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PHARM

Pharmacology of parasympathetic nervous system

Pharmacology I

Spring Semester 2022

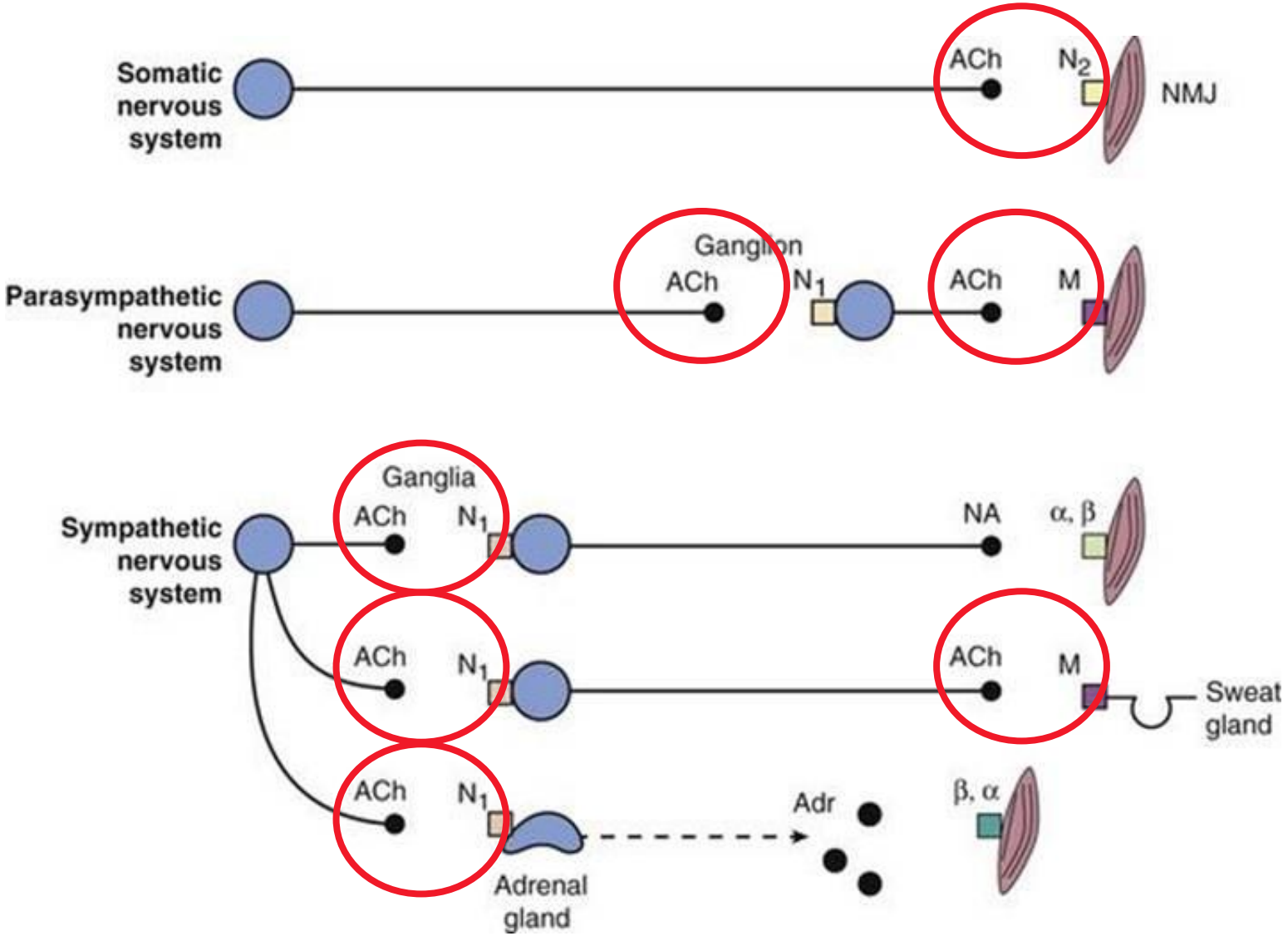
Department of Pharmacology and Toxicology

