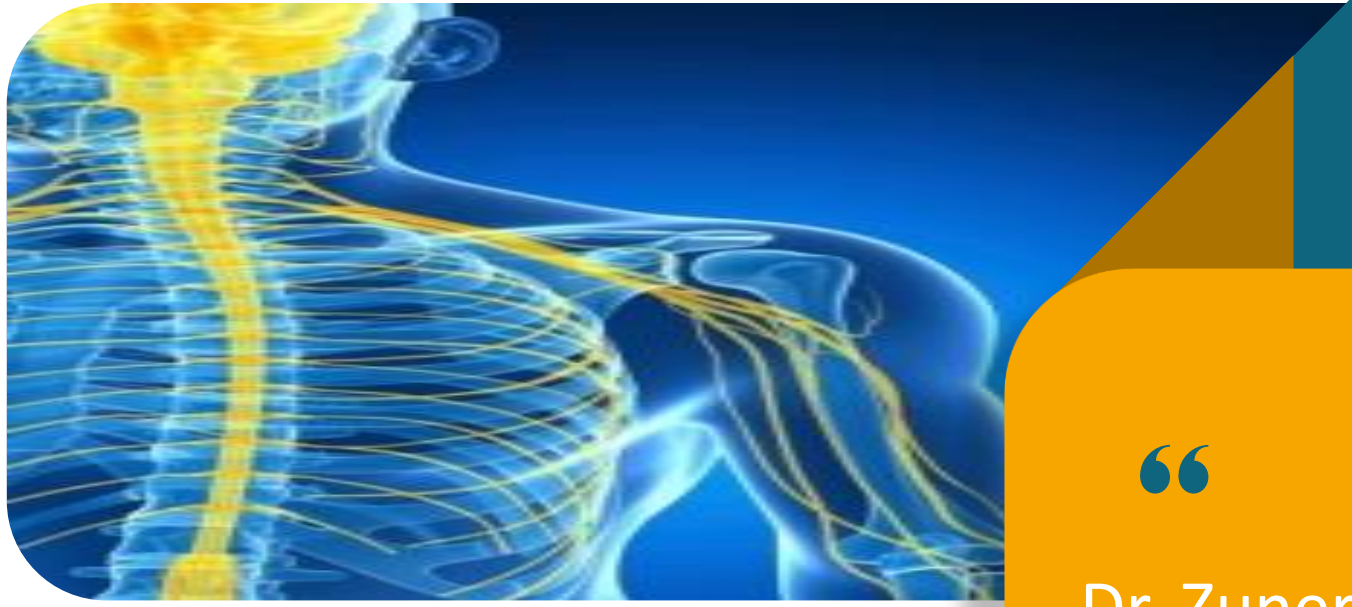


PARASYMPATHOMIMETICS
(Directly Acting Cholinomimetics)

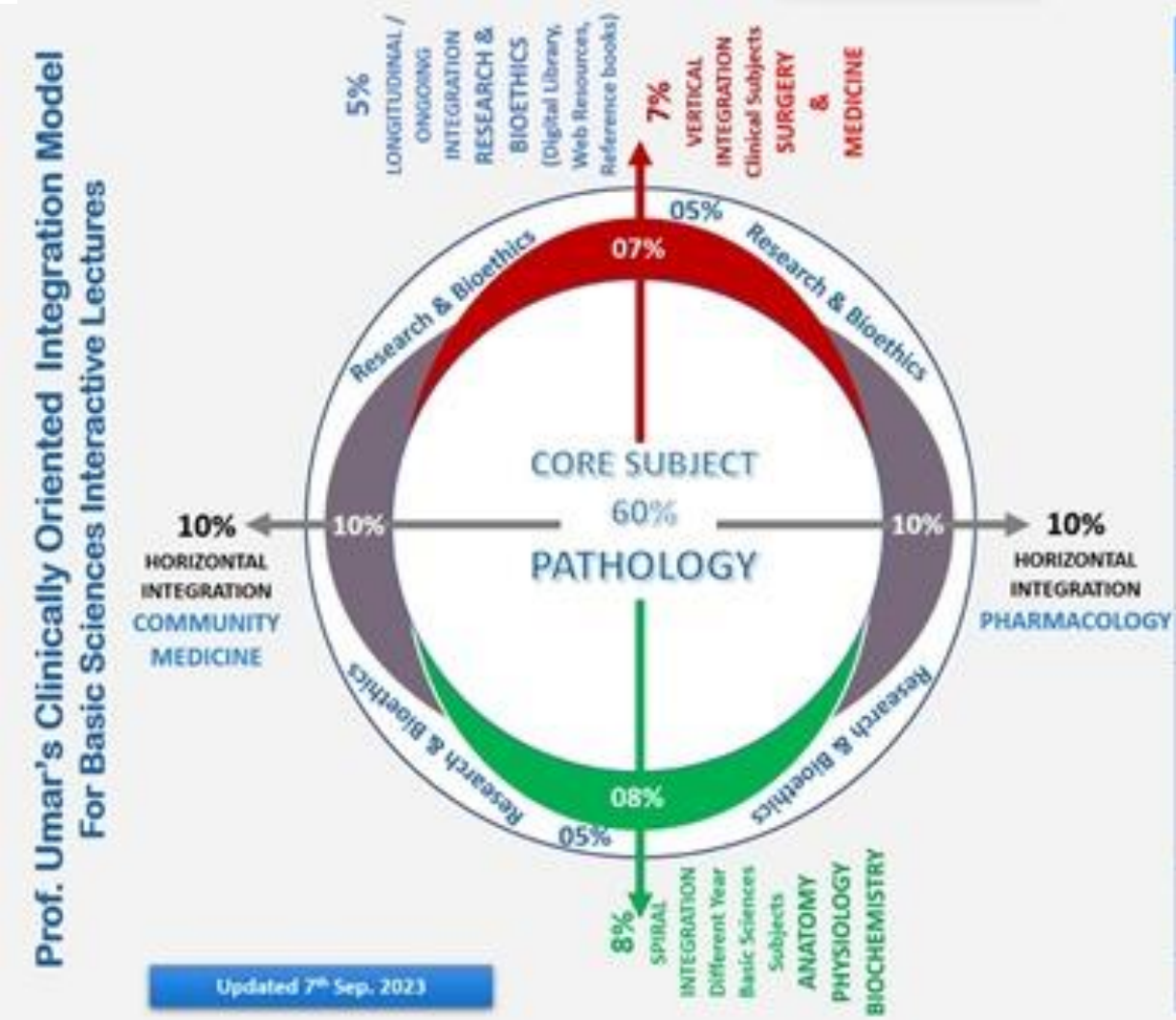
Dr. Zunera Hakim

- Katzung's Basic & Clinical Pharmacology, 16th Edition
- Goodman and Gilmans The Pharmacological Basis of Therapeutics, 13th Edition

MOTO & VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

UMAR'S MODEL OF INTEGRATION



Model 3rd Year Pathology LGIS (≈30 slides)	
Core Subject – 60% (≈ 18-20 slides)	
Pathology (≈ 18-20 slides)	
Horizontal Integration – 20% (≈ 5-6 slides)	
Same Year Subjects	• Pharmacology (10%) (≈ 2-3 slides) • Community Medicine (10%) (≈ 2-3 slides)
Vertical Integration – 07% (≈ 2-3 slides)	
Clinical Subjects	• Medicine (3-5%) (≈ 1-2 slides) • Surgery (3-5%) (≈ 1-2 slides)
Spiral Integration – 08% (≈ 2-3 slides)	
Different Year Basic Sciences Subjects	• Anatomy (1-3%) (≈ 1-2 slides) • Physiology (1-3%) (≈ 1-2 slides) • Biochemistry (1-3%) (≈ 1-2 slides)
Longitudinal / Ongoing Integration – 05% (≈ 1-2 slides)	
Research & Bioethics (≈ 1-2 slides)	

LEARNING OBJECTIVES

At the end of the lecture, students of 3rd Year MBBS will be able to;

01 Recall the organization and physiology of parasympathetic system

02 Classify cholinomimetics

03 Identify location of cholinergic receptors and molecular mechanism of their activation

04 Describe the pharmacological effects produced by the activation of these receptors

05 Describe uses and adverse effects of cholinomimetics

Pre-Lecture Assessment

1. Which of the following cholinomimetic has the shortest duration of action?

A. Carbachol
B. Bethanechol
C. Acetylcholine (Ach)
D. Cevimeline
E. Methacholine

2. How many acetylcholine bind with ligand-gated ion (N+) channel?

A. One B. Two C. Three D. Four E. Five

3. AcH is packaged into vesicles by VAT with efflux of which ions ?

A. Hydrogen
B. Sodium
C. Potassium
D. Calcium
E. Chloride

Pre-Lecture Assessment

4. In the ligand-gated ion channel, Ach binds to:

A) Alpha subunits
B) Beta subunits.
C) Gamma subunits
D) A&B
E) A & C

5.Which muscarinic cholinomimetic can be used to diagnose asthma?

A. Carbachol
B. Bethanechol
C. Acetylcholine (Ach)
D. Cevimeline
E. Methacholine

Pre-Lecture Assessment

6. What is the primary reason for the limited therapeutic usefulness of Acetylcholine (ACh)?

A. Rapid degradation by cholinesterases
B. Slow degradation by cholinesterases
C. Low affinity for all types of cholinoceptors
D. High selectivity for all types of cholinoceptors
E. Selectivity for nicotinic receptors

7. Which of the following direct-acting cholinomimetics is mainly muscarinic in action?

A. Bethanechol
B. Carbachol
C. Acetylcholine
D. Atropine
E. Pilocarpine

Pre-Lecture Assessment

8.A 65 year-old retired woman reports to ER after becoming suddenly ill following her evening meal. Her presenting features include marked perspiration, excessive tear formation, nausea, drooling, pinpoint pupils & bradycardia. When asked about her recent history, she mentions having made a salad for dinner containing store bought lettuce, tomatoes, vinegar & oil dressing, and some wild mushrooms that she hand-picked from the overgrown section of City Park .Assuming she is suffering from food poisoning, what active ingredient would best explain her signs & symptoms?

