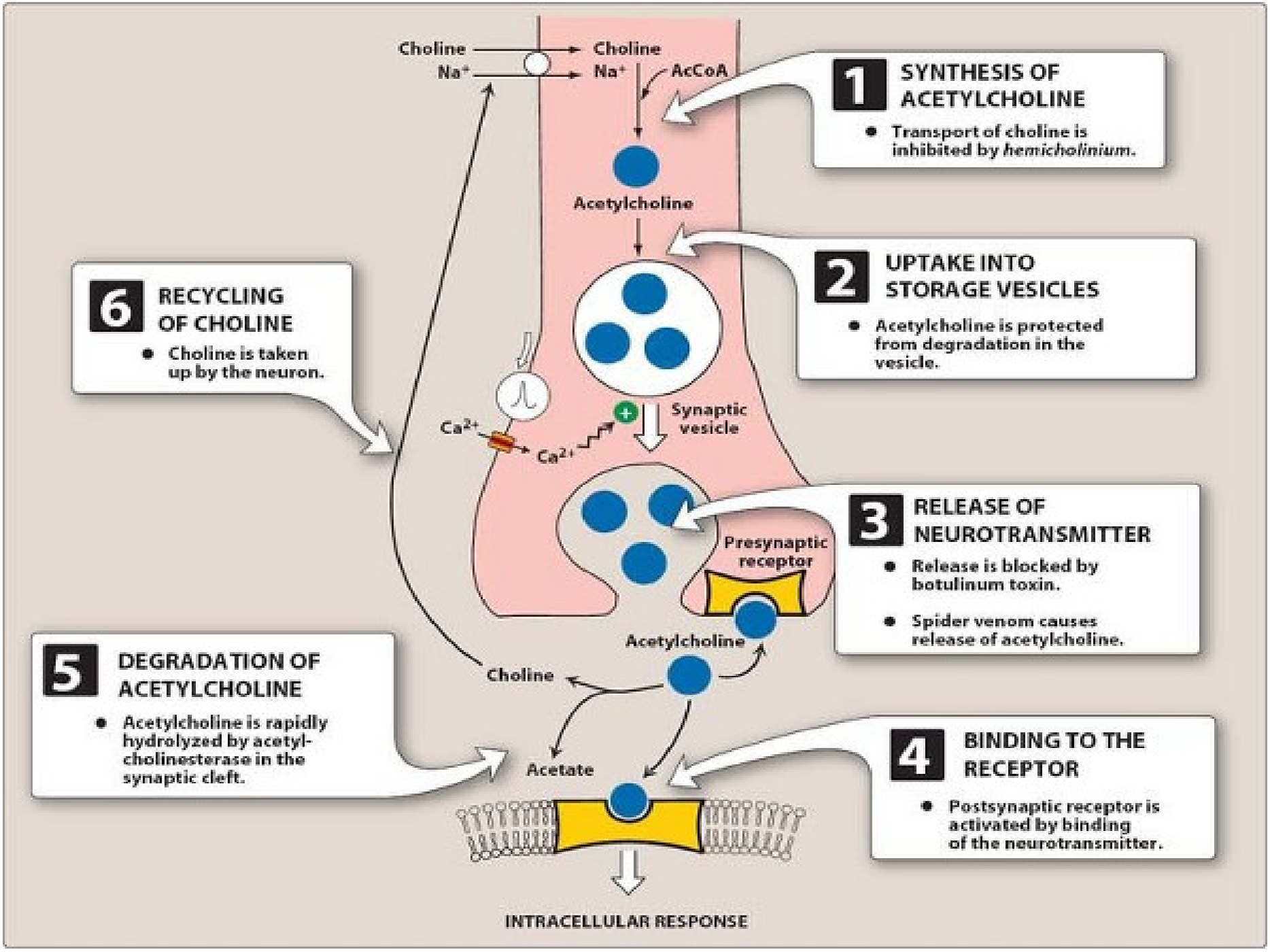
- And hydrolysed into choline & acetic acid is catalysed by choline esterases--- breakdown