Faculty of Pharmacy MU

Cholinergic fibres

Cholinergic fibres = fibres that release **acetylcholine (ACh)**

- All **parasympaphetic** fibres
- All preganglionic fibres (sympathetic and parasympathetic)
- All somatic motor neurons → to skeletal muscles
- (Post-ganglionic sympathetic fibres → to sweat glands)



https://doctorlib.info/pharmacology/medical-pharmacology-therapeutics/4.html

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Acetylcholine

- Synthesis in cytoplasm of nerve terminal

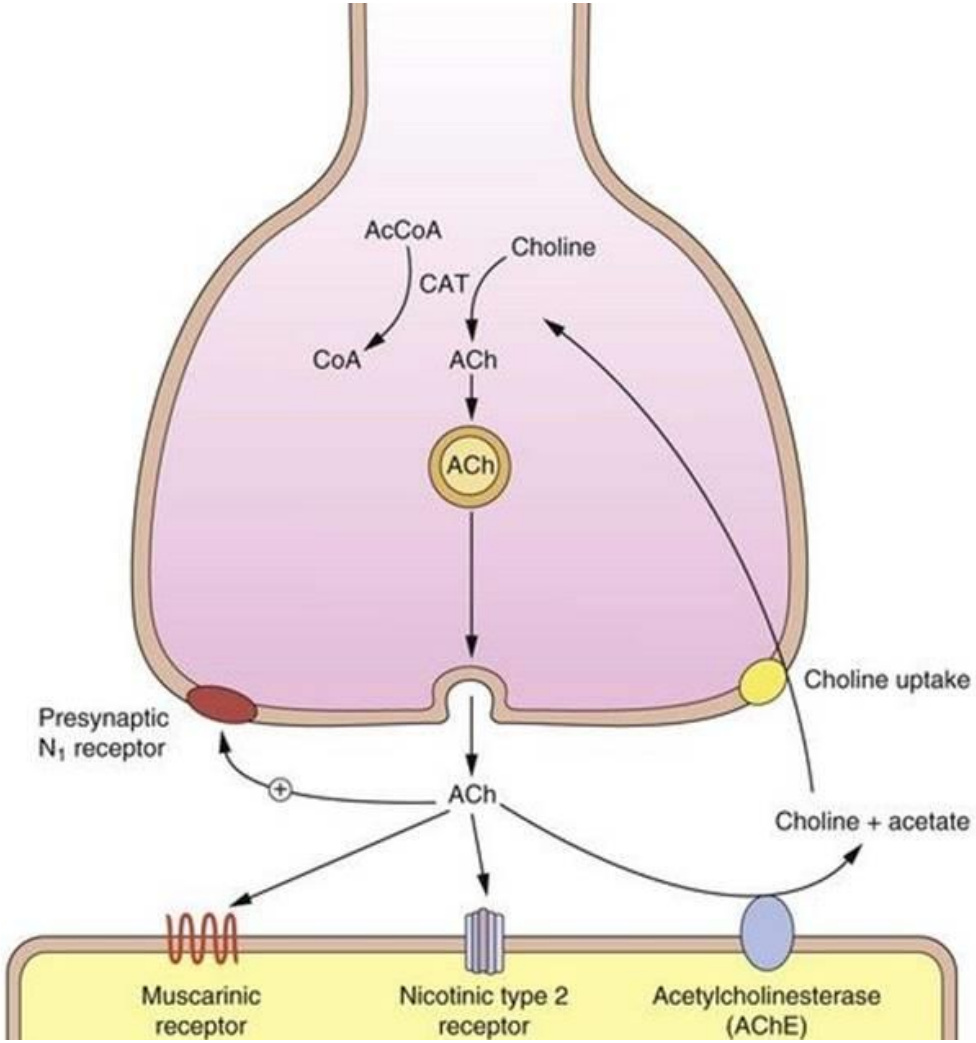
  → from choline and acetyl-coenzyme A (acetyl-CoA) by enzyme choline acetyltransferase

  → Transport into the synaptic vesicles

  → Depolarization of the nerve terminal → the release of ACh into the synaptic cleft