A. Atropine
B. Muscarine
C. Scopolamine
D. Hysocine
E. Cocaine

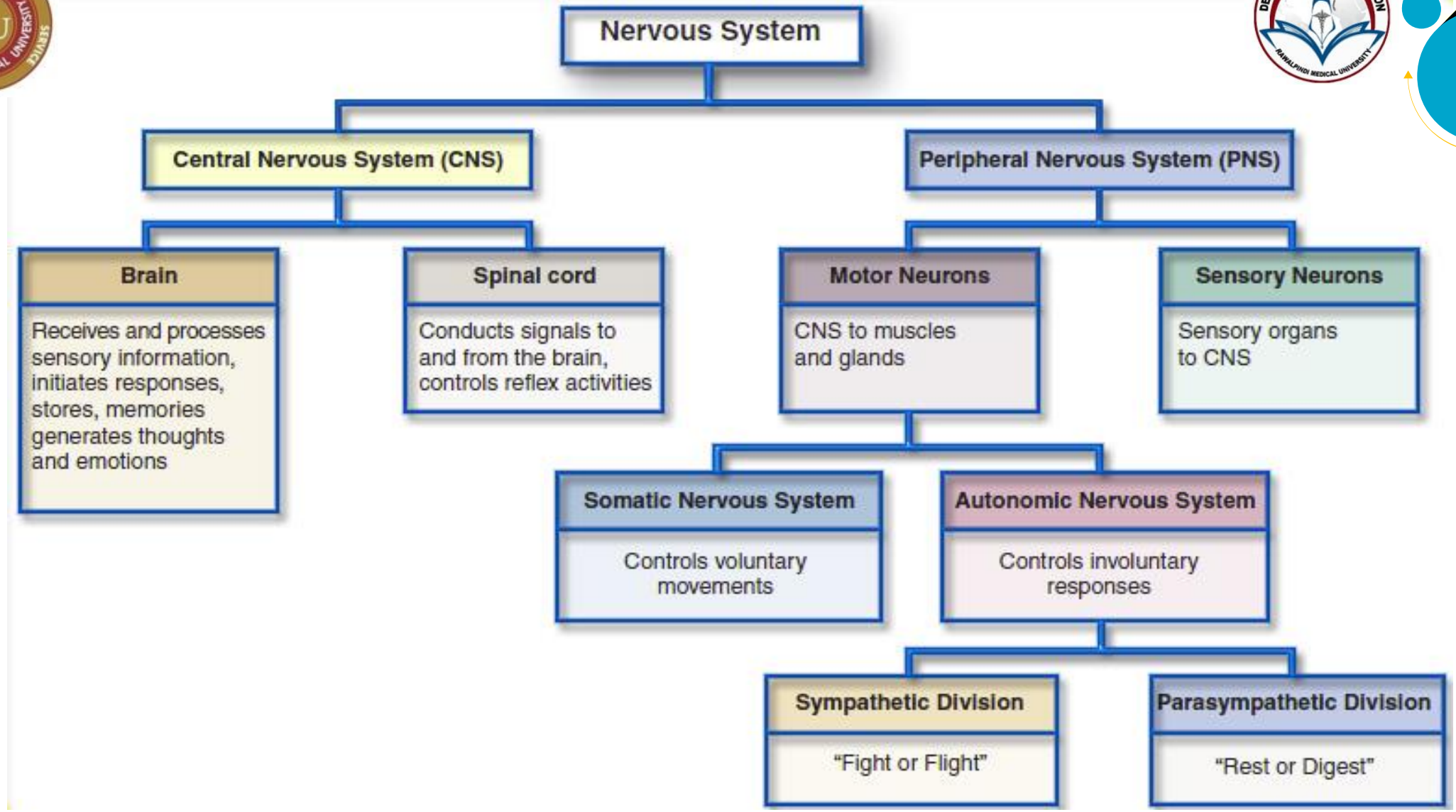
Pre-Lecture Assessment

9. A 43 year-old patient is recovering from abdominal surgery and develops post-operative urinary retention. A drug that you could give orally to treat this condition is:

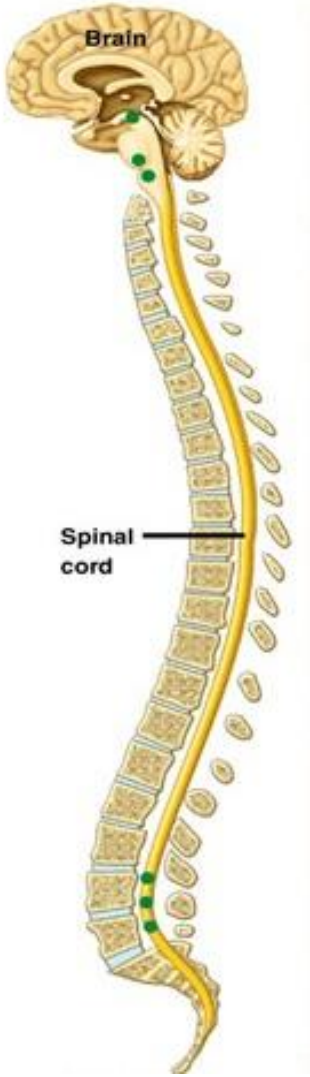
A. Bethanechol
B. Atropine
C. Acetycholine
D. Pilocarpine
E. Clonidine

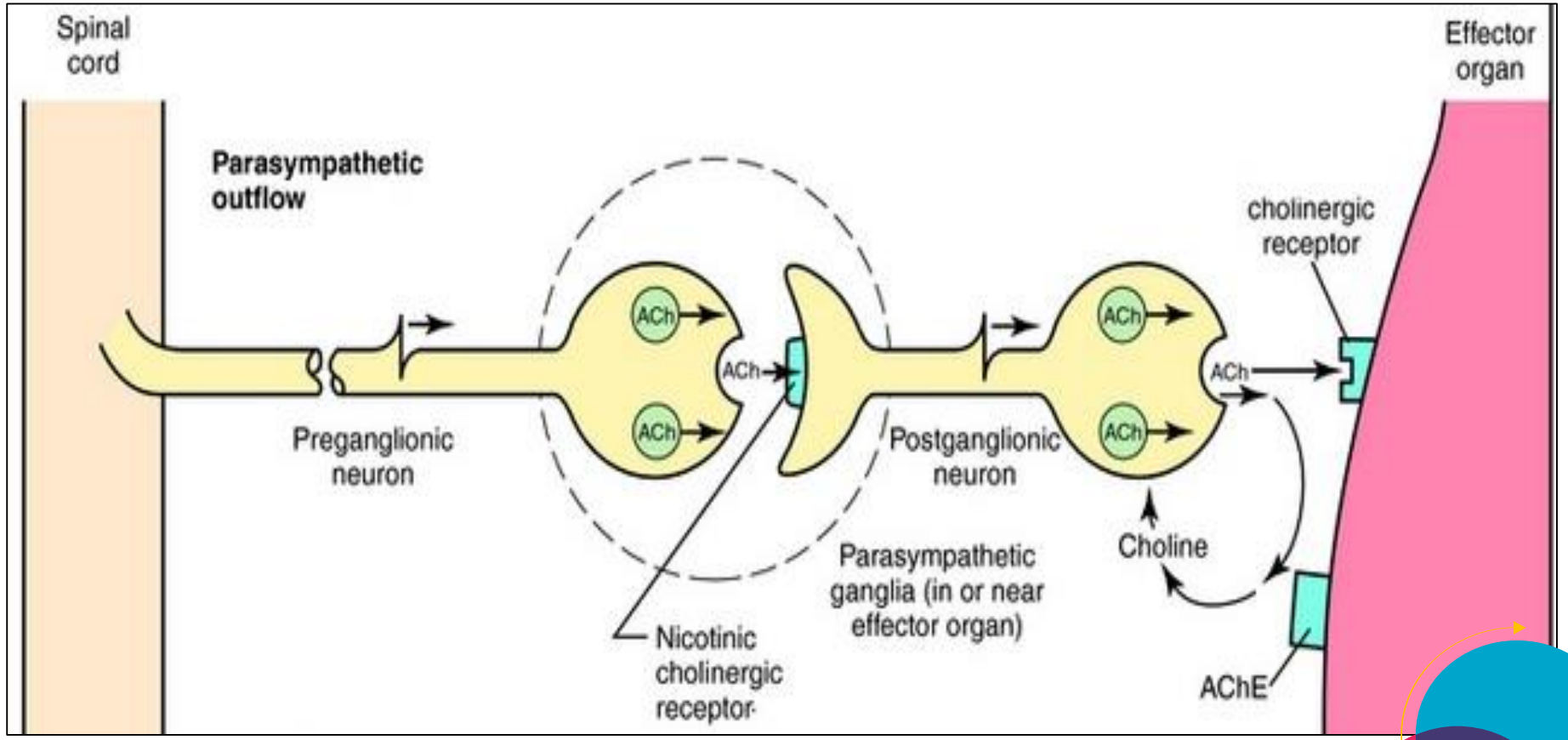
10. Which one of the following drugs are used to treat dry mouth symptom that associated with Sjogren's syndrome?

