DRUG ACTING ON ANS

ADRENERGIC SYSTEM

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Adrenergic system

INTRODUCTION

- **Noradrenaline/Norepinephrine** : It is act as transmitter at postganglionic sympathetic sites (except sweat gland, hair follicles and some vasodilator fibers) and in certain areas of brain.
- **Adrenaline/epinephrine** : It is secreted by adrenal medulla and may have a transmitter role in the brain.
- **Dopamine** : It is a major transmitter in basal ganglia, limbic system, chemoreceptor trigger zone, anterior pituitary, etc.

Adrenergic system

Steps in synthesis of catecholamine (CAs)

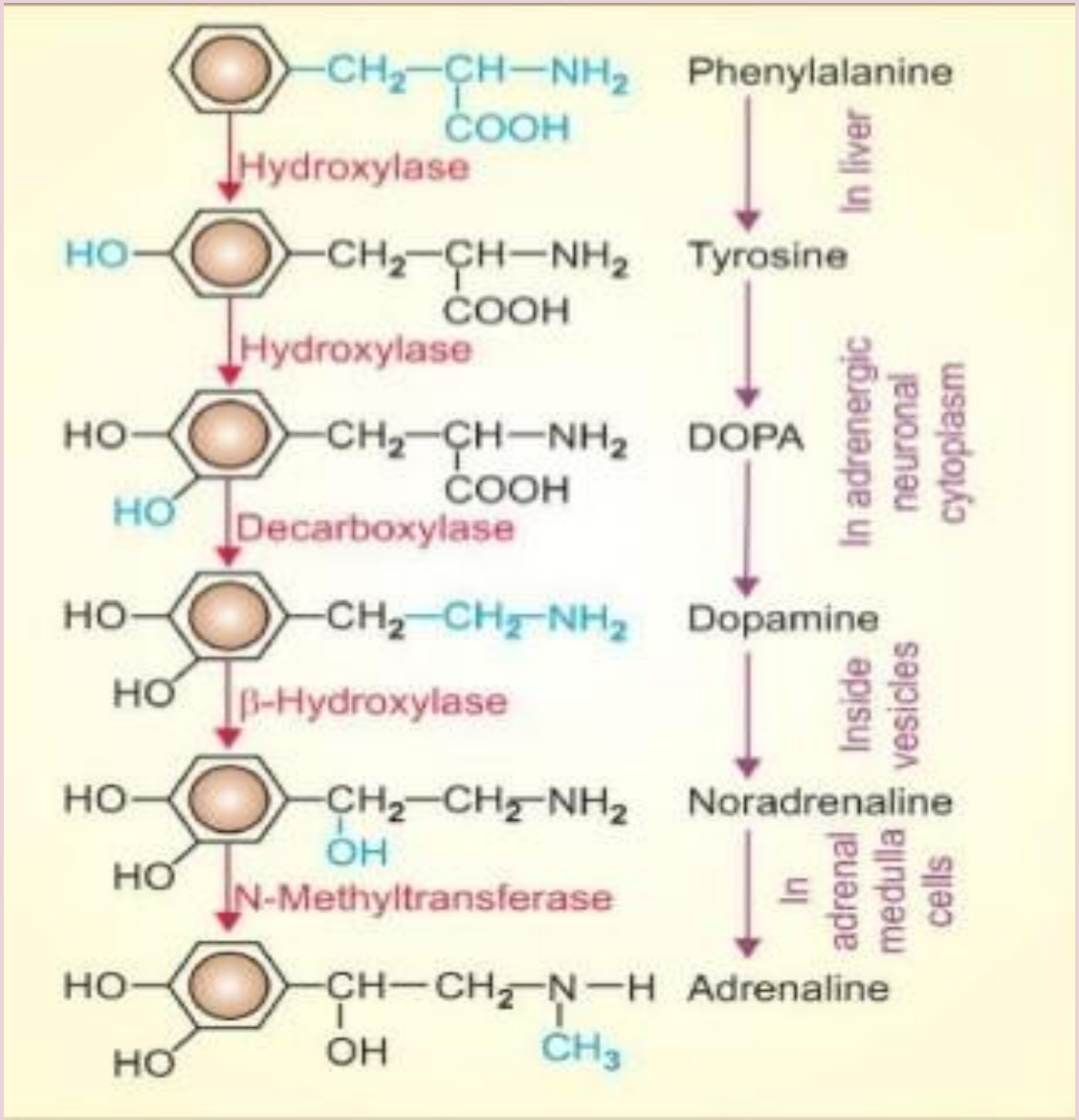
1)Synthesis of CAs

2)Storage of CAs

3)Release of CAs

4)Uptake of CAs

5)Metabolism of CAs



1.synthesis of CAS

- catecholamine are synthesized from the amino acid phenylalanine.