  → Interaction with post- or presynaptic receptors

  → Rapid degradation by **acetylcholinesterase**



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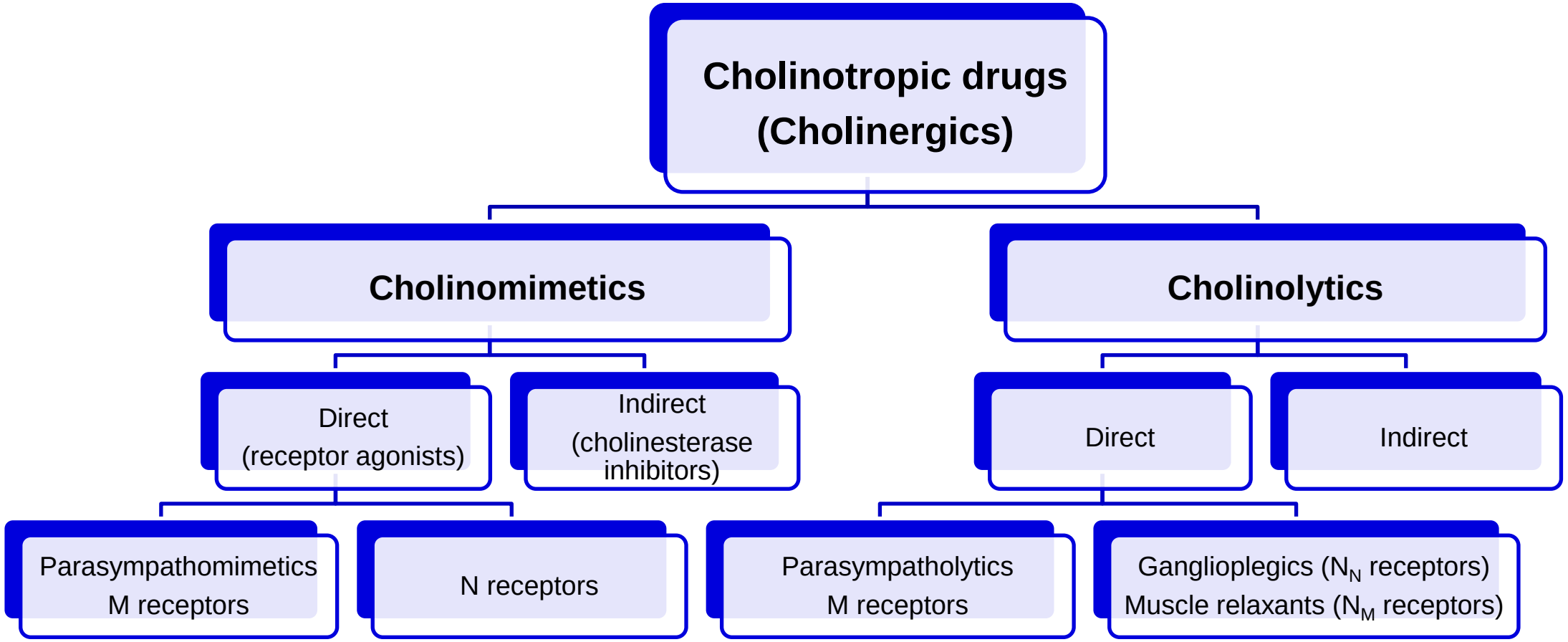
Acetylcholine receptors

Nicotinic		Muscarinic		
Nicotinic Muscular (N_M)	**Nicotinic Ganglionic (N_N)**	**M_1 ('neural')**	**M_2 ('cardiac')**	**M_3 ('glandular/ smooth muscle')**
Skeletal neuromuscular junction	Autonomic ganglia CNS	CNS peripheral neurons on gastric parietal cells	myocardium, smooth muscle, some presynaptic sites; CNS neurons	exocrine glands vessels CNS neurons
Receptors coupled with Na^+/K^+ ion channels		coupled with **G_q** protein	coupled with **G_i** protein	coupled with **G_q** protein
skeletal muscle contraction	neurotransmission in the autonomic nervous system modulatory effects in CNS	CNS excitation (memory) Gastric secretion	Cardiac inhibition Neural inhibition	↑ glandular secretions Smooth muscle contraction Vasodilatation Ocular accommodation


Cholinotropic drugs (Cholinergics)
Cholinomimetics
Cholinolytics
Direct (receptor agonists)
Indirect (cholinesterase inhibitors)
Direct
Indirect
Parasympathomimetics M receptors
N receptors
Parasympatholytics M receptors
Ganglioplegics (N_N receptors)
Muscle relaxants (N_M receptors)