A. Carbachol
B. Bethanechol
C. Acetylcholine (Ach)
D. Cevimeline
E. Methacholine

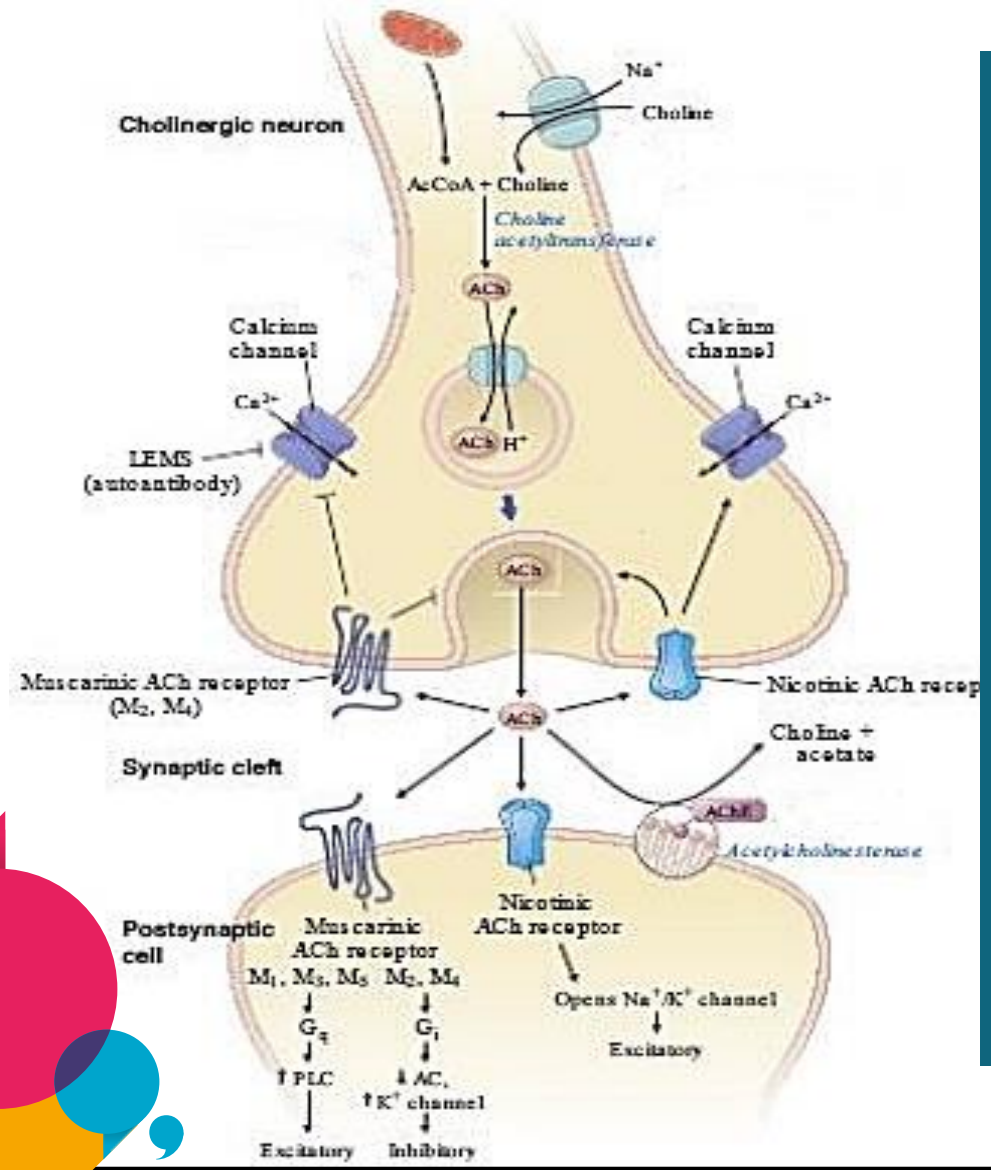

Nervous System
Central Nervous System (CNS)
Peripheral Nervous System (PNS)
Brain
Receives and processes sensory information, initiates responses, stores, memories generates thoughts and emotions
Spinal cord
Conducts signals to and from the brain, controls reflex activities
Motor Neurons
CNS to muscles and glands
Sensory Neurons
Sensory organs to CNS
Somatic Nervous System
Controls voluntary movements
Autonomic Nervous System
Controls involuntary responses
Sympathetic Division
"Fight or Flight"
Parasympathetic Division
"Rest or Digest"

Parasympathetic Neurotransmission





Parasympathetic Neurotransmission



Termination of effect of released Ach

Released AcH is metabolized by

1. Acetycholinesterase

cholinergic neuroeffector junction and NMJ

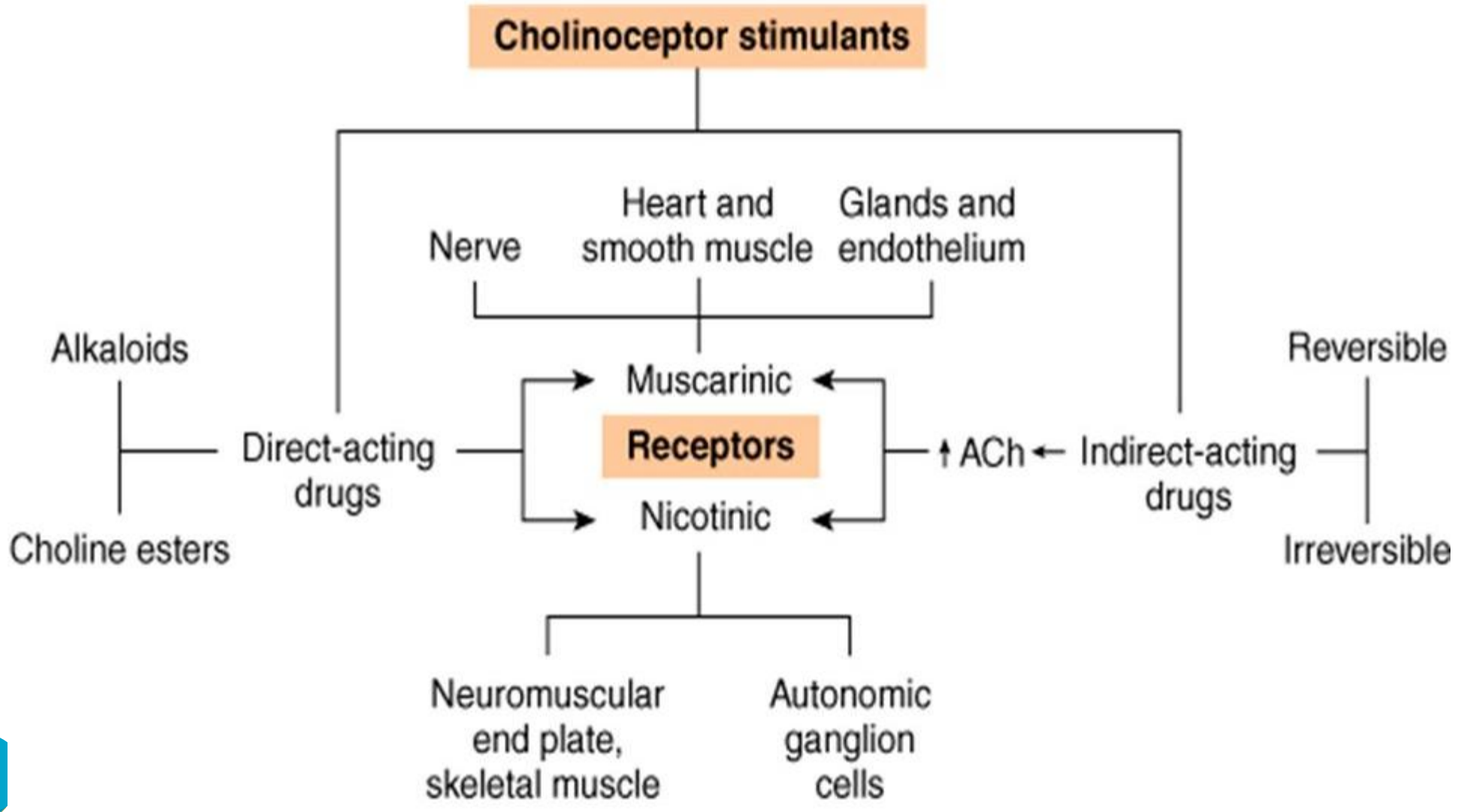
2. Butyrylcholineterase (Pseudocholinesterase)

liver and plasma

PARASYMPATHOMIMETICS/CHOLINOMIMETICS

Drugs that mimic the actions of the parasympathetic nervous system stimulation on target organs are called **parasympathomimetics,** or **cholinomimetics**

CLASSIFICATION OF PARASYMPATHOMIMETICS



CLASSIFICATION OF PARASYMPATHOMIMETICS

A. Directly Acting Cholinomimetics

Drugs acting on cholinoceptors

B. Indirectly Acting Cholinomimetics

Drugs inhibiting acetylcholinesterase and increasing the concentration of endogeneously released acetycholine augmenting acetycholine signal transduction

CLASSIFICATION
(Directly Acting)

I. Choline Ester

Acetyl choline
Carbachol
Methacholine
Bethanechol

II. Cholinomimetic Alkaloids

a. Mainly Muscarinic Agonists

Natural Alkaloids:

Muscarine
Pilocarpine
Arecholine

Synthetic Alkaloid:

Oxotremorine,Cevimiline

b. Mainly Nicotinic Agonists

Natural Alkaloids:

Nicotine
Lobeline

Synthetic Alkaloids:

Dimethylphenylpiperazinium(DMPP)
Vareniciline

CHOLINOCEPTORS

1

Muscarinic receptors

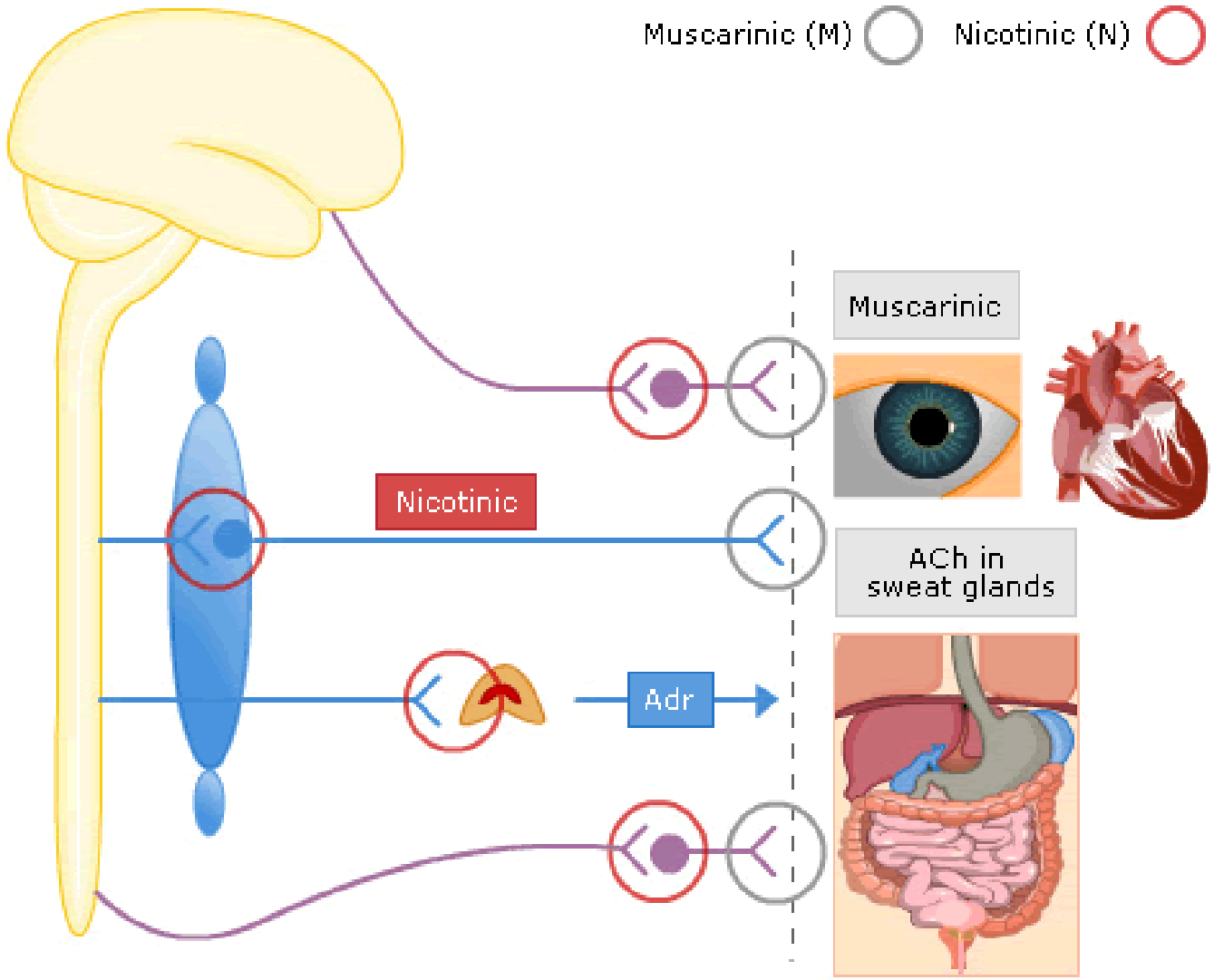
i. M1
ii. M2
iii. M3
iv. M4
v. M5

2

Nicotinic receptors

i. Nicotinic Nm
ii. Nicotinic Nn

LOCATION OF CHOLINOCEPTORS



CHOLINOCEPTORS

Table 13.2 Muscarinic receptor subtypes[a]