- Tyrosine hydroxylase is a specific and the rate limiting enzyme. **when its inhibited by alpha-methyl-tyrosine(AMPT) result in depletion of CAs.**

- Synthesis of noradrenaline occurs in all adrenergic neurons, while that of adrenaline occurs only in the adrenal medullary cells.

2) Storage of CAS

- Noradrenaline storage in synaptic vesicles or “granules” within the adrenergic nerve terminal.

- The vesicular membrane actively takes up dopamine from the cytoplasm and the final step of synthesis of NA takes place inside the vehicle which contain dopamine beta-hydroxylase.

- Noradrenaline is strode as a complex with ATP which is absorbed on a protein chromogranin.

3) Release of CAS

- The nerve impulse couples release of catecholamine takes place by exocytosis and all the vesicular contents noradrenaline or adrenaline, ATP, dopamine, beta hydroxylase.

- The release is modulated by presynaptic receptors, of which alpha2 inhibitory control is dominant.

4) Uptake of CAS

- **Axonal UPTAKE:** An active amine pump is present at the neuronal membrane which transport NA by a NA+ coupled mechanism. It takes up NA at a higher rate then Adr and had been labeled uptake-1.

- **Vesicular uptake:** The membrane of intracellular vesicles has another amine pump the vesicular monoamine transporter which transport catecholamine from the cytoplasm to the interior of the storage vesicle. This uptake is inhibited by reserpine resulting in depletion of Cas.

- **Extra neuronal uptake:** it is also called as uptake-2 and carried out by extra neuronal amine transporter.