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Parasympathomimetics

- Parasympathetic stimulation
- **Cardiovascular system**
  - Activation of M receptors, ↓ activity of sympathetic system
    → decreased heart rate
    → vasodilatation (activation of M_3 receptors – indirect effect → ↑ release of NO)
- **Respiratory system**
  → bronchoconstriction
  → ↑ tracheobronchial secretions
- **Gastrointestinal system**
  - ↑ salivation
  - ↑ production of gastric acid
  - ↑ peristalsis
  - ↓ contraction of sphincters

Parasympathomimetics

- Parasympathetic stimulation
- **Urogenital system**
  - Detrusor muscle **contraction** by activation of M_3 receptors
  - Internal urethral sphincter muscle **relaxation**
  - (detrusor relaxation blocked by M2 receptors)
- **Eye**
  - musculus sphincter pupilae – contraction → **miosis**
  - musculus ciliaris – contraction
    → circular fibers contraction → **short-range focus**
    → longitudinal fibers contraction → facilitates the outflow of aqueous humor → ↓ **intraocular pressure**
- **Glands**
  - ↑ secretion

Parasympathomimetics

Adverse effects – intoxication

- Consequences of muscarinic ACh receptor stimulation
  - Sweating, lacrimation, and salivation; mucosal secretion; red face
  - Nausea, vomiting, diarrhea, abdominal cramps
  - Urinary urgency
  - Bronchoconstriction, caught
  - Bradycardia

Parasympathomimetics

I. Direct-Acting Parasympathomimetics

- Direct stimulation of M receptors
- Effect – parasympathetic stimulation

a. **Choline esters**

b. **Alkaloids**

II. Indirect-Acting Parasympathomimetics/Cholinomimetics

= Inhibitors of cholinesterases

a. **Reversible**

b. **Irreversible**

Parasympathomimetics

I. Direct parasympathomimetics

a. Choline esters

- Stimulates M and also N receptors
- Quaternary amine compounds
- **Acetylcholine**
  - Fast degradation by cholinesterases after i.v. administration
  - Non-selective – targets M and N receptors
  - Does not cross blood-brain barrier
  - Not absorbed after p.o. administration
  - It is not used in theraphy

Parasympathomimetics

I. Direct parasympathomimetics

a. Choline esters

- **Carbachol**
  - Agonist of M and N receptors
  - Slightly inhibits ACHE
  - High adverse effects (affects GIT, urogenital system etc.)
  - In the past for the treatment of glaucoma
  - Indication: induction of miosis in eye surgery (intraocular application)
- **Mathecholine, Bethanechol**
  - Not used any more

Parasympathomimetics

I. Direct parasympathomimetics

b. Alkaloids

- **Pilocarpine**
  - *Pilocarpus jaborandi*
  - Tertiary nitrogen in the structure
  - Agonist of M receptors, partial agonist of N receptors
  - Facilitates the outflow of aqueous humor → ↓ intraocular pressure
  - Induction of miosis
  - Topical opthalmic application
  - Indication: glaucoma

Parasympathomimetics

I. Direct parasympathomimetics

b. Alkaloids

– Arecoline

- *Areca catechu* (abuse of areca nuts – „betel nuts“ for slight stimulatory effects; risk of precancerous lesions which frequently progresses to oral cancer)
- Tertiary nitrogen in the structure – cross the blood-brain barrier
- Non-selective (M and N receptors)
- Toxicology

– Muscarine

Parasympathomimetics

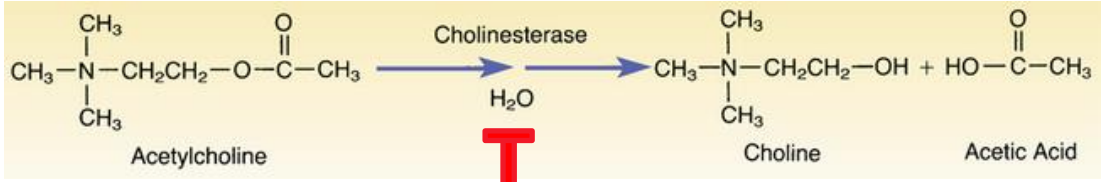
II. Indirect-Acting Parasympathomimetics/Cholinomimetics