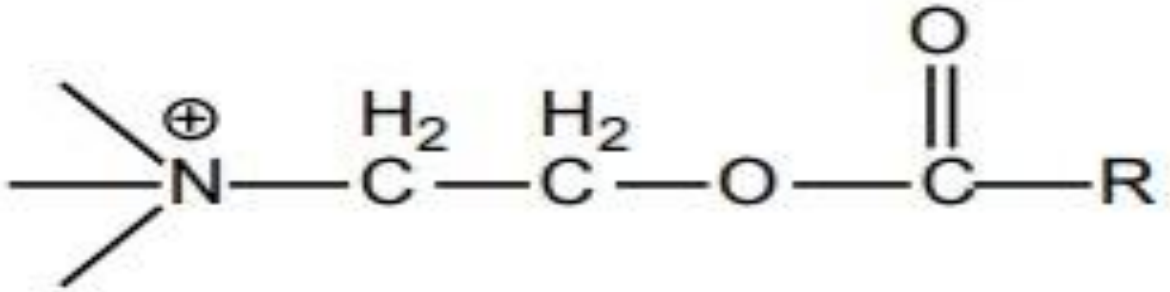
	M_1 ('neural')	M_2 ('cardiac')	M_3 ('glandular/ smooth muscle')	M_4	M_5
Main locations	Autonomic ganglia (including intramural ganglia in stomach) Glands: salivary, lacrimal, etc. Cerebral cortex	Heart: atria CNS: widely distributed	Exocrine glands: gastric (acid-secreting parietal cells), salivary, etc. Smooth muscle: gastrointestinal tract, eye, airways, bladder Blood vessels: endothelium	CNS	CNS: very localised expression in substantia nigra Salivary glands Iris/ciliary muscle
Cellular response	↑ IP_3, DAG Depolarisation Excitation (slow epsp) ↓ K^+ conductance	↓ cAMP Inhibition ↓ Ca^{2+} conductance ↑ K^+ conductance	↑ IP_3 Stimulation ↑ $[Ca^{2+}]_i$	↓ cAMP Inhibition	↑ IP_3 Excitation
Functional response	CNS excitation (? improved cognition) Gastric secretion	Cardiac inhibition Neural inhibition Central muscarinic effects (e.g. tremor, hypothermia)	Gastric, salivary secretion Gastrointestinal smooth muscle contraction Ocular accommodation Vasodilatation	Enhanced locomotion	Not known

CHOLINOCEPTORS

Table 13.1 Nicotinic receptor subtypes[a]

	Muscle type	Ganglion type	CNS types		Notes
Main molecular form	$(\alpha1)_2\beta1\delta\varepsilon$ (adult form)	$(\alpha3)_2(\beta2)_3$	$(\alpha4)_2(\beta2)_3$	$(\alpha7)_5$	–
Main synaptic location	Skeletal neuromuscular junction: mainly postsynaptic	Autonomic ganglia: mainly postsynaptic	Many brain regions: pre- and postsynaptic	Many brain regions: pre- and postsynaptic	–
Membrane response	Excitatory Increased cation permeability (mainly Na^+, K^+)	Excitatory Increased cation permeability (mainly Na^+, K^+)	Pre- and postsynaptic excitation Increased cation permeability (mainly Na^+, K^+)	Pre- and postsynaptic excitation Increased cation permeability	$(\alpha7)_5$ receptor produces large Ca^{2+} entry, evoking transmitter release

STRUCTURE ACTIVITY RELATIONSHIP



Quaternary ammonium group (or) onium

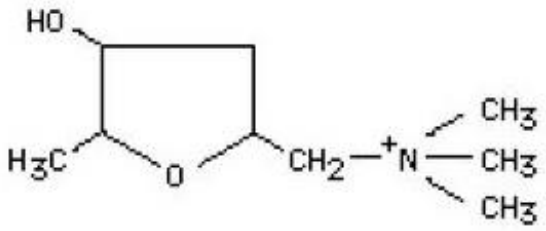
Choline (or) ethylene bridge

Ester function (or) acyloxygroup

STRUCTURE ACTIVITY RELATIONSHIP

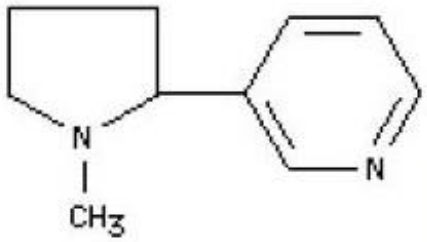
TOXIC

ACTION CHIEFLY MUSCARINIC



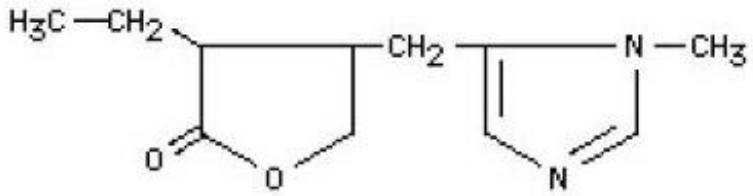
Muscarine

ACTION CHIEFLY NICOTINIC

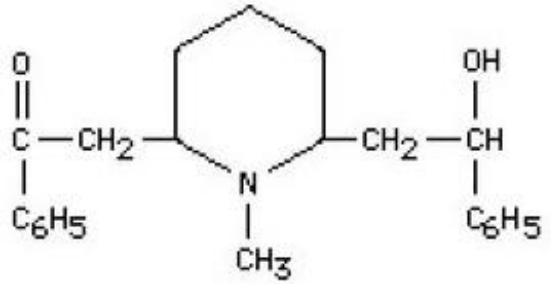


Nicotine

Tertiary amines: better absorption and distribution



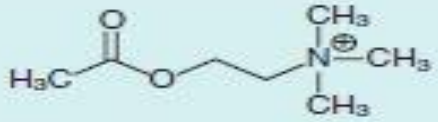
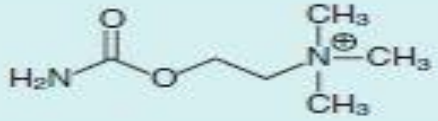
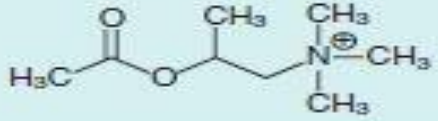
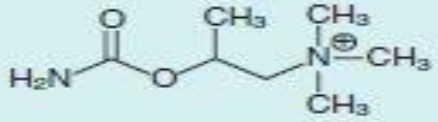
Pilocarpine



Lobeline

RECEPTOR SELECTIVITY

Table 13.3 Muscarinic agonists

Compound	Structure	Receptor specificity		Hydrolysis by cholinesterase
		Muscarinic	*Nicotinic*	
Acetylcholine		+++	+++	+++
Carbachol		++	+++	–
Methacholine		+++	+	++
Bethanechol		+++	–	–
Muscarine		+++	–	–
Pilocarpine		++	–	–
Oxotremorine		++	–	–
Cevimeline		++[c]	–	–