5)Metabolism action

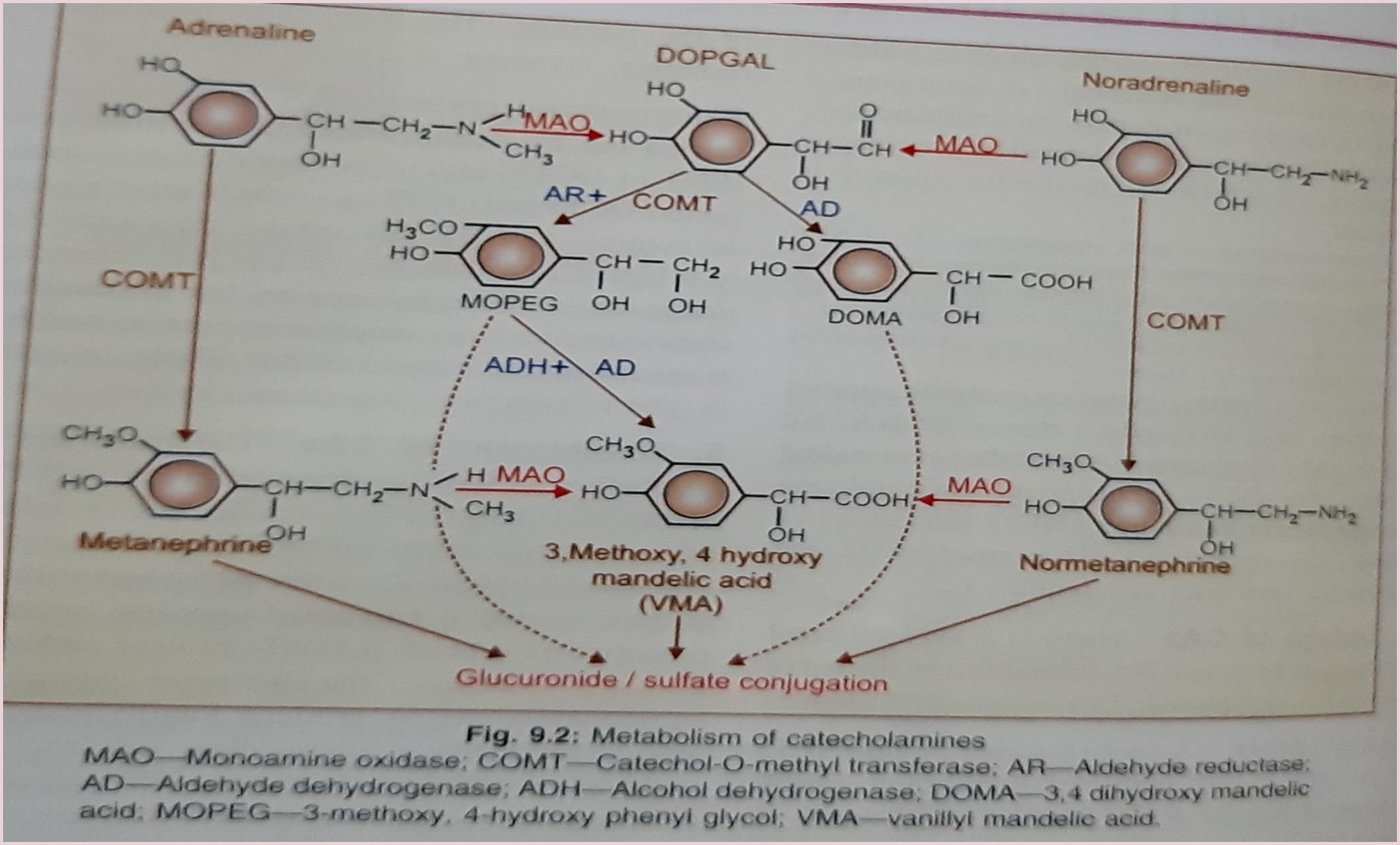
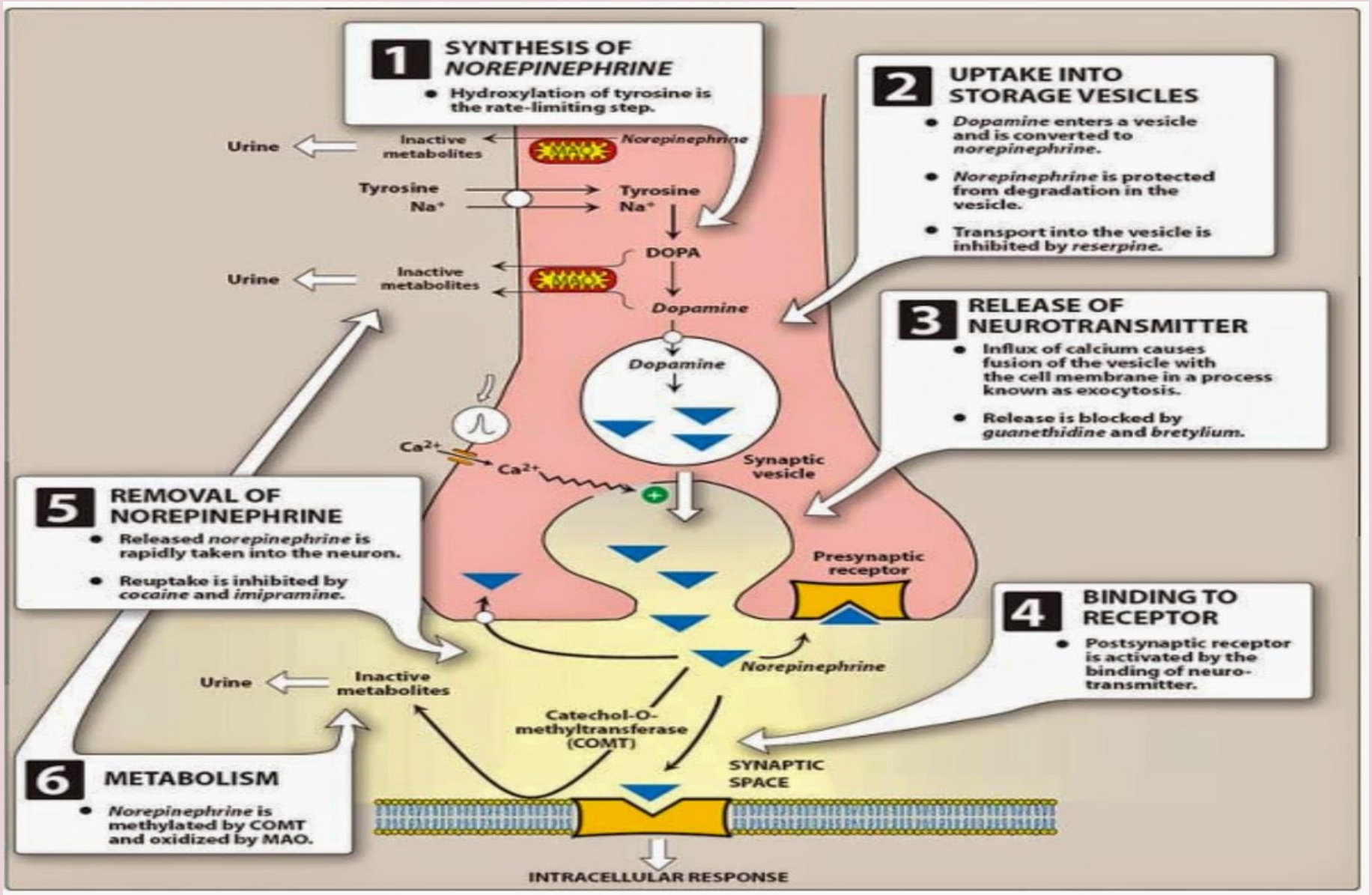


