

Autonomic Pharmacology

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Autonomic Pharmacology

□ Nervous system:

❖ CNS: → Brain
→ Spinal cord

❖ Peripheral NS: → Somatic nerves
→ ANS

Autonomic Pharmacology

□ ANS:

❖ Autonomous

- Responsible for visceral involuntary functions
- Important to maintain life
- E.g. Smooth & Cardiac m., exocrine glands.

❖ Consists of:

- Sympathetic system (Thoraco-lumbar)
- Parasympathetic system (Cranio-sacral)
- Enteric nervous system

Autonomic Pharmacology

- Consists of:
 - ❖ Medullary centers
 - ❖ Preganglionic fibers
 - ❖ Ganglia
 - ❖ Postganglionic fibers

Autonomic Pharmacology

Sympathetic

Parasympathetic

Act at

acts at rest

Stress, trauma, hypoglycaemia

opposes sympathetic

Cold & Exercise

**regulates digestion, bowel
and urinary function**

fight or flight response

Direct-acting Cholinomimetics

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Direct-acting cholinomimetics

❖ **Cholinomimetics:-**

Agents that mimic or simulate actions of Ach

❖ Ach is neurotransmitter of cholinergic nerves acts on cholinceptors in:

➤ Ganglia

➤ Postsynaptic endings of the parasympathetic sys

➤ Adrenal medulla

➤ NMJ endplates

Pathway of Acetylcholine

- ❑ Synthesized in the cytoplasm of cholinergic nerve terminals from Acetyl-CoA & choline:
- ❖ By the action of choline acetyl transferase enzyme (CAT).



Pathway of acetylcholine:

- Storage in vesicles

- Release:

- Action potential:

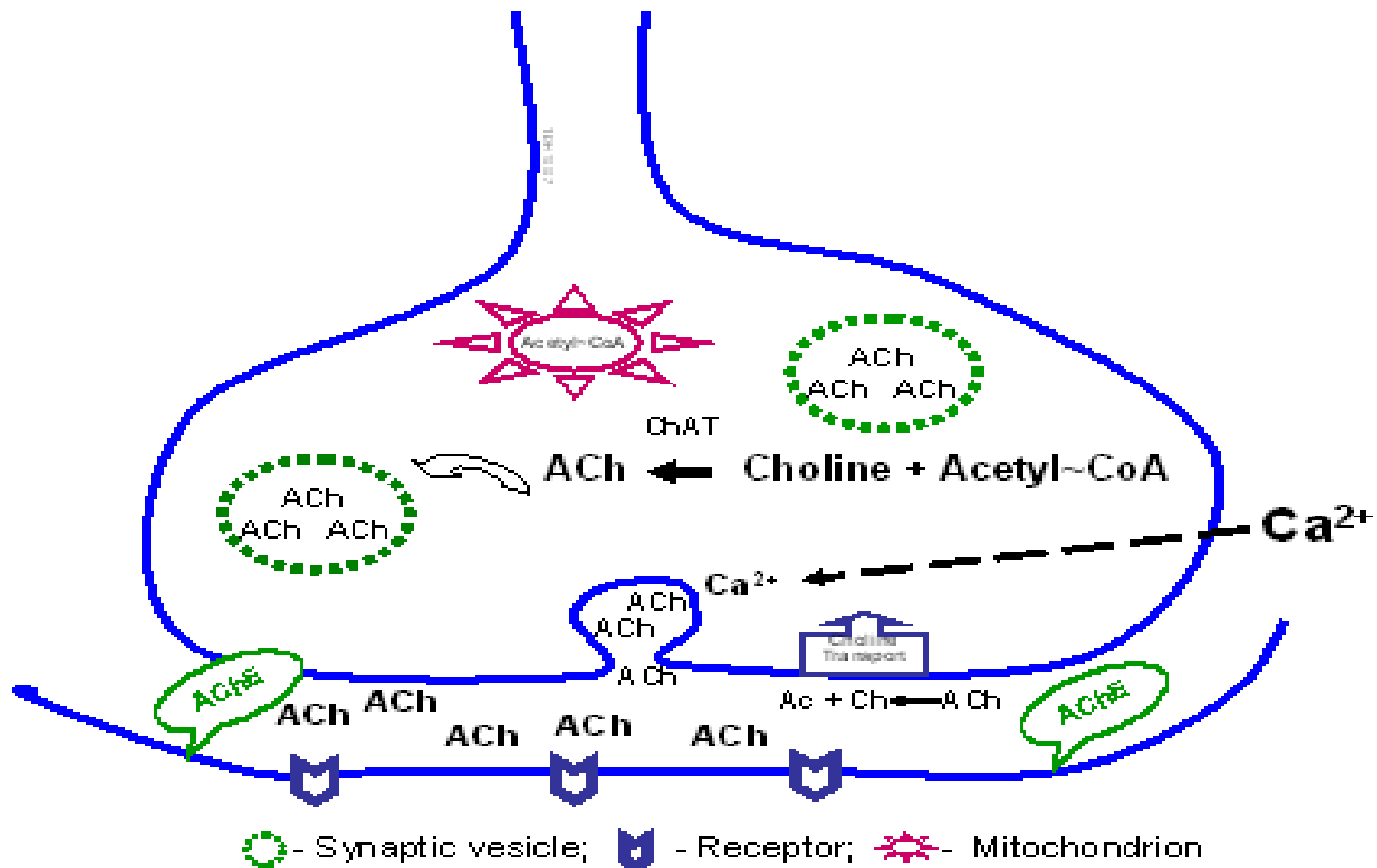
- Depolarization: —————→

- Influx of Ca: Increase intraneuronal Ca: —————→

- Fusion of storage vesicles with membrane —————→

- Expulsion & release of Ach (exocytosis)

Synthesis & Release Of Ach



Pathway of acetylcholine:

- Binding and activation of cholinceptors

- Actions

- Degradation:

Cholinesterase

Ach $\xrightarrow{\hspace{2cm}}$ Choline + Acetate

- Cholinesterase is specific to Ach

- Pseudocholinesterase (PCE) in plasma and liver is not specific

Acts on others as suxamethonium

- Genetic absence PCE $\xrightarrow{\hspace{2cm}}$ Prolonged apnoea

Pathway of Ach: Recycling

- ❑ Recycling of choline back into neurons
- ❖ Inhibitors of Ach Pathway:
 - Release: Botulinum toxins
 - Binding of Ach: Anti-cholinergic drugs

Locations & Function of Cholinoceptors

❑ Muscarinic receptors:

❖ M_1	CNS		Excitatory
❖	Parietal cells	↑	Gastric secretion
❖ M_2	Myocardium	↓	Rate, contractility
❖ M_3	Vascular SM		Relaxation
❖	Endothelium		Nitric oxide

Muscarinic cholinceptors

❖ M_3	Circular M of iris	Miosis
❖ M_3	Exocrine, GIT	↑ Secretions
❖ M_3	GIT & Bladder wall	Contraction
❖ M_3	Sphincters	Relaxation
❖ M_3	Bronchi	Constriction

Muscarinic receptors

- ❖ In corpora cavernosa of penis:
 - Through release of nitric oxide
 - And vasodilatation
 - Leads to erection

Nicotinic receptors

- ❖ Nicotinic N_N Ganglia (stimulation)
- ❖ Nicotinic N_N Adrenal medulla
(Adrenaline & NA
release)
- ❖ Nicotinic N_M NMJ endplates
(Muscle contraction)