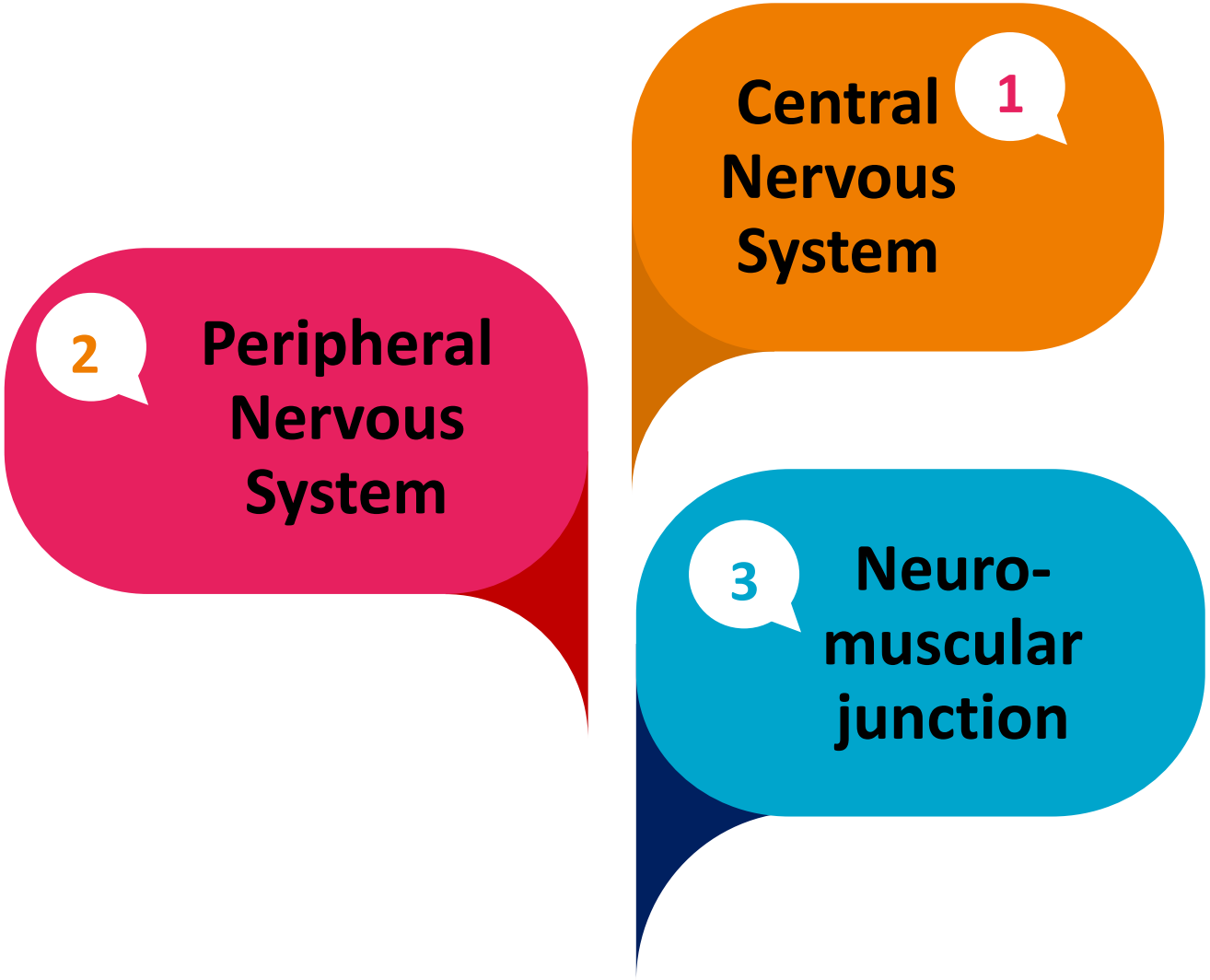
EFFECTS OF ACETYLCHOLINE

- **Muscarinic action of acetylcholine**

  Effects of AcH on visceral effectors innervated by parasympathetic system (smooth muscles, heart and exocrine glands)

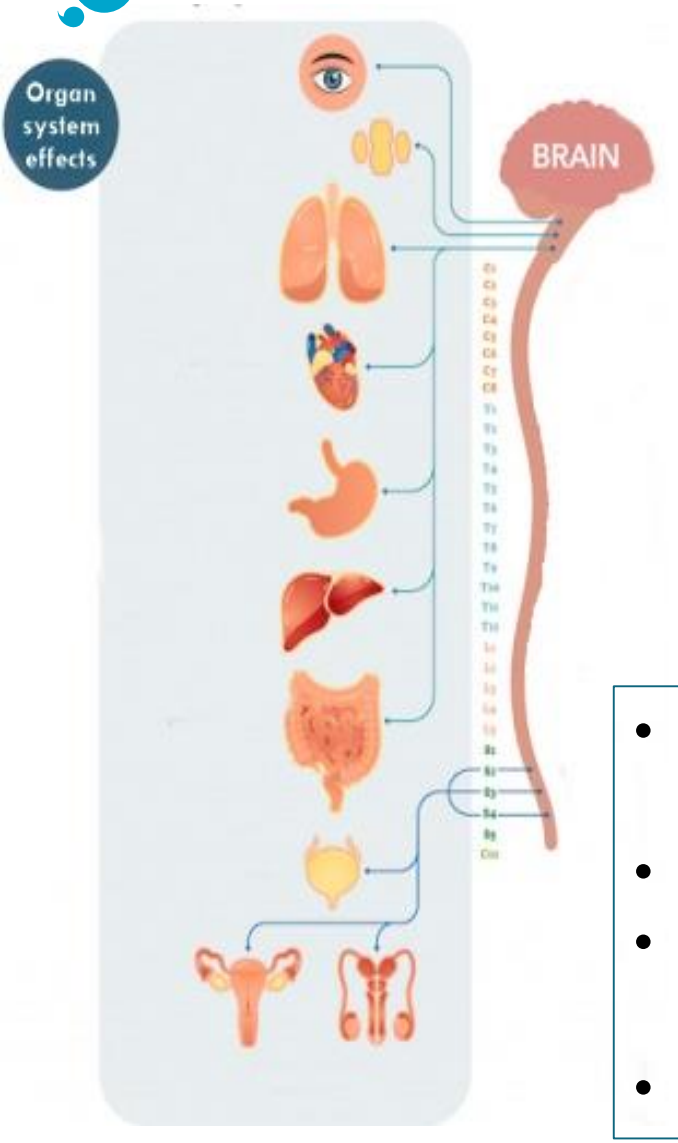
- **Nicotinic action of acetycholine**
  Effects of AcH on autonomic ganglia and adrenal medulla

ORGAN SYSTEM EFFECTS OF CHOLINOMIMETICS



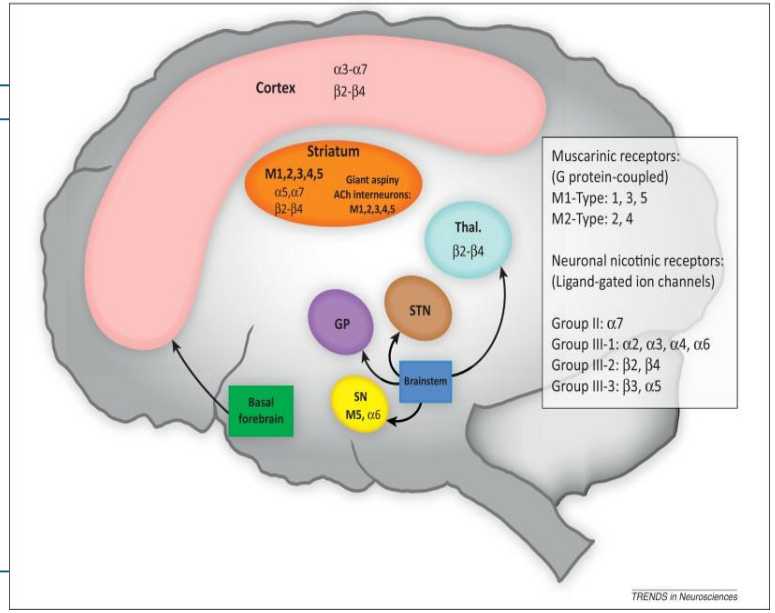
ORGAN SYSTEM EFFECTS OF CHOLINOMIMETICS

CENTRAL NERVOUS SYSTEM

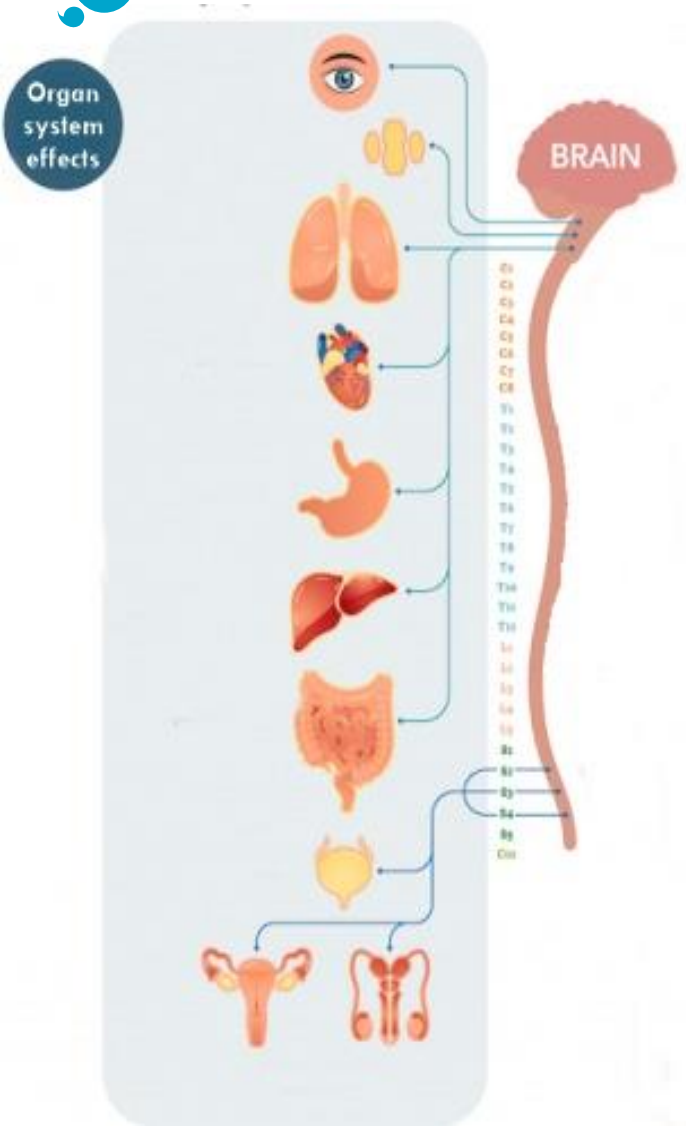


- M1 mAChR mediate cognition-enhancing effects of AcH (cerebral cortex and hippocampus)
- M2 and M4 mAChR mediate muscarinic antinociception at the spinal and the supraspinal level
- M3 mACHR stimulate release of insulin and increase energy expenditure (body fat mass)

- Nicotinic receptors mainly in spinal cord, brainstem & cortex
- Regulate release of neurotransmitters
- Effects range from mild altering action to fatal convulsions
- Mediate cognition and pain perception