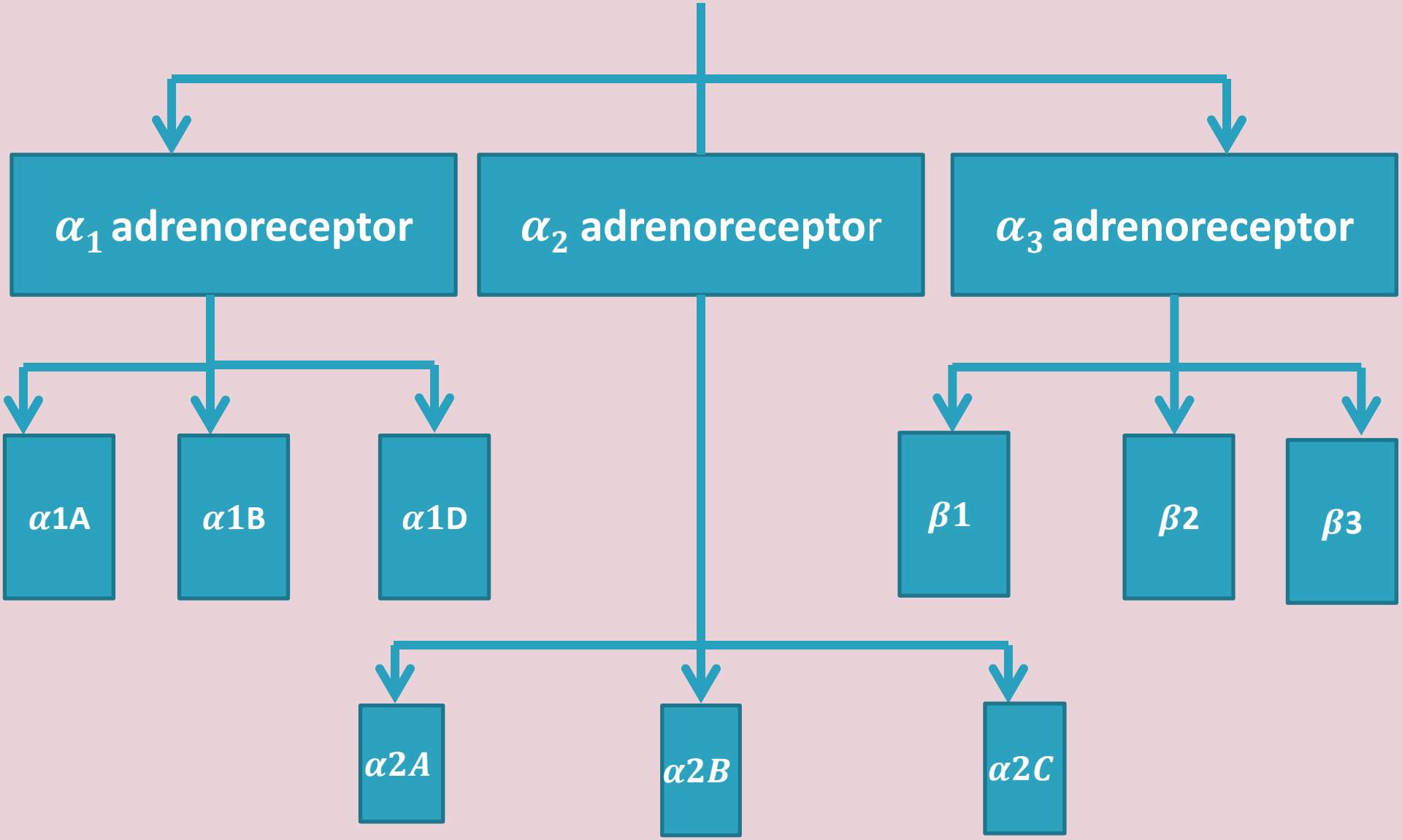
Fig. 9.2: Metabolism of catecholamines

MAO—Monoamine oxidase; COMT—Catechol-O-methyl transferase; AR—Aldehyde reductase; AD—Aldehyde dehydrogenase; ADH—Alcohol dehydrogenase; DOMA—3,4 dihydroxy mandelic acid; MOPEG—3-methoxy, 4-hydroxy phenyl glycol; VMA—vanillyl mandelic acid.