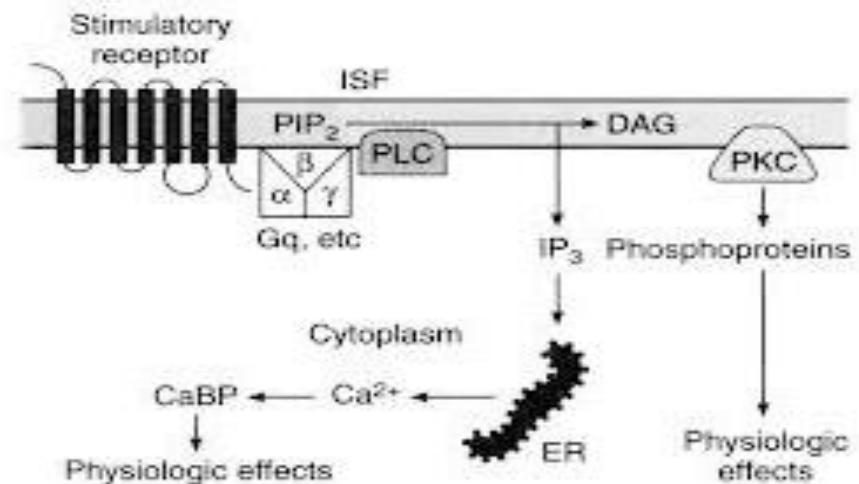
Mechanism of Ach signal transduction

❖ Muscarinic receptors:

- G-protein coupled receptors
- Second messengers (as DAG, IP₃, cGMP)

❖ Nicotinic receptors:

- Ion channel receptors



Acetylcholine

- ❖ Has little therapeutic value
 - Multiple actions
 - Binds & activates muscarinic & nicotinic receptors
 - Short t $\frac{1}{2}$

Pharmacodynamics of Ach

□ Muscarinic stimulation on the CVS:

- Decrease SV & CO

By -ve (chronotropic, inotropic & dromotropic)

- Decrease ABP:

➤ Stimulation of vascular M₃ receptors

➤ Increase nitric oxide

Pharmacodynamics of Ach

- Eye:
 - ❖ Miosis:
 - Contraction of the circular muscle of the iris
 - ❖ Accommodation to near vision:
 - Contraction of the ciliary muscle
 - ❖ Decrease IOP

Pharmacodynamics of Ach

- ❑ Exocrine glands:
 - Increase secretion
- ❑ Increase intestine movement with relaxation of sphincter: → defecation
- ❑ Contraction of urinary bladder wall with relaxation of the sphincter: → urination

Pharmacodynamics of Ach

- Bronchi:
 - Broncho-constriction
 - Mucosal hypersecretion

Pharmacodynamics of Ach

- ❑ Stimulation of nicotinic cholinceptors:
 - ❖ Effects on ganglia
 - ❖ Adrenal medulla
 - ❖ NM Junction transmission

Direct acting cholinomimetics

❖ Choline esters:

- Bethanechol, Carbachol, Methacholine
 - Resist degradation by cholinesterases
 - Have longer duration of action than Ach

❖ Natural alkaloid:

- Pilocarpine
 - Acts directly on the eye

Bethanechol

- ❖ Derivative of Ach which has little or no nicotinic effect.
 - Good muscarinic activity on bladder & GIT
- ❖ Prokinetic agent
- ❖ Leads to easier urination and defecation
- ❖ Used in treatment of:
 - Postoperative or post-labour urinary retention or paralytic ileus (Prokinetic)