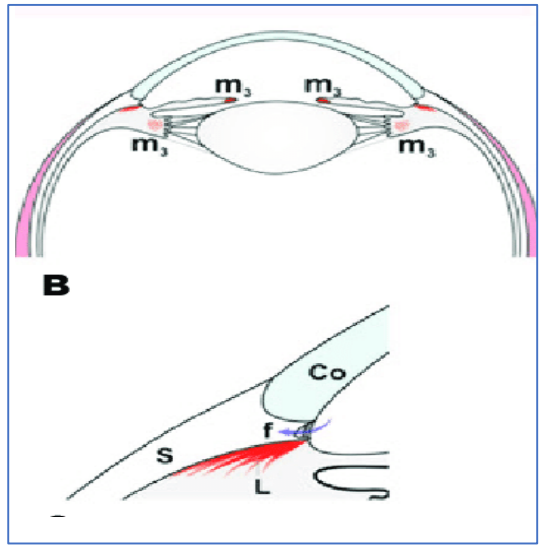


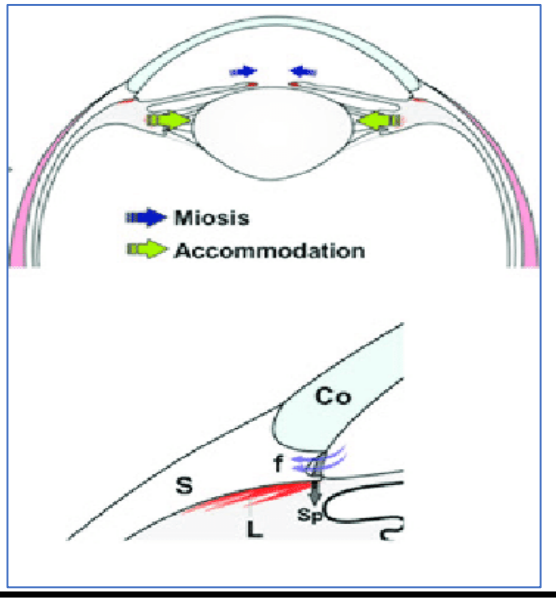
ORGAN SYSTEM EFFECTS OF CHOLINOMIMETICS



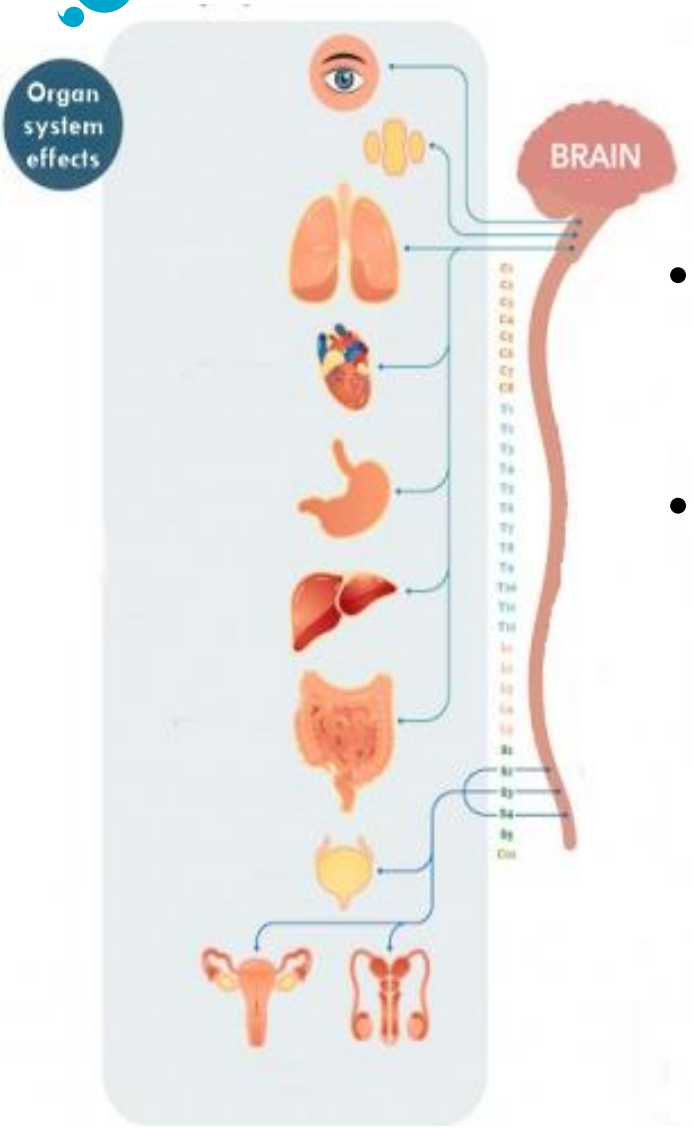
EYE

- Constriction of the pupillary constrictor (M3) resulting in **miosis**
- Contraction of ciliary muscle (M3) accommodating the eye for near vision
- Increasing the drainage of aqueous humor
- Increase secretion of lacrimal gland (M3)



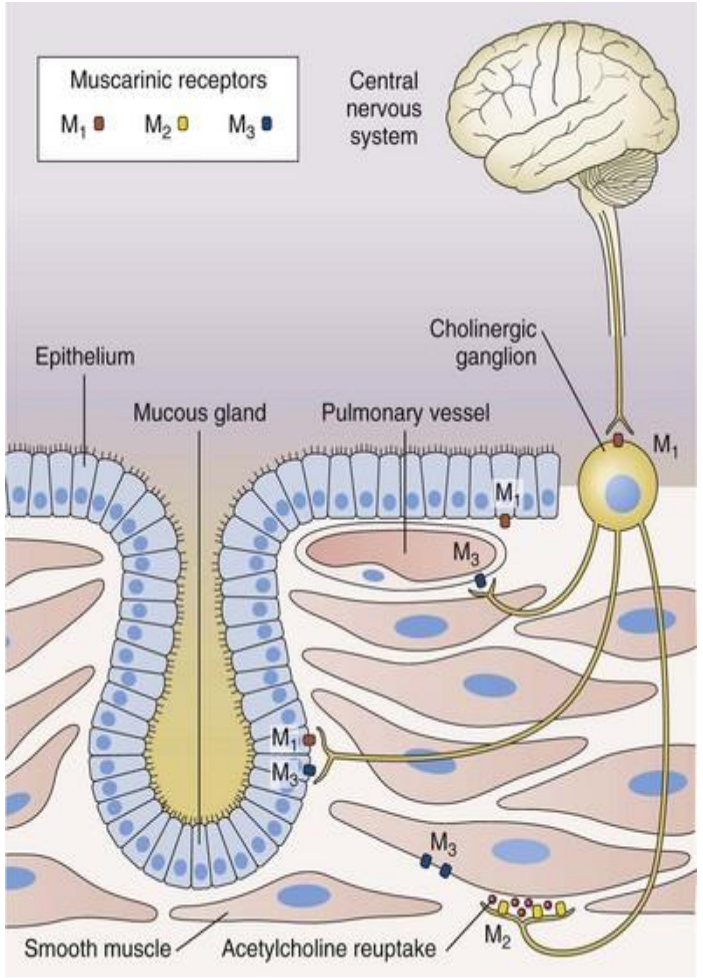


ORGAN SYSTEM EFFECTS OF CHOLINOMIMETICS

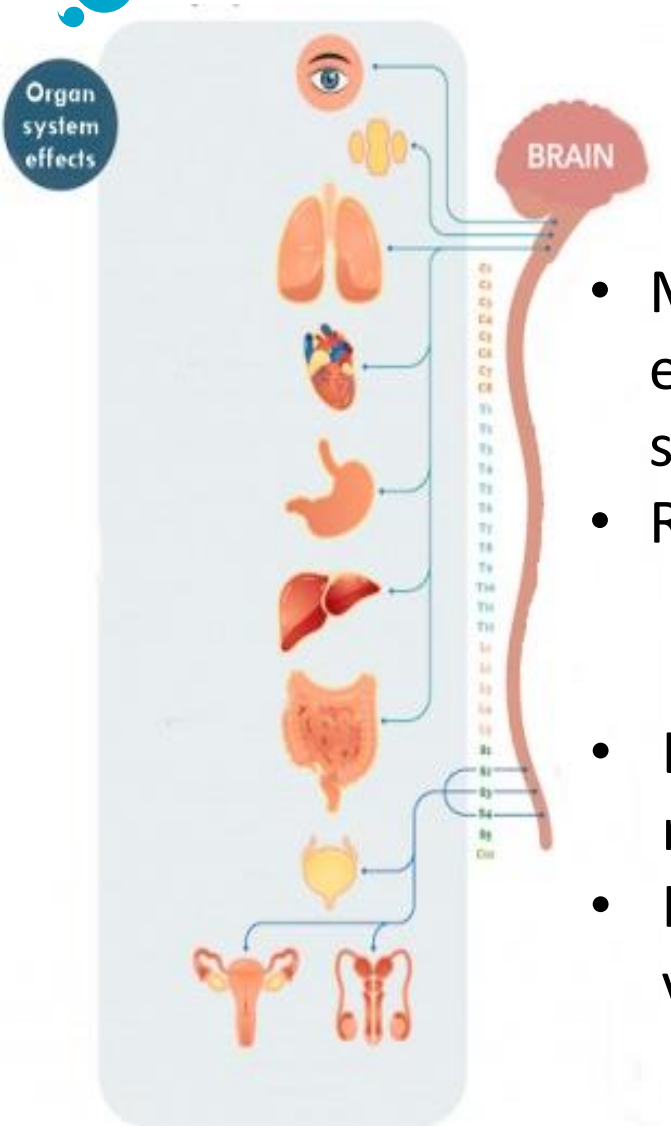


RESPIRATORY SYSTEM

- Contraction of bronchial smooth muscle leading to bronchoconstriction (M3)
- Stimulation of glands in the tracheobronchial tree