Synthesis of catecholamine



Classification of adrenergic receptor



Characteristics of subtype of Adrenergic receptor

Receptor	Agonist	Antagonist	Tissue	Response
α_1	Phenylephrine	Prazosin	Vascular Smooth muscle	Contraction
			Liver	Glycogenolysis Gluconeogenesis
			Intestinal Smooth muscle	Hyperpolarization & relaxation
			Heart	Increased contractile
α_2	Clonidine	Yohimbine	Pancreatic Islets	Decreased insulin secretion
			Platelets	Aggregation
			Vascular smooth muscle	contraction

Characteristics of subtype of Adrenergic receptor

Receptor	Agonist	Antagonist	Tissue	Response
β_1	Dobutamine	Metoprolol	Juxtaglomerular Cell	Increased renin Secretion
			Nerve terminals	Decreased release of NE
			Heart	Increased force and rate of contraction and AV nodal conduction velocity
β_2	Salbutamol, terbutaline	α methayl propranolol	Smooth muscle	Relaxation
			Skeletal muscle	Glycogenolysis
			Liver	Glycogenolysis Gluconeogenesis
β_3			Adipose tissue	Lipolysis

Adrenergic Drug (sympathomimetic)

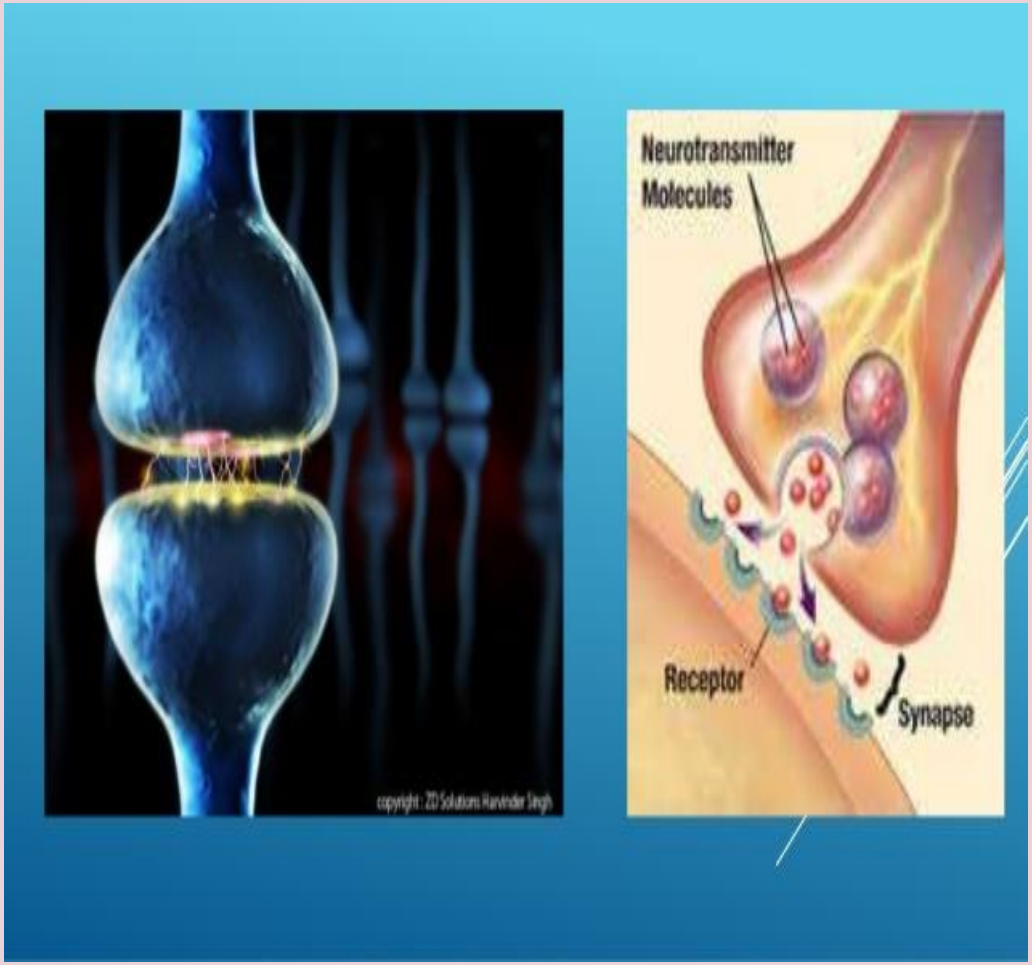
- **Direct sympathomimetic** : They act directly as agonist on alpha and beta adrenoceptor –Adr, NA, isoprenaline, methoxamine, salbutamol and others

- **Indirect sympathomimetic** : They act on adrenergic neuron to release NA which then acts on the adrenoceptor- tyramine , amphetamine.