2 main types of **cholinesterase r**

1. Acetylcholinesterase (AchE) or true cholinesterase

2. Butyrocholinesterase (BuChE) or Pseudocholinesterase

Synthesis, Storage and Release of Ach


Choline
Na+
Choline
Na+
AcCoA
Acetylcholine
Synaptic vesicle
Ca2+
Ca2+
Presynaptic receptor
Acetylcholine
Choline
Acetate
INTRACELLULAR RESPONSE
1 SYNTHESIS OF ACETYLCHOLINE
Transport of choline is inhibited by hemicholinium.
2 UPTAKE INTO STORAGE VESICLES
Acetylcholine is protected from degradation in the vesicle.
3 RELEASE OF NEUROTRANSMITTER
Release is blocked by botulinum toxin.
Spider venom causes release of acetylcholine.
4 BINDING TO THE RECEPTOR
Postsynaptic receptor is activated by binding of the neurotransmitter.
5 DEGRADATION OF ACETYLCHOLINE
Acetylcholine is rapidly hydrolyzed by acetylcholinesterase in the synaptic cleft.
6 RECYCLING OF CHOLINE
Choline is taken up by the neuron.

Noradrenaline (NA) and Dopamine (DA)

- NA & DA------ are monoamine

- Act as neurotransmitter at post ganglionic sympathetic nerve ending & some part of brain.

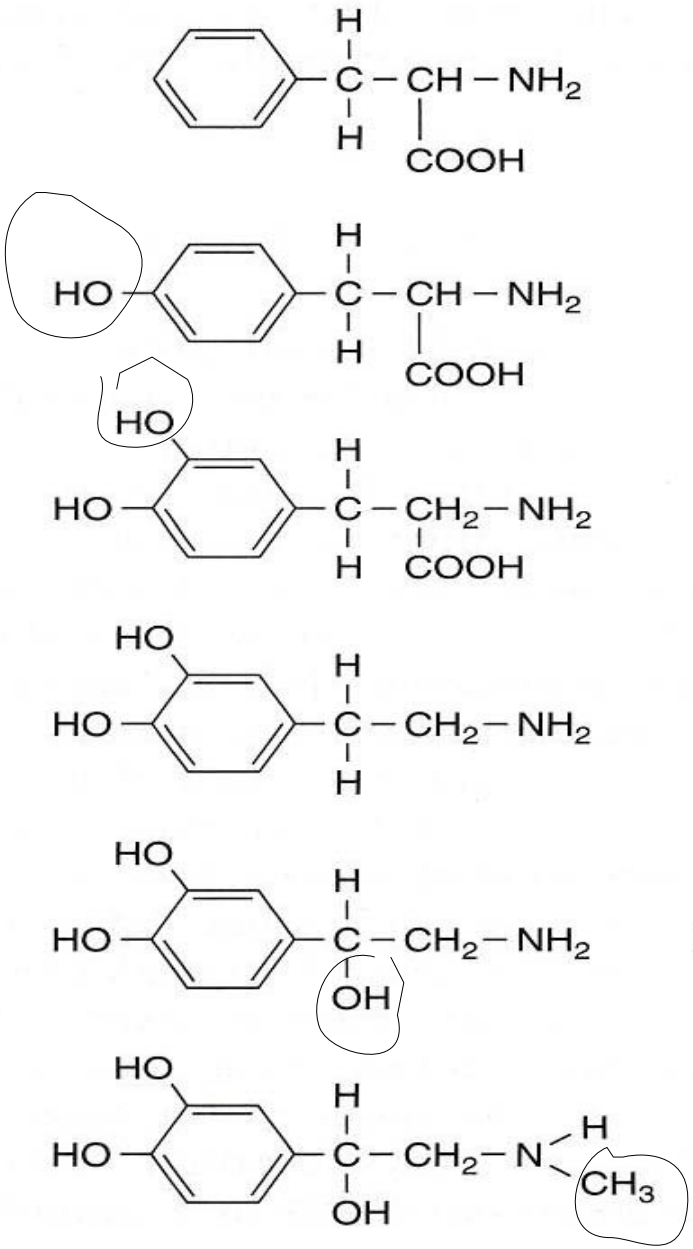
- Synthesize and stored in the vesicle within the terminal axone.