= **Inhibitors of cholinesterases** (acetylcholinesterase > butyrylcholinesterase)

Acetylcholinesterase – specific for ACh; membrane-bound

Butyrylcholinesterase – non-selective; plasmatic and tissue enzyme

- Inhibits degradation of acetylcholine → ↑ concentration of ACh at cholinergic synapses
- Non-selective acting – M and N receptors



https://nursekey.com/cholinesterase-inhibitors-and-their-use-in-myasthenia-gravis/

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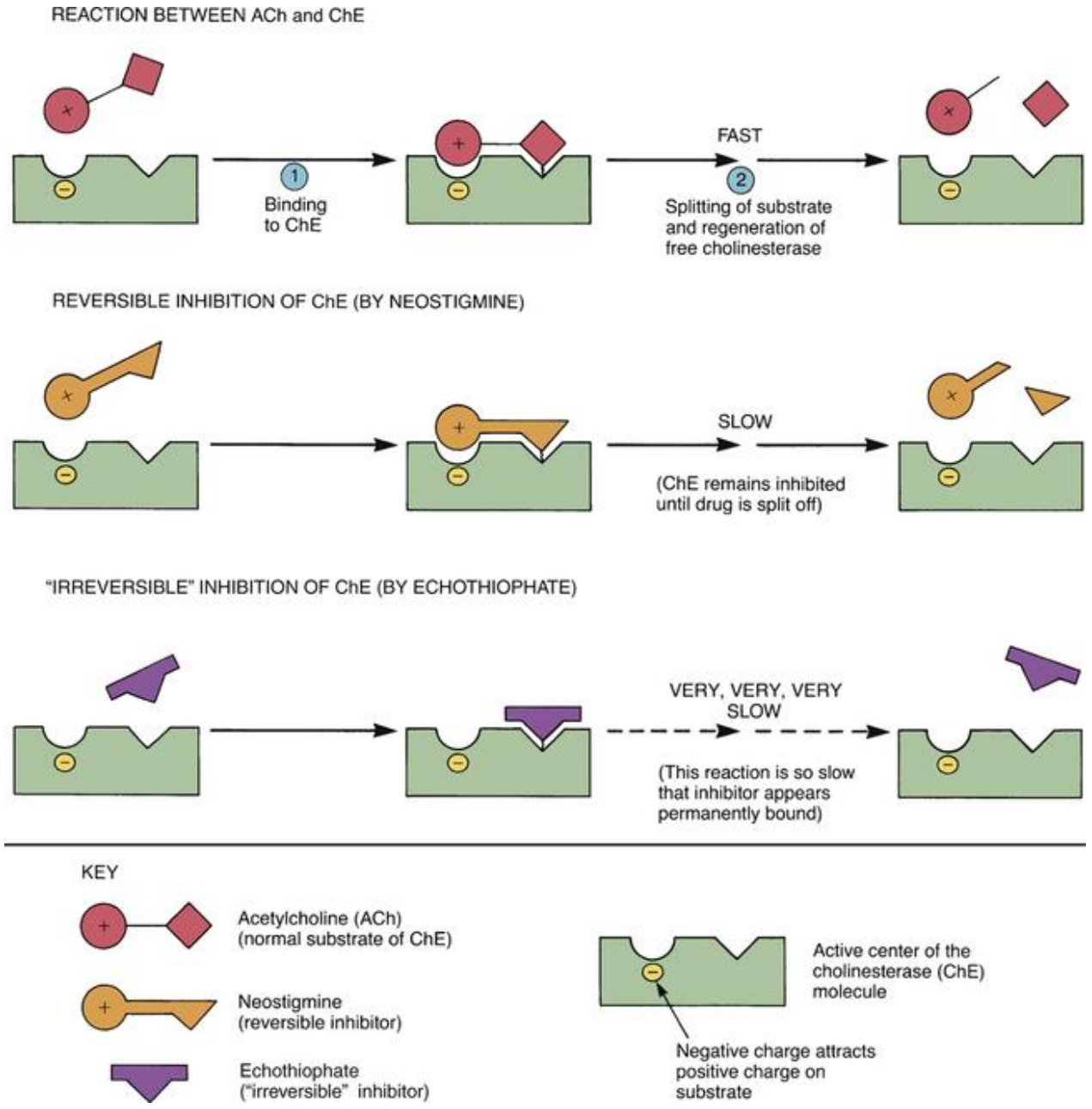

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Parasympathomimetics

II. Indirect-Acting Parasympathomimetics/Cholinomimetics

= **Inhibitors of cholinesterases** (acetylcholinesterase > butyrylcholinesterase)

- Inhibition reversible or irreversible
- Affect the transmission to the neuromuscular junctions = ↑ the strength of muscle contraction; intoxication → fasciculation, convulsions, muscle paralysis
- Adverse effects: depolarization blockade of ganglia and neuromuscular junctions
  muscle weakness, diarrhea, vomiting, bradycardia, bronchial hypersecretion, hypersalivation

a. Reversible

➢ Short-acting **edrophonium** (5–15 min)

- Test for diagnosis of myasthenia gravis

Reversible cholinesterase inhibitors

a. Reversible

- Longer acting:
  - **Physostigmine**
    - alkaloid *Physostigma venenosum*
    - Tertiary amine
    - Lipophilic – cross the blood-brain barrier
  - **Neostigmine** (short half-time)**, pyridostigmine, distigmine** (long half-time)
    - Quaternary amines
  - **Donepezile, rivastigmine**
    - Specific, reversible inhibitors acetylcholineterase
    - Predominantly central effect
    - For symptomatic therapy of Alzheimer's dementia

Reversible cholinesterase inhibitors

Indications:

- Reversal of the effects of **non-depolarizing neuromuscular blocking agents** (neostigmine, pyridostigmine)
- Therapy and prophylaxis of postoperative **intestinal atony**, **paralytic ileus** (distigmine)
- **Hypotonic bladder**
- Theraphy of **myathenia gravis**
- ↓ **intraocular pressure**, induction of miosis (physostigmine)
- Theraphy of **intoxication by anticholinergic agents** e.g. tricyclic antidepressants, antiparkinsonic therapeutics etc.

Irreversible cholinesterase inhibitors

II. Indirect-Acting Parasympathomimetics/Cholinomimetics

b. Irreversible inhibitors of acetylcholinetsrease

Organophosphates

- Toxicology
- Insecticides (parathion, malathion, chlorpyrifos etc.)
- Nerve agents (sarin, tabun, soman)
- High lipophilicity – easily cross all barriers; rapid onset of action, long lasting

Irreversible cholinesterase inhibitors

Organophosphates

- Symptoms of intoxication – miosis, headache, ↑ gland secretion (salivation, sweating), bradycardia, ↓ blood pressure,

→ central inhibition of respiratory and cardiac centers → loss of consciousness, respiratory arrest

- Therapy of intoxication – AChE reactivators: **pralidoxime**
  - Atropine – blockage of M receptors
  - Preventive effects – reversible iAChE

Cholinolytics

Direct-acting

– Agents directly blocking cholinergic receptors

a. **Parasympatholytics** – inhibition of M receptors
b. **Ganglionic blockers** – inhibition of N_N-receptors
c. **Non-depolarizing neuromuscular blockers** – inhibition of N_M-receptors

Indirect-acting

e.g. presynaptic inhibition of ACh release

Parasympatholytics

- Inhibition of cholinergic transmission – antagonists of M receptors

Effects:

- **Cardiovascular system**
  - Low doses – slight bradycardia
  - Higher doses – inhibition of M_2 receptors – tachycardia
- **Respiratory system**
  - Bronchodilatation, ↓ secretion, ↓ mucociliary function
- **Gastrointestinal system**
  - ↓ peristalsis, ↓ secretion
  - Relaxation
  - ↓ gastric acid production

Parasympatholytics

- **Urogenital system**
  - Relaxation of smooth muscles of bladder
  - Reduced frequency of urination
- **Glands**
  - ↓ salivation, ↓ lacrimation, ↓ sweating
- **Eye**
  - Mydriasis
  - Relaxation of musculus ciliaris → accommodative dysfunction, near vision impairment
  - ↑ intraocular pressure
- **CNS**
  - Only tertiary amines
  - ↓ tremor and muscle rigidity (e.g. in Parkinson's disease)
  - Antiemetic effect

Parasympatholytics

- **Tertiary amines**
  - Absorption after p.o. application
  - Cross biological membranes → e.g. blood-brain barrier
  - Effect in CNS
  - e.g. alkaloids – atropine, scopolamine, hyoscyamine
- **Quaternary amine structures**
  - Low lipophilicity, ↓ cross through biological membranes
  - Low absorption from gastrointestinal system
  - e.g. N-butyl-scopolamine

Parasympatholytics

- **Atropine**
  - *Atropa belladona*
  - Non-selective parasympatolytic agents – all types of M receptors (high doses affects N_N receptors)
  - Effects:
    - Low doses – bradycardia, ↓ glandular secretion
    - Medium doses – tachycardia, mydriasis, accommodative dysfunction, ↓ salivation
    - High doses – dry and hot skin, headache, urinary retention, ↓ peristalsis

    → excitation of CNS, delirium, hallucinations, coma

Parasympatholytics

- **Atropine**
  - **Indications: mydriaticum**, cycloplegicum

    preanesthetic agent – prevention of vagal bradycardia, ↓ glandular secretion

    in **bradyarrhythmia**

    to **suppress** the **effects of iAChE**
  - **Adverse effects** – consequences of muscarinic ACh receptor inhibition

    → tachycardia, mucosal dryness, ↑ body temperature, urinary retention, obstipation etc.
  - **Contraindications:** glaucoma, tachyarrhytmia, GIT, urinary obstruction

Parasympatholytics

Scopolamine

- Tertiary amine
- CNS depression
- Indications: antiemetic, mydriaticum

Homatropine

- Ophtalmology – mydriaticum

Tropicamide

- M_4 receptor blockade
- Indication: mydriaticum, cycloplegicum

Parasympatholytics

Indication → Parkinson's disease

- **Biperiden, procyclidine**
  - Tertiary amines
  - Antagonism of cholinergic activity in CNS
  - ↓ tremor and rigidity
  - Adverse effects: blurred vision, urinary retention, nausea, constipation, ↓ salivation etc.
  - Contraindications: glaucoma, tachyarrhytmia, GIT, urinary obstruction, cognitive deficits and dementia

Parasympatholytics

Quaternary amine parasympatolytics

- ↑ peripheral effects with reduced CNS effects
- effective at lower doses

Spasmolytics

- Reduction of tonus of GIT smooth muscles (including the gallbladder and bile ducts) and smooth muscles of urinary tract; suppression of glandular secretion
- Contraindications: gastrointestinal obstruction, p.e. administration – tachyarrhythmia
- Drug interactions: the risk of inducing changes in the bioavailability of other drugs

Parasympatholytics

Quaternary amine parasympatolytics – Spasmolytics

N-butyl-scopolamine

- Lower antimuscarinic effects and more pronounced antinicotine effects in GIT ganglia

  → reduction of smooth muscle contraction in internal organs without significant effect on glandular secretion
- p.o. administration, i.v., i.m., s.c.
- ↓ absorption from the GIT, it does not cross blood-brain barrier

Parasympatholytics

Quaternary amine parasympatolytics – Spasmolytics

Otilonium

- Combination of calcium channel blockade and mild antimuscarinic effects
- **Indications:** irritable bowel syndrome and painful spastic conditions of the distal intestinal tract

Fenpiverinium

- It was marketed as a combination drug with pitofenone hydrochloride and metamizole

Parasympatholytics

Quaternary amine parasympatolytics

Bronchodilators

- blockade of muscarinic receptors in respiratory system

  → bronchodilatation + attenuate mucus secretion
- For inhalational administration
- **Indications:** chronic obstructive pulmonary disease, less in asthma
- **Contraindications:** glaucoma, prostatic hyperplasia, urinary obstruction etc.
- Synergic effect with β2-sympathomimetics

Parasympatholytics

Quaternary amine parasympatolytics

Bronchodilators

- **SAMA** (Short-Acting Muscarinic Antagonists) (cca 6 h)
  - Non-selective inhibitor of muscarinic receptors (M1, M2, M