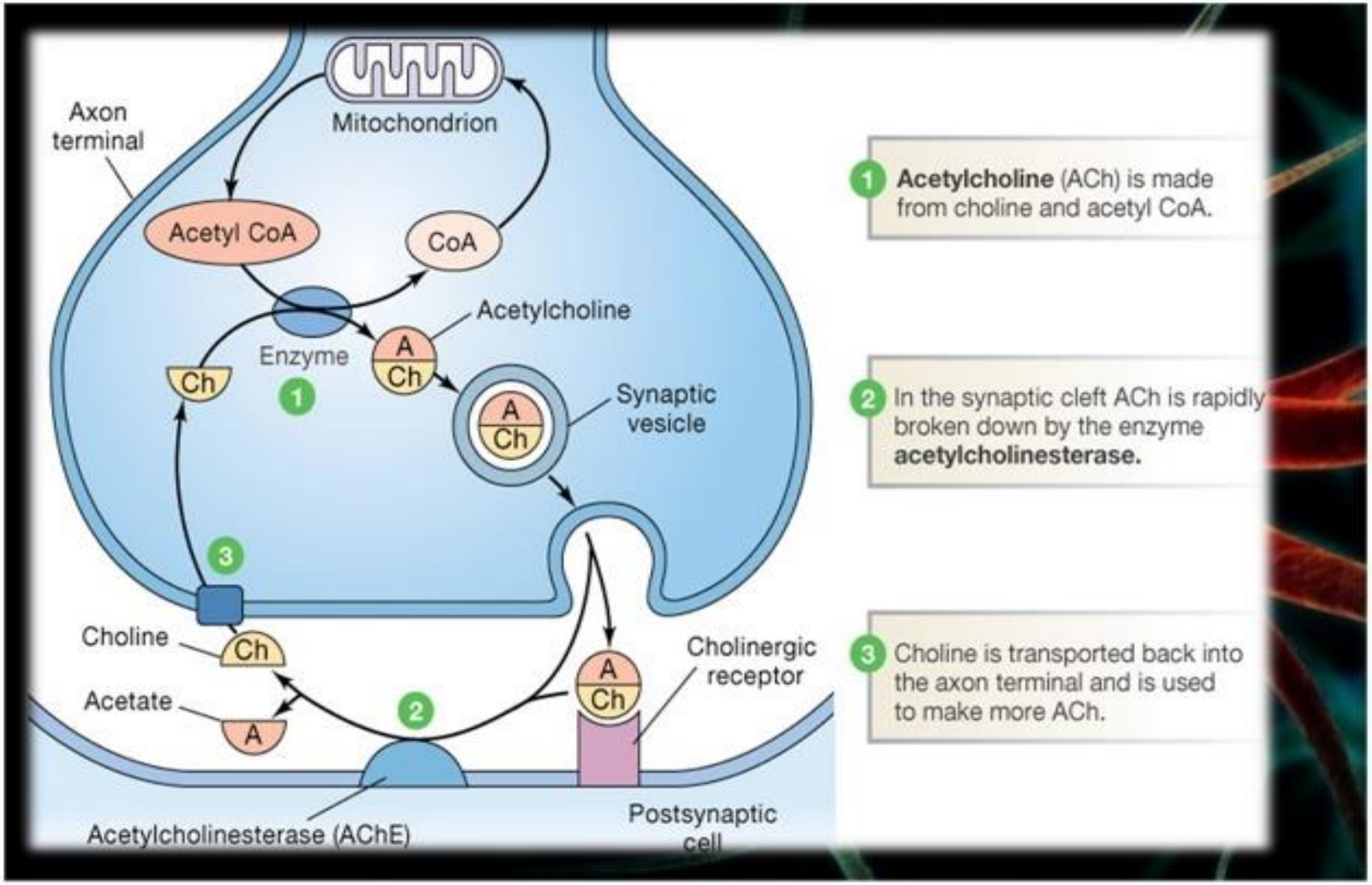
- **Mixed action sympathomimetic** : They act directly as well as indirectly- ephedrine, dopamine, mephetermine