Synthesis

3 Catecholamines (dopamine, noradreanline and adrenaline)

synthesized sequientially from amino acid phenylalanine.

Figure 14.3 Pathway of catecholamine biosynthesis.



Phenylalanine
(1) Phenylalanine Hydroxylase
Tyrosine
(2) Tyrosine Hydroxylase
Dopa
(3) L-Aromatic Amino Acid Decarboxylase
Dopamine
(4) Dopamine β -Hydroxylase
Norepinephrine
(5) Phenylethanolamine N-Methyltransferase (PNMT)
Epinephrine

cytoplasm

vesicles

Adrenal medulla

- Adrenaline is formed in the adrenal medulla by methylation of NA

- And it is stored in the chromaffin granules.

- Glucocorticoids causes induction of the enzyme NA-N-Methyl transferase

  ↓

  And thus control the rate of synthesis of adrenaline.

Release of adrenaline

- Adrenaline is released into the blood stream on stimulation of adrenal medulla.

1. Stress

↓

↑ Release of cortisole (from adrenal CORTEX)

↓

↑ Release of adrenaline (from adrenal Medulla)

2. Glucagon, histamine, angiotensin II and bradykinin

Releases adrenaline

Mechanism of neurohumoral Transmission
1. Cholinergic transmission

- Ach stored in the synaptic vesicle (Termed as **depot Ach)**.

↓

25 % is released into synaptic cleft from vesicle as a result of nerve impulses (**Releasable Ach**)

↓

Change in permiablility of the effector cell (**Influx of Na & outflux of K**)