Carbachol

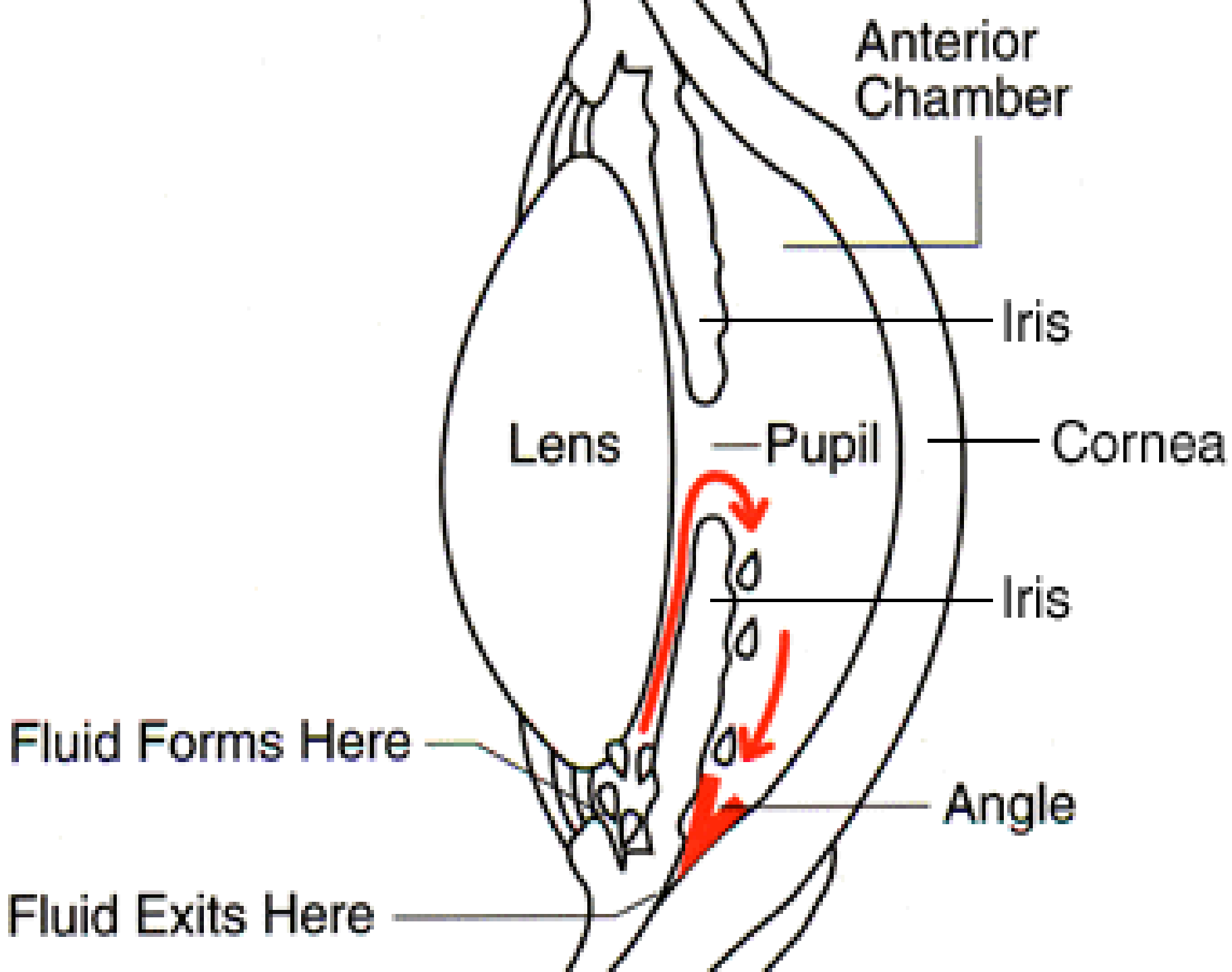
- ❖ Derivative of Ach
- ❖ Has muscarinic & nicotinic actions
- ❖ Limited systemic uses because of its nicotinic stimulatory effects on ganglia & adrenal Medulla with consequent changes in the CVS & other systems.
- ❖ Used topically as miotic agent to decrease high IOP in glaucoma

Pilocarpine

- ❖ Natural alkaloid
- ❖ Resistant to cholinesterase
- ❖ Its muscarinic action in eye result in miosis & contraction of ciliary muscle
- ❖ Used topically in glaucoma
 - To lower high IOP in glaucoma
 - In open or close-angle glaucoma

Mechanism of pilocarpine action

- ❖ Improves outflow of aqueous humour
- ❖ Opens fluid pathways
- ❖ Enhances aqueous flow through canal of Schlemm:
 - Contraction of ciliary M & circular muscle of iris
- ❖ Stimulates salivation and sweating



Indications of direct cholinomimetics

- ❖ Stimulate bladder & bowel function after surgery or labour (Bethanechol)
- ❖ Glaucoma (Pilocarpine & Carbachol)
- ❖ Pilocarpine orally to treat xerostomia of Sjogren's syndrome

Adverse effects of direct cholinomimetics

- ❖ Excessive sweating, salivation
- ❖ Flushing, hypotension
- ❖ Abdominal colic, diarrhoea
- ❖ Bronchospasm
- ❖ Pilocarpine: impaired accommodation to far vision & darkness (also carbachol)

Synthesis of NO