Cholinergic system

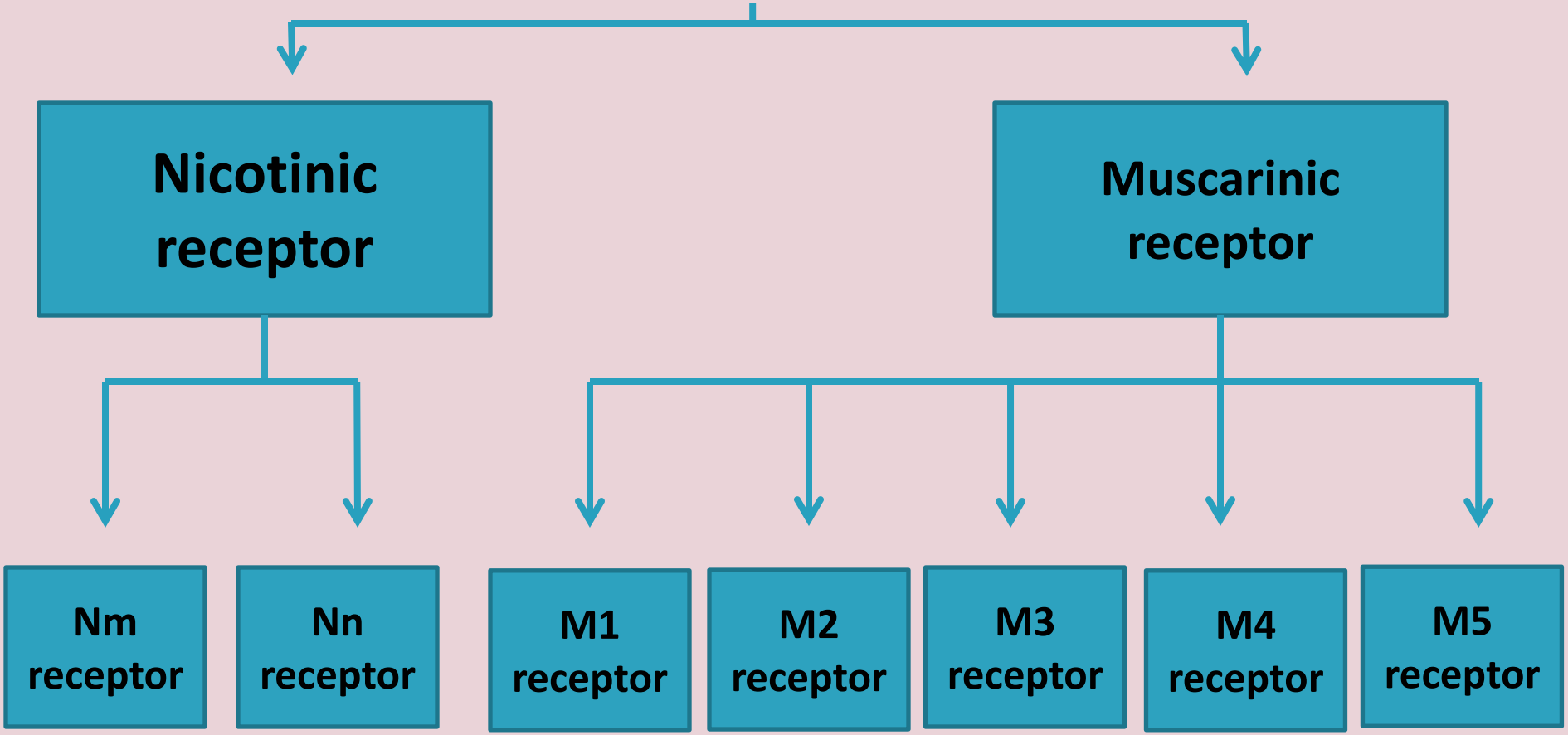
- Chemical sites in effector cells or at synapses through which acetylcholine extract its action
- Eg Choline receptor response to acetylcholine in neuro-synapse



Mechanism of acetylcholine



Classification of Cholinergic receptors

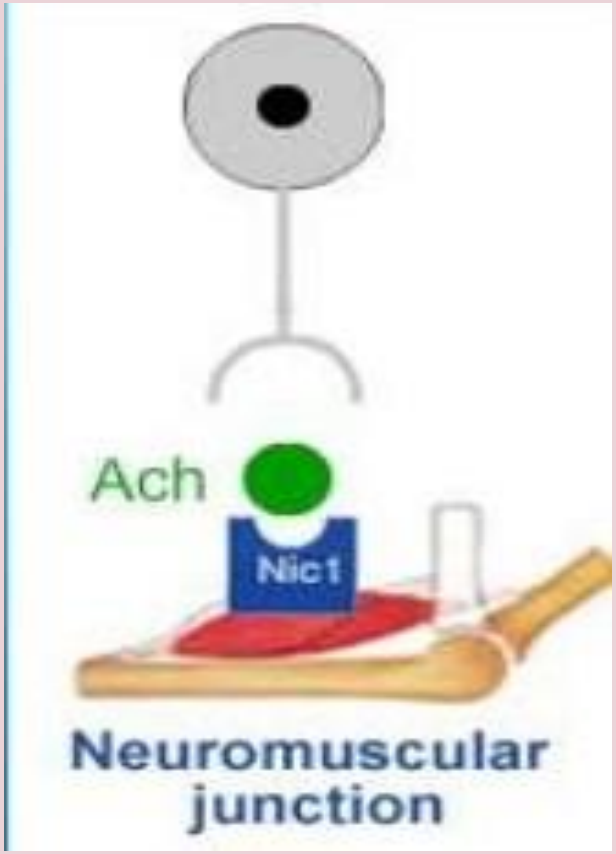


Nicotinic receptors

Nm receptor	Nn receptor
Neuromuscular junction.	Autonomic ganglia, CNS and adrenal medulla.