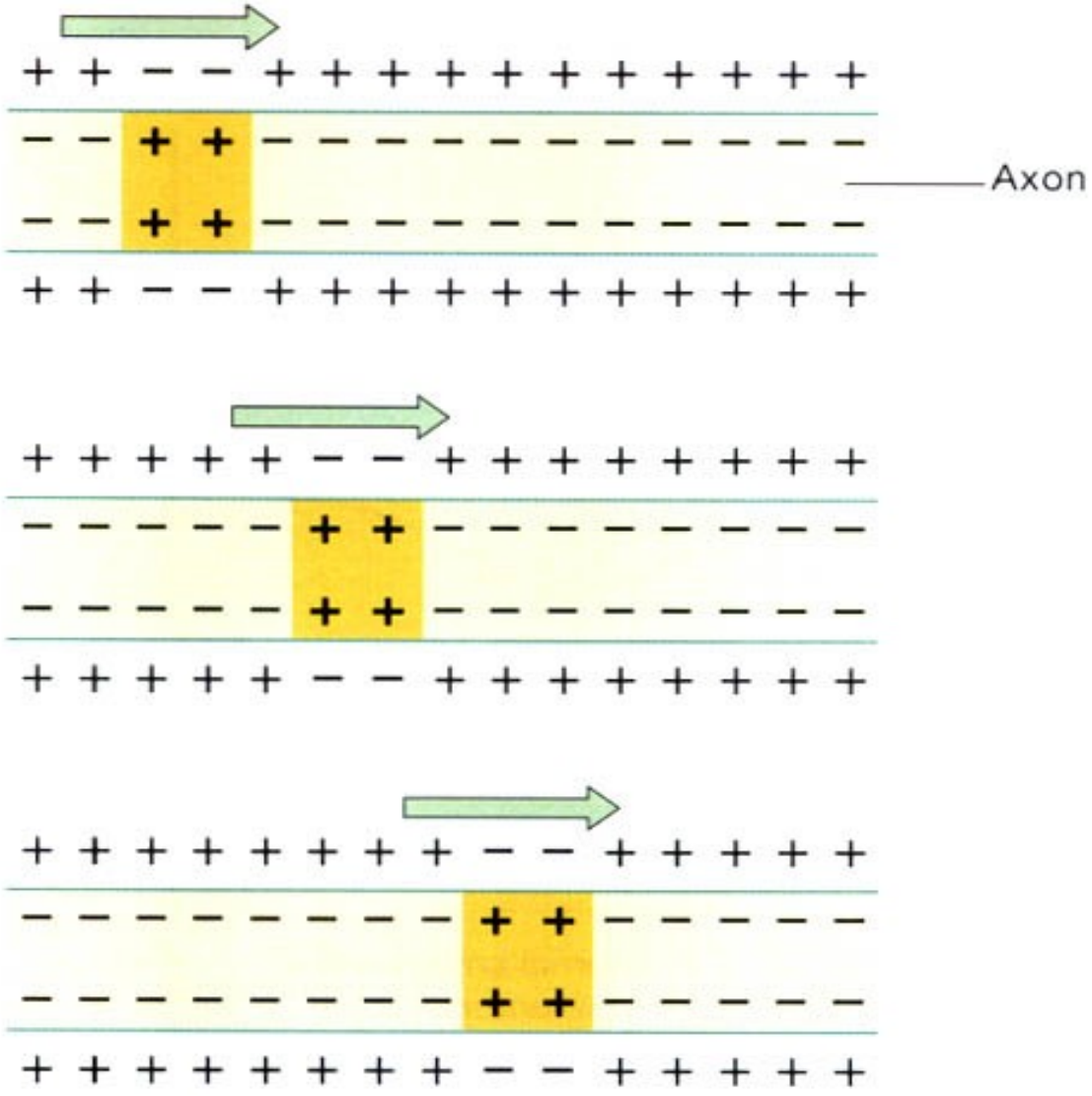
↓

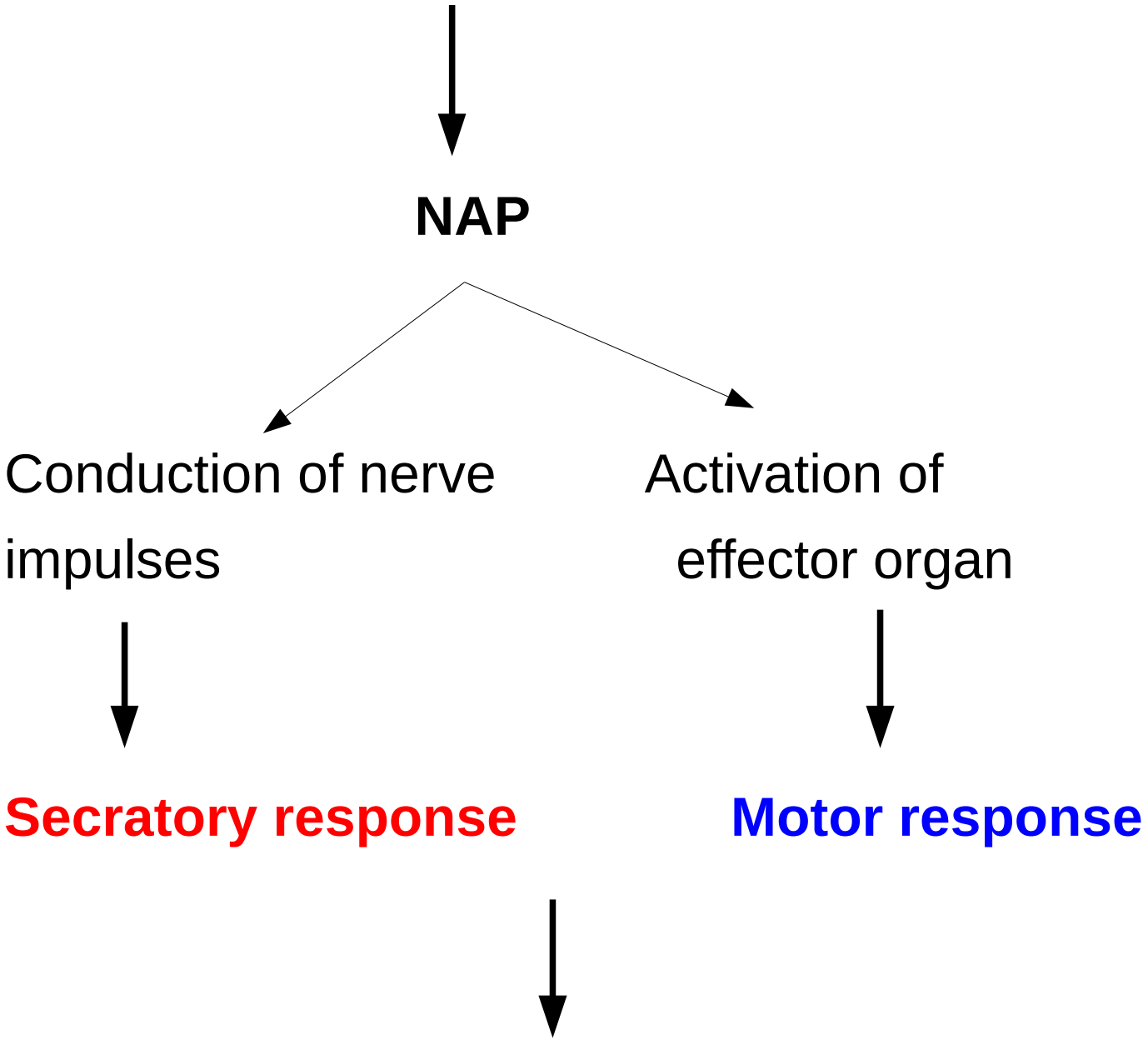
Depolarization

↘

Generate Nerve Action Potential (NAP)

Propogation of Nerve Action Potential (NAP)




NAP
Conduction of nerve impulses
Activation of effector organ
Secratory response
Motor response

Released Ach

Rapidly degraded by true cholinesterase

REVERSE IONIC CHANGE

Repolarization

2. Adrenergic transmission

2 seperate system are exist at adrenergic neuron.

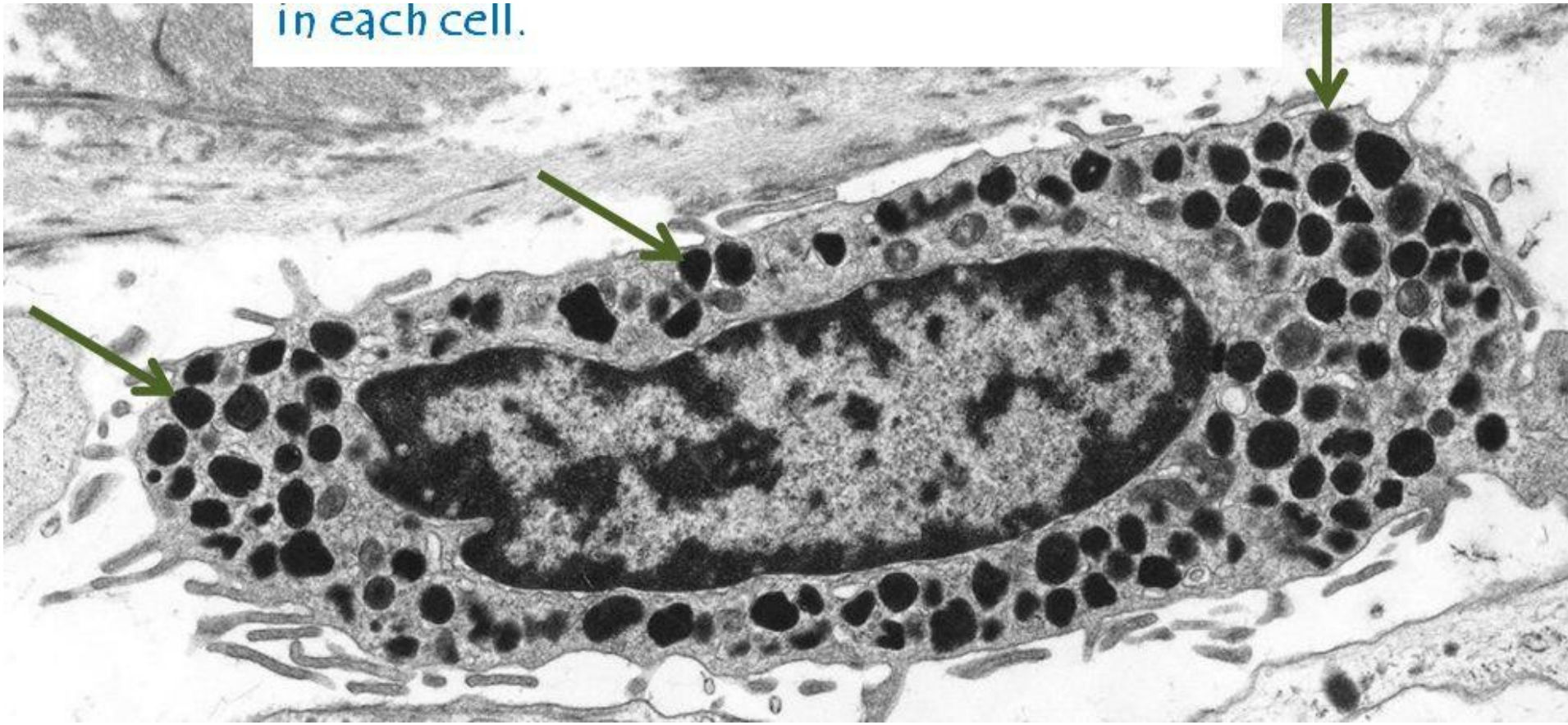
1. Vesicular monoamine transporter (VMAT)

- **Location**- vesicular granule wall
- Concerned with intraneuronal amine storage mechanism

2. Norepinephrine transporter (NET)

- It is act as Neuronal membrane amine pump
- Responsible for reuptake

Granules in side the vesicle



- NA exists in several pools
- **Major portion-**

  Over 60 % is present in protein bound form as granules.

  ↓

  In granules it exist with Ca++ & ATP.

  ↓

  Influx of Ca++ into axonal terminals (Following nerve impulses)

  ↓

  Fusion of vesicle with plasma membrane

  ↓

  Exocytosis of NA

Reuptake of NA

Involve active transport mechanism.

Mobile or functional pool of NA:

- Only a part of the stored NA is available for release into synaptic cleft as a result of neve impulses is called as **Mobile or functional pool of NA.**

- And it is in equilibrium with a fixed or non functional pool.

Presynaptic regulation of NA release

2 mechnism regulate NA release

1. Positive feedback mechanism- Mediated by presynaptic beta receptor.

2. Negative feedback mechanism- Mediated by presynaptic alpha 2 receptor.

Presynaptic regulation of NA release.....

Stimulation of Beta R by agonist

↓

Accelerate realease of NA

↓

Concentration of **NA become high**

↓

stimulation of Presynaptic alpha 2 receptor

↓

Secreation of **NA is terminated**

Presynaptic regulation of NA release.....

- Combined effect of the **positive and negative feedback mechanism** – control the need oriented release of the transmitter.

- **Alpha 1 receptor antagonist** eg phenoxybenzamine enhanced **NA release**.

- Drug could produced the action by **altering the release of these neurotransmitter** centrally or peripherally.

Metabolism of **NA & UPTAKE**

- **A small part** of released NA

  Metabolised **outside** the cell by enzyme COMT.

- Small portion is **metabolised intracellularly** by MAO

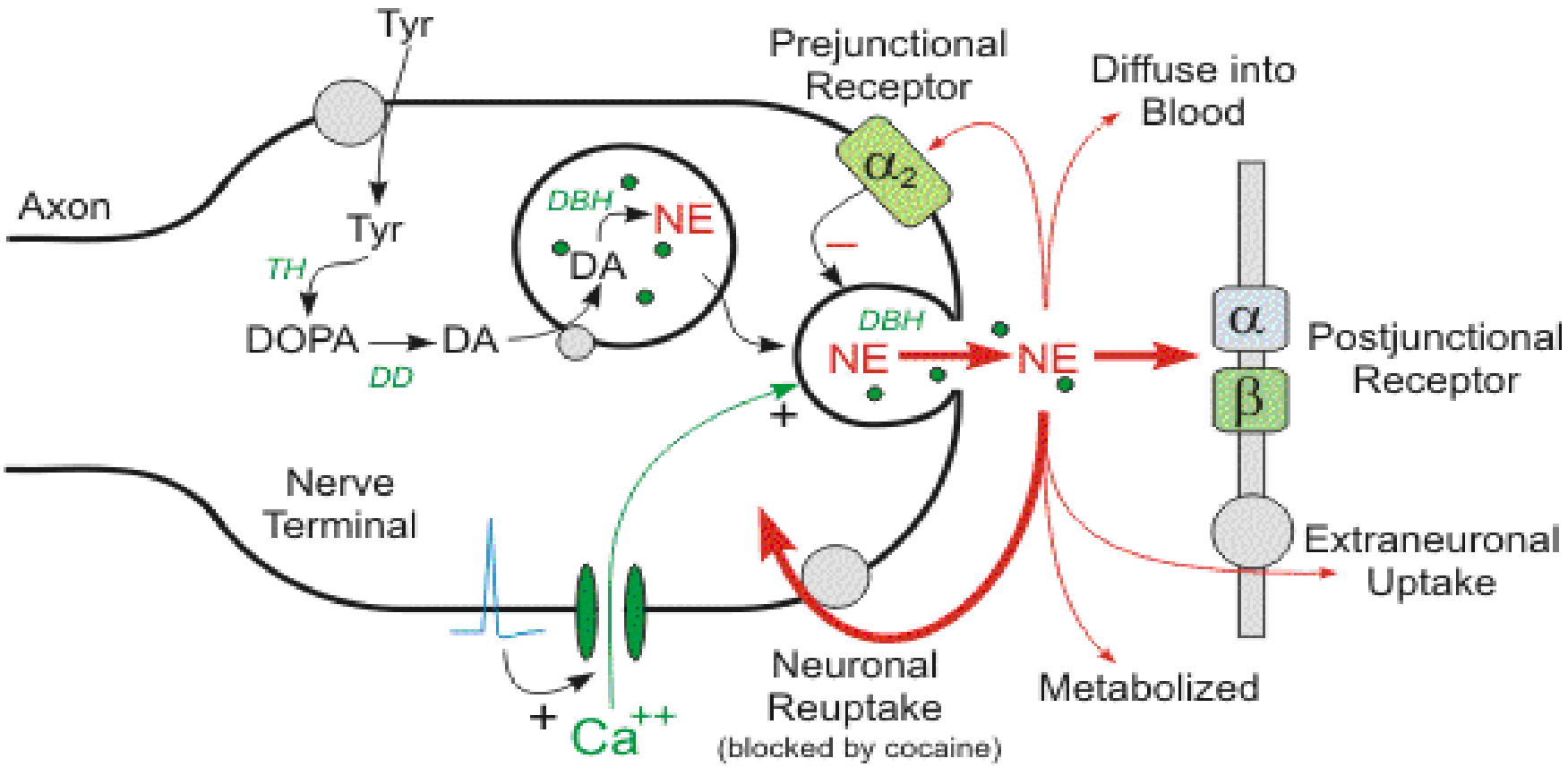
- **But large part (75-80%)** is taken back into the cell by active process

And **restore** mostly in mobile pool.

- Uptake and restorage are the major route of NA inactivation

- And **enzyme destruction** plays ONLY MINOR ROLE.