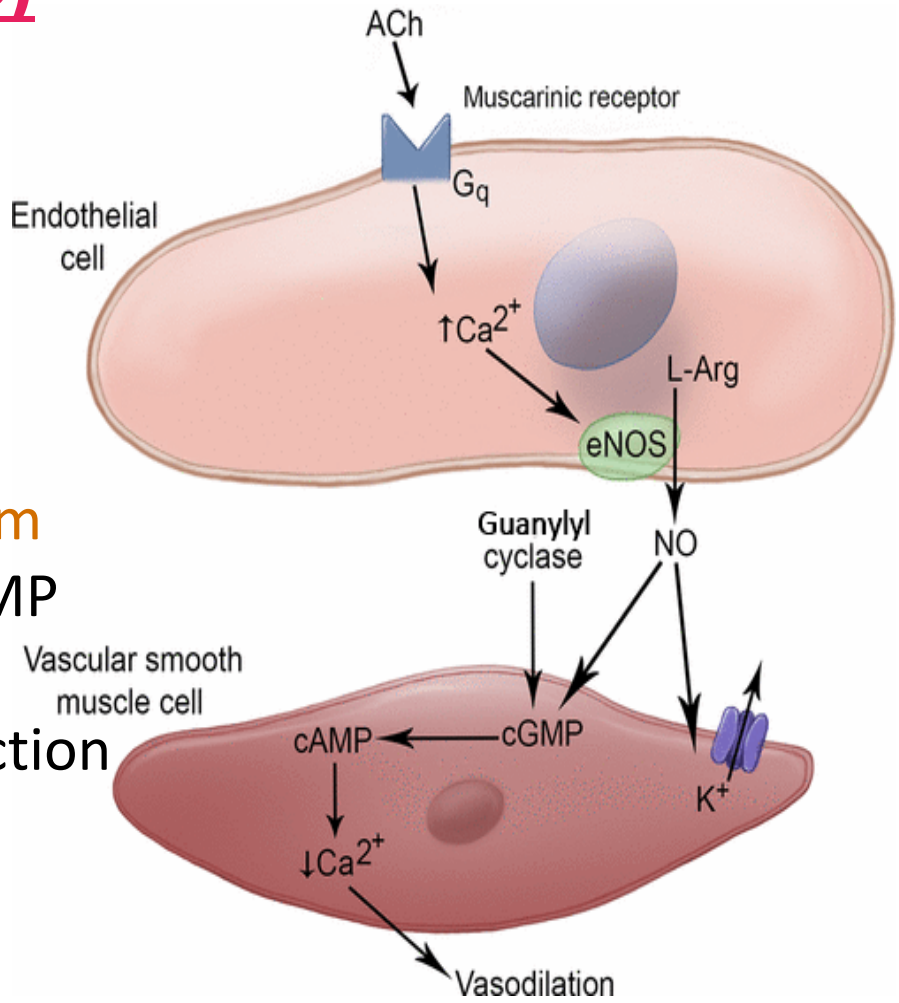


ORGAN SYSTEM EFFECTS OF CHOLINOMIMETICS

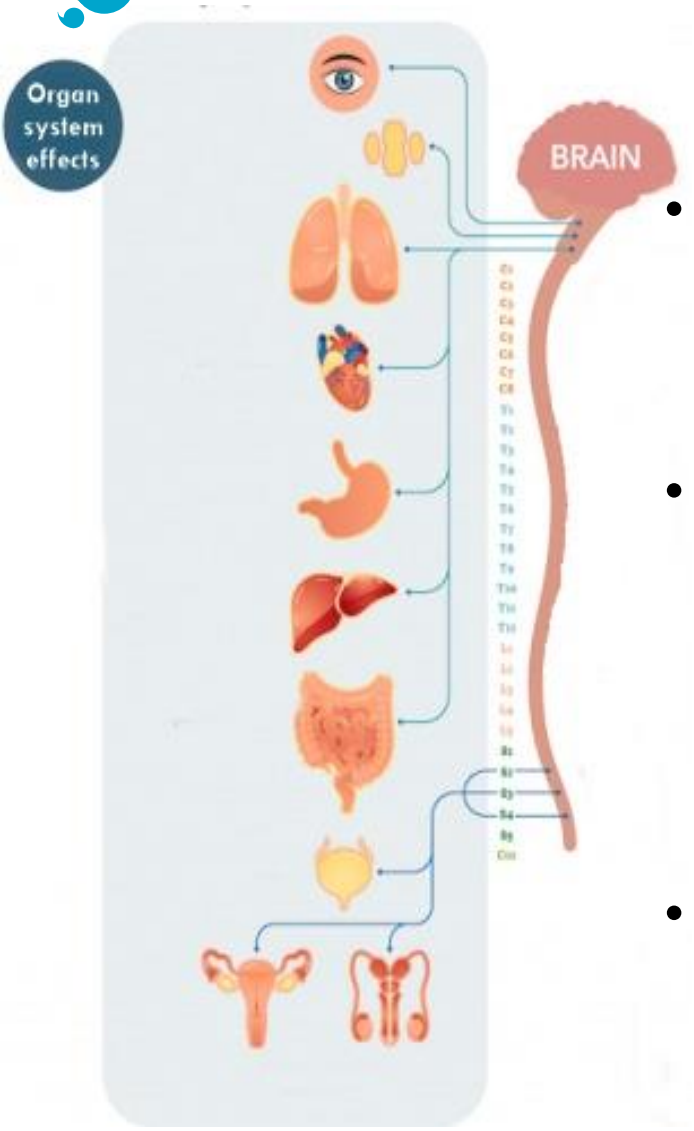


CARDIOVASCULAR SYSTEM (VESSELS)

- M3 receptors are present both on the endothelial cells & vascular smooth muscle
- Response depends upon
  - Dose of the agonist
  - Presence/absence of endothelium
- Low dose ($3x10^{-7}M$) results in NO/cGMP mediated vasodilation
- High dose ($10^{-7}M$) causes vasoconstriction via M3 mediated increase in Ca+

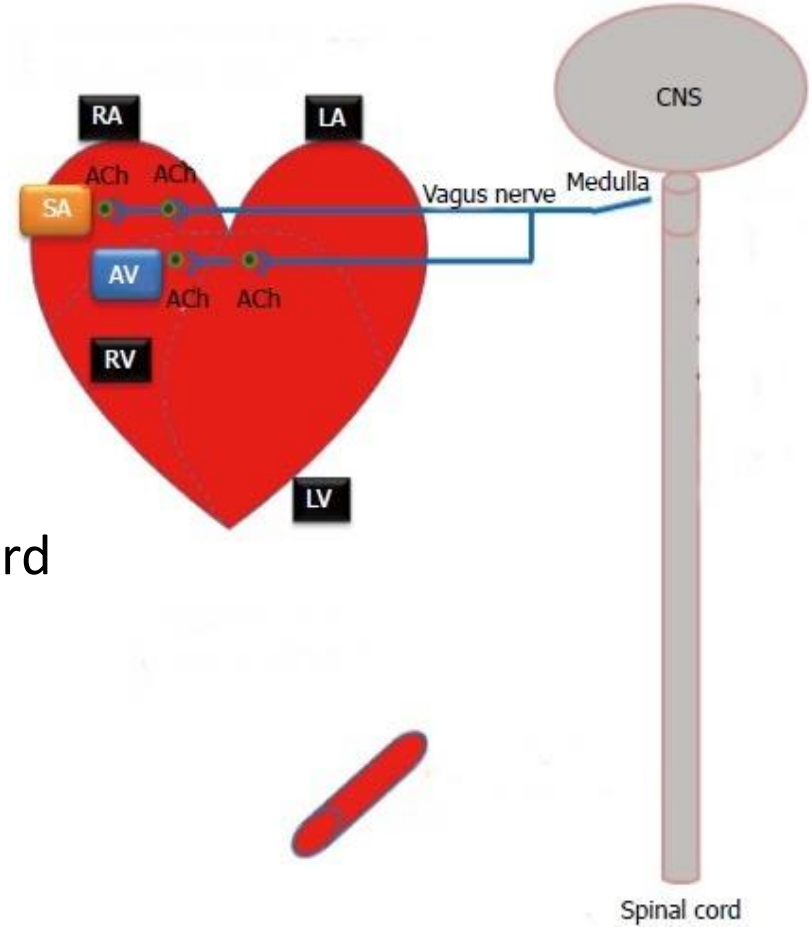


ORGAN SYSTEM EFFECTS OF CHOLINOMIMETICS

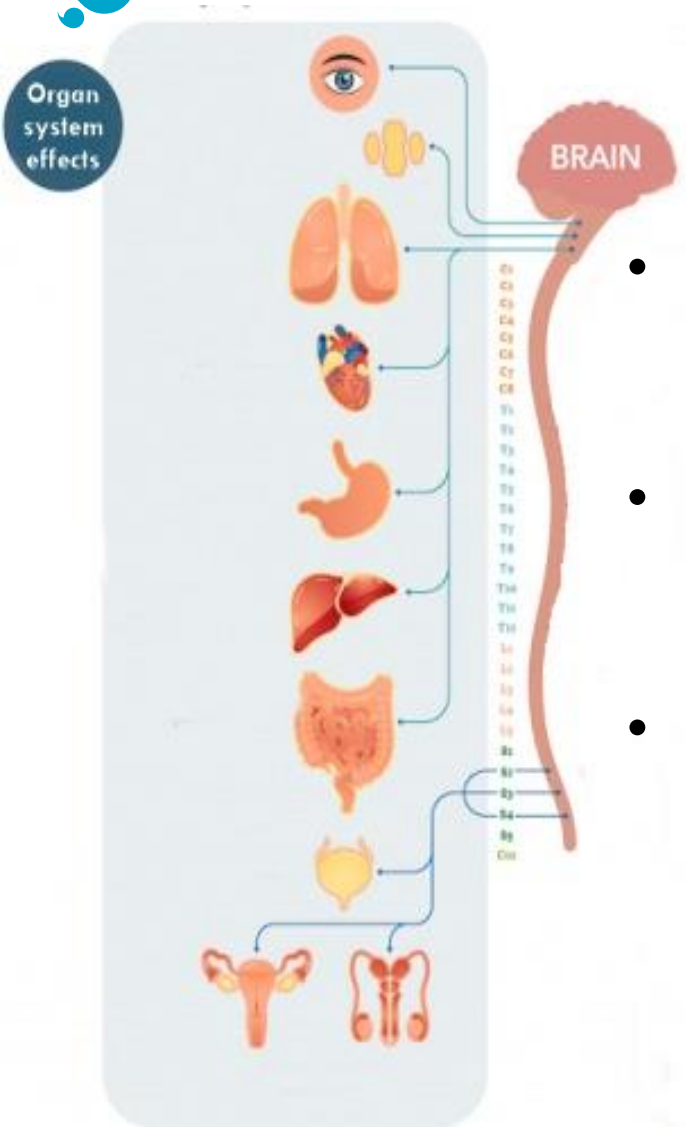


CARDIOVASCULAR SYSTEM (HEART)

- Indirect tachycardia due to compensatory sympathetic stimulation in response to low dose vasodilation
- High concentration directly activates M2 receptors in SA and AV node resulting in bradycardia and slowing of AV conduction (increase K+ permeability, decrease in inward Ca+ current)
- Decrease contraction of the atria (hyperpolarization and decrease in cAMP)