NM RECEPTOR

- These receptor are located at the neuromuscular junction
- Acetylcholine receptor of the NM subtype are the only acetylcholine receptor that can be found at the neuromuscular junction



N_N RECEPTOR

- As mentioned before nicotinic receptor play a key role in the transmission of cholinergic signals in the autonomic nervous system

- Nicotinic receptor of the Nn subtype can be found both at cholinergic and adrenergic ganglia but not the target tissues (eg. Heart bladder)

- These receptor are also present in the CNS and adrenal medulla.

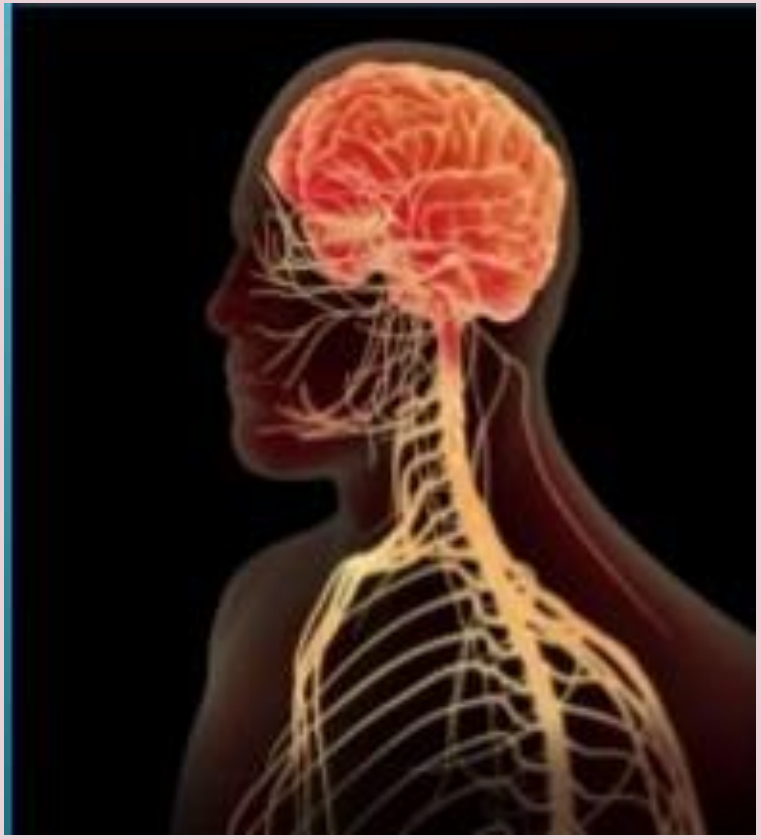
Muscarinic receptor

M1 receptor	M2 receptor	M3 receptor	M4 receptor	M5 receptor
CNS	HEART	SMOOTH MUSCLE	CNS	CNS

M1, M4 and M5 receptor

- **CNS:** These receptor are involved in complex CNS responses such as memory arousal attention and analgesia.

- M1 receptor are also found at gastric parietal cells and autonomic ganglia



M2 RECEPTOR

HEART :

Activation of M2 receptor lowers conduction velocity at sinoatrial and atrioventricular nodes thus lowering heart rate.

M3 RESEPTOR

SMOOTH MUSCLE:

Activation of M3 receptor at the smooth muscle level produce that include bronchial tissue bladder exocrine gland among other

CHOLINERGIC NEURONS

- 1.**Central cholinergic neurons:** arise from CNS including all somatic nerves

- 2.**Peripheral cholinergic neurons:** arise from autonomic ganglia including all parasympathetic and sympathetic cholinergic postganglionic nerves

DRUG ACTING ON CHOLINEGRIC RECEPTOR

- PARASYMPATHOMIMETIC DRUGS
- (A)**DRUG ACTING DIRECTLY:**
- MUSCARINIC : AGONIST : Methacholine , pilocarbine,
- NICOTONIC :AGONIST: Carbachol

- (B)**DRUG ACTING INDIRECTLY:**
- REVERSIBBLE : Prostigmine
- IRREVERSIBLE: Parathion

Action on muscarinic receptor

Eye: circular muscle of iris ciliary muscle and lacrimal gland possess M3 receptor.

Contracition of ciliary muscle

Loosen the sensory ligaments

⇩

Lens more convex

⇩

Accommodated for near vision

Heart

- Parasympathetic supply is only up to SA node atria and AV node.
- Effect on the M2 receptor activation at SA node and atria causes decrease in heart and decrease in force of contraction respectively.
- AV node causes decrease in conduction velocity and increase in refractory period.

Nicotinic action

Autonomic ganglia: higher dose causes dangerous muscarinic effect especially on heart high dose of Ach stimulate both the sympathetic as well as the parasympathetic ganglia causing tachycardia & rise in bp.

THANK YOU