Synthesis and metabolism of norepinephrine at adrenergic neuronal ending



Tyr = tyrosine; TH = tyrosine hydroxylase; DD = DOPA decarboxylase;
DA = dopamine; DBH = dopamine β-hydroxylase; NE = norepinephrine

Enzymes of metabolism

- MAO & COMT
- **Distribution**:

  widely distributed throughout the body including

  - Brain
  - Liver and kidney (Highest concentration)
  - Intestinal mucosa

- **There are 2 type of MAO**

  1. MAO-A

  - It oxidise mainly NA & 5-HT

  - Inhibited selectively by v low concentration of chlorgyline & moclobemide.

MAO-B:

- It oxidizes DA in the brain

- selectively inhibited by selegiline.

- Tyramine and dopamine are the **substrate** for both forms of enzyme.

- Liver contain **equal amount of both MAO** enzyme while **brain contain MAO- B**.

Neurotransmitter uptake mechanism and drugs

- 2 type of uptake process designated as

  - Uptake$_1$

  - Uptake$_2$

Uptake1:

- It is the picking up of catecholamines from extracellular space by **adrenergic neurones.**

- Catecholamines taken up by **uptake 1** are transfer to the storage vesicle.

- It is mediated by **carrier mediated process**.

- It demonstrate great affinity for NA than Adrenaline.

Uptake2

- Picking up of catecholamine by the effector cells in peripheral tissue such as

  - Vascular smooth muscle

  - heart

  - exocrine gland

- It demonstrate higher affinity for adrenaline and isoprenaline than for NA
- Such uptake is followed by rapid degeneration of the catecholamine.

- **Uptake 1**- uptake with retension
- **Uptake 2**- uptake followed by metabolism

Drugs and uptake process

- Noradrenergic **uptake 1 & uptake 2** transport systems

  ↓

  can be **blocked selectively** by a number of drug.

- Many sympathomimetic amines are also **taken up by Uptake 1 process** and act as competative substrate

  ↓

  Inhibit NA uptake

Inhibitor of NA & Uptake1 & Uptake2

- **Inhibitor of uptake 1:**

  Cocain, tricyclic antidepressants, phenoxybenzamine, Amphetamine, MAOI and Chlorpromazine.

- **Inhibitor of uptake 2:**

  Normetanephrine, Glucocorticoids, Phenoxybenzamine,

Drugs modify synthesis, storage and uptake 1 mechanism

1. Drug that supply amine precursor:

- l-dopa used in parkinsone disease.

- It is the precursor of dopamine.

2. Blocking the uptake 1 of NA by inhibiting NET:

Eg. Tricyclic antidepressents like imipramine used in the tratment of **mental depression**, Cocain.

3. Interfering with the synthesis of NA eg alpha methyl tyrosine.

4. Promoting the release of NA from storage site eg. Tyramine

5. Inhibiting the transport into the vesicle thus interfere with storage of NA leading to depletion from sites eg. Antihypertensive drug reserpine

6. Blocking the release of NA from binding store in nerve terminals eg Guenthidine- used in the treatment of hypertension.

7. Promoting the synthesis of false transmitter- alpha methyl dopa.

8. Blocking post synaptic receptores: eg. Adrenergic receptor blocking drugs.

9. Inhibiting the intraneural degradation of NA: Eg. MAO inhibitor used as antidepressant.

Drugs act on cholinergic system

- Act by

  1. Blocking the synthesis of Ach:

  eg. Hemicolinium- block uptake of precursor choline

  2. **Blocking the uptake of Ach into synaptic vesicle**

  Eg. Vesamicol

3. Inhibiting the release of Ach

eg. Botulinum toxin

4. Increase the release of Ach

Eg. Black widow spider toxin

5. Preventing the destruction of Ach

eg. Anticholinesterase

6. Intereacting with post synaptic receptores:

A. Muscarinic receptor

- Muscarine (agonist)
- Atropine (Antagonist)

B. Nicotinic receptor on ganglia (N_N)

- DMPP – dimethylphenylpiperazinium (as agonist)
- Hexamethonium (as antagonist)

C. Nicotinic receptores on NMJ (N_M)

- PTM- Phenyltrimethylammonium (Agonist)
- dTubercurarine (Antagonist)