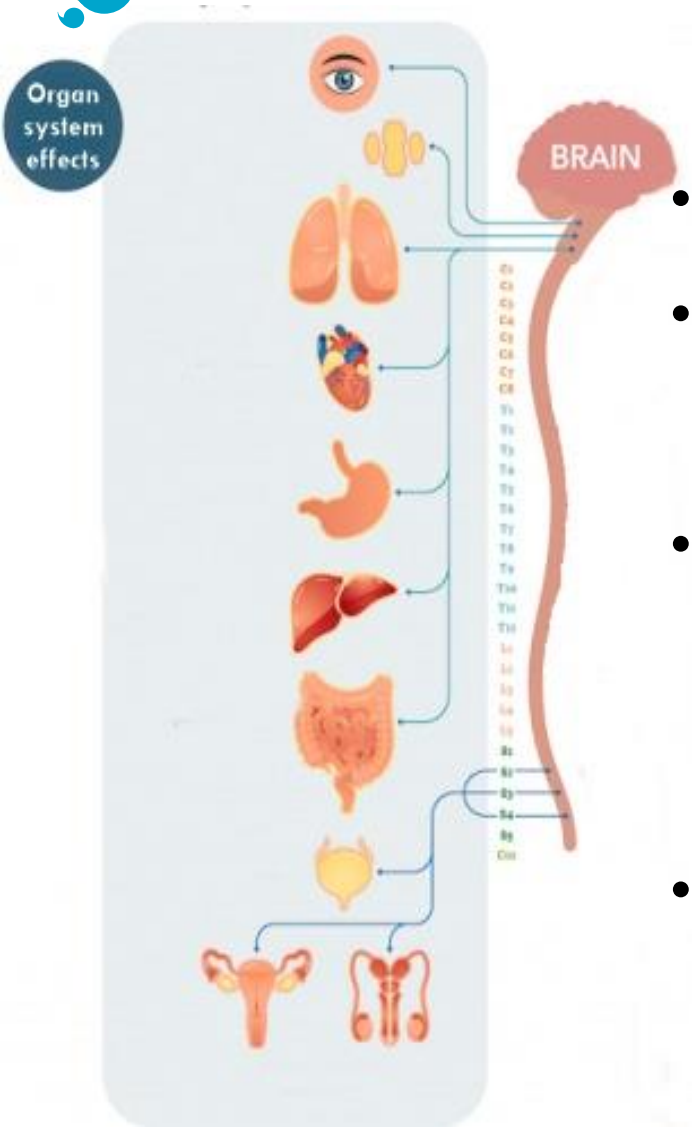
ORGAN SYSTEM EFFECTS OF CHOLINOMIMETICS



GASTROINTESTINAL TRACT

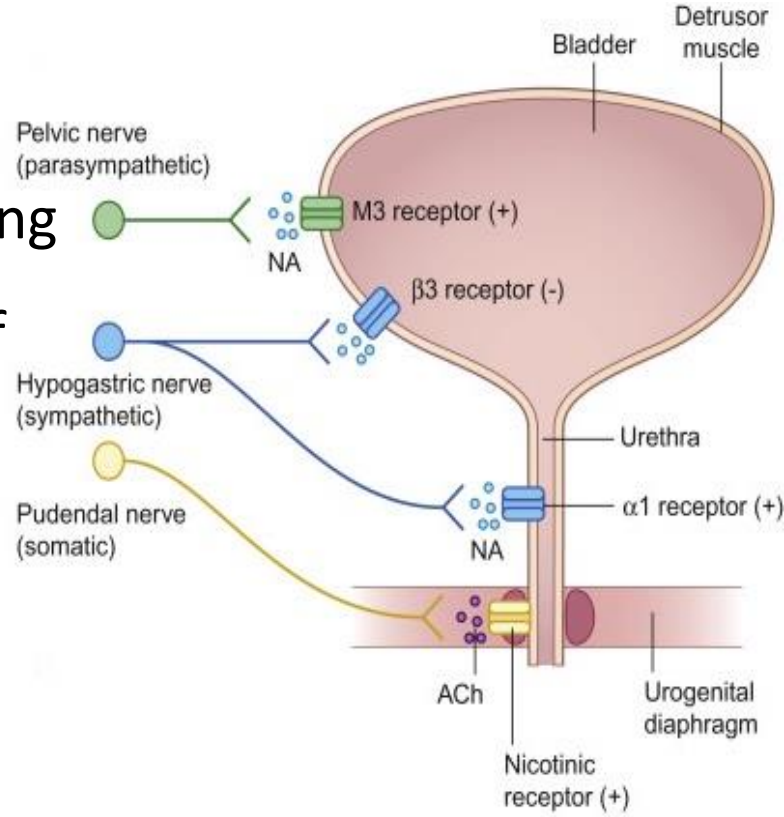
- Contraction of gastrointestinal smooth muscle (M3) increasing gastrointestinal motility (increase Ca+ influx)
- Stimulate salivary, gastric, and other secretions in the gastrointestinal tract (salivary & gastric > pancreatic & small intestine)
- Relaxation of sphincters (M3)

ORGAN SYSTEM EFFECTS OF CHOLINOMIMETICS

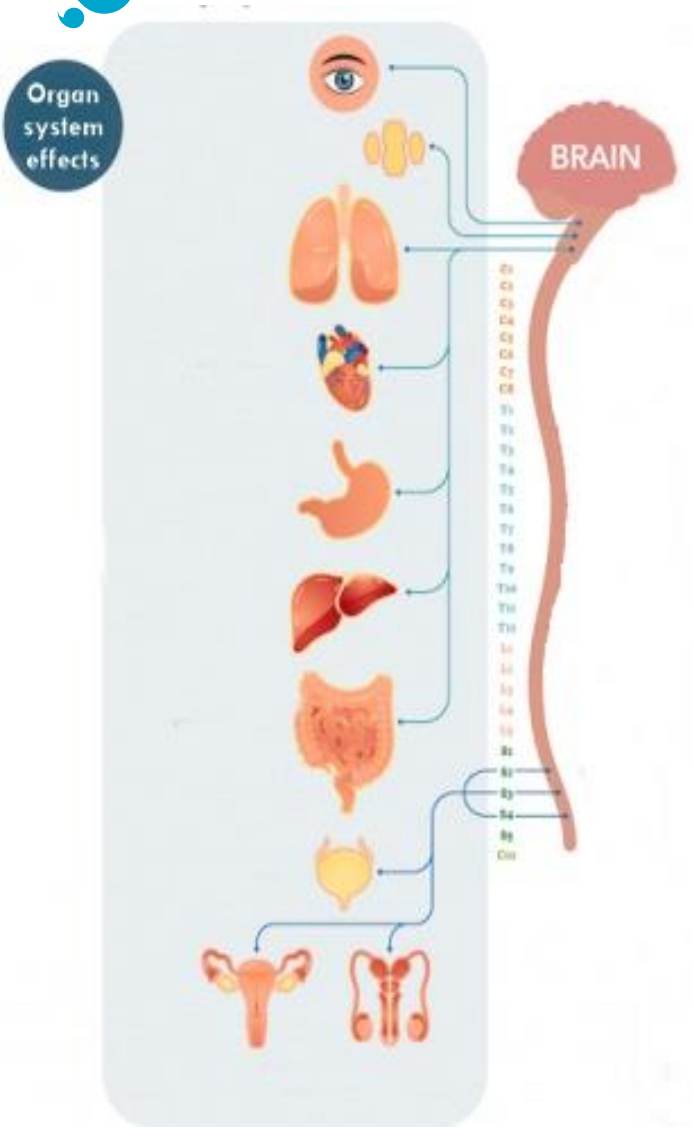


GENITOURINARY TRACT

- Contraction of detrusor muscle (M3)
- Relaxation of sphincter (M3) leading to voiding of urine
- M2 cause bladder contraction by reversing β receptor cAMP mediated relaxation of detrusor muscle
- Contraction of pregnant uterus (M3)



ORGAN SYSTEM EFFECTS OF CHOLINOMIMETICS



SECRETORY GLANDS

- M3 mediated increase in secretion of
  - Lacrimal gland
  - Salivary gland
  - Nasopharyngeal gland
  - Sweat gland
  - Tracheobronchial glands
  - Gastrointestinal glands

PHARMACOKINETICS

- Acetylcholine & other Choline esters with a permanently charged **quaternary ammonium group** are poorly absorbed & distributed to the CNS (hydrophilic)
- All are **hydrolysed in the GIT**, rate of hydrolysis differs depending on their susceptibility for the enzyme.
- Carbamic acid esters carbachol and bethanechol have longer duration of action.
- The tertiary cholinomimetic alkaloids (pilocarpine, nicotine, lobeline) are well absorbed from most sites of administration
- Muscarine, a quaternary amine is less completely absorbed from the GIT and is toxic too when mushroom containing this is ingested
- **Excretion** mainly by the kidneys

THERAPEUTIC USES

Drug	Receptor Specificity	Hydrolyzed by Cholinesterase	Route of Administration	Clinical Use
Choline Esters				
Acetylcholine	Muscarinic and nicotinic	Yes	Intraocular Intracoronary	Miosis during ophthalmic surgery Coronary angiography
Bethanechol	Muscarinic	No	Oral or subcutaneous	Gastrointestinal and urinary stimulation
Carbachol	Muscarinic and nicotinic	No	Topical ocular Intraocular	Glaucoma Miosis during ophthalmic surgery
Plant Alkaloids				
Muscarine	Muscarinic	No	None	None
Nicotine	Nicotinic	No	Oral or transdermal	Smoking cessation programs
Pilocarpine	Muscarinic	No	Topical ocular Oral	Glaucoma Xerostomia
Other Drugs				
Cevimeline	Muscarinic	No	Oral	Xerostomia
Varenicline	Nicotinic	No	Oral	Smoking cessation

ADVERSE EFFECTS

MUSCARINIC EXCESS

Nausea, vomiting, diarrhea, urinary urgency, salivation, sweating, cutaneous vasodilatation, bronchoconstriction, bradycardia, hypotension and shock

"All faucets turned on syndrome"

NICOTINIC EXCESS

- **Acute**

i. CNS stimulation, cause convulsions, coma and respiratory arrest.

ii. Skeletal muscle depolarization and respiratory paralysis.

iii. Hypertension and cardiac arrhythmia

- **Chronic**

i. Increased risk of vascular disease

ii. Sudden coronary death

iii. Aggravation of peptic ulcer in smokers

CONTRAINDICATIONS

- Bronchial asthma
- GI or urinary tract obstruction
- Peptic ulcer
- Recent myocardial infarction
- Coronary insufficiency
- Hyperthyroidism

RESEARCH

Johnson, Chad R., Brian D. Kangas, Emily M. Jutkiewicz, Jack Bergman, and Andrew Coop. 2022. "Drug Design Targeting the Muscarinic Receptors and the Implications in Central Nervous System Disorders" *Biomedicines* 10, no. 2: 398. https://doi.org/10.3390/biomedicines10020398

BIOETHICS

Hammond D, Reid JL, Rynard VL*, et al* Indicators of dependence and efforts to quit vaping and smoking among youth in Canada, England and the USA *Tobacco Control* 2022;**31:**e25-e34.

ARTIFICIAL INTELLIGENCE

Researchers use computer simulations to study how neuroreceptors respond to nicotine

Oliveira, A.S.F., *et al.* (2019) A General Mechanism for Signal Propagation in the Nicotinic Acetylcholine Receptor Family. *Journal of the American Chemical Society*. doi.org/10.1021/jacs.9b09055.

Researchers are now working with Achieve Life Sciences to design and develop molecules that mimic nicotine, and computer simulations that will help test their potential effectiveness. This work builds on previous studies using chemical synthetic approaches to develop new smoking cessation aids, which will be investigated and tested in simulation scenarios.