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MEDICINAL CHEMISTRY – I

UNIT 3

TOPIC :

- **Cholinergic neurotransmitters :**
  Biosynthesis and catabolism of acetylcholine.
  Cholinergic receptors (Muscarinic & Nicotinic) and their distribution.

Cholinergic Neurotransmitters

- Cholinergic neurotransmitters are chemical messengers that transmit nerve impulses by binding to cholinergic receptors (nicotinic or muscarinic) on the target cell.
- Major neurotransmitter: Acetylcholine (ACh)
  It is the primary neurotransmitter of the cholinergic system.
- Functions of Acetylcholine:
  1. Neuromuscular junction – activates skeletal muscle contraction.
  2. Autonomic nervous system – regulates involuntary functions (e.g., heart rate, digestion, glandular secretion).
  3. Central nervous system (CNS) – supports higher brain functions such as memory, learning, and attention.

Biosynthesis of Acetylcholine (ACh)

- Location: Takes place mainly in the nerve terminals of cholinergic neurons.
- Key enzyme: Choline acetyltransferase (ChAT).
- Substrates required:
  - Choline (derived from diet or recycled after ACh breakdown)
  - Acetyl-CoA (produced in mitochondria)

Reaction:

$$Choline + Acetyl - CoA \xrightarrow{\text{Choline acetyltransferase}} Acetylcholine + CoA$$

Catabolism of Acetylcholine

- **Location**: Occurs mainly in the **synaptic cleft** immediately after neurotransmission.
- **Key enzyme**: **Acetylcholinesterase (AChE)** – a very fast-acting enzyme.

Reaction:

$$Acetylcholine \xrightarrow{AChE} Choline + Acetate$$

Fate of products:

- **Choline** → taken back into the presynaptic neuron (recycled for ACh synthesis).
- **Acetate** → diffuses away and enters metabolic pathways.

- **Importance**:
  - Ensures **rapid termination** of ACh action at the synapse.
  - Prevents continuous stimulation of receptors (which could cause paralysis or toxicity).
  - The breakdown occurs within **milliseconds**.

Cholinergic Receptors

- Cholinergic receptors are **specialized proteins** located on the surface of cells (neurons, muscles, glands) that bind **acetylcholine (ACh)** and mediate its physiological effects.
- **Major types**:
  1. **Muscarinic receptors (M1–M5)** – belong to **G-protein coupled receptor family**.
  2. **Nicotinic receptors (NN, NM)** – belong to **ligand-gated ion channel family**.

1. Muscarinic Receptors (M1–M5)

- GPCR type → act through **second messengers**.
- Subtypes and distribution:

Subtype	Coupling (G-protein)	Major Distribution	Function
M1	Gq	CNS (hippocampus, cortex), autonomic ganglia, gastric parietal cells	↑ Cognitive functions (memory, learning), ↑ Gastric acid secretion, neuronal excitation
M2	Gi	Heart (atria, SA & AV	↓ Heart rate (bradycardia), ↓

		node), CNS	conduction, ↓ neurotransmitter release
M3	Gq	Smooth muscle (bronchi, bladder, GIT), exocrine glands, eye (pupil)	Smooth muscle contraction, ↑ glandular secretion (saliva, tears, sweat), miosis (pupil constriction)
M4	Gi	CNS (striatum, hippocampus)	Inhibits neurotransmitter release, role in motor control
M5	Gq	CNS (substantia nigra, brain vasculature)	May modulate dopamine release, vasodilation in cerebral blood vessels

2. Nicotinic Receptors

- **Ligand-gated ion channels** (Na^+/K^+ channel).
- Subtypes:

Subtype	Location	Function
NN (Neuronal Nicotinic)	Autonomic ganglia (sympathetic & parasympathetic), adrenal medulla	Mediates transmission in ganglia, stimulates catecholamine release (adrenaline, noradrenaline)
NM (Muscle Nicotinic)	Neuromuscular junction (skeletal muscle)	Mediates skeletal muscle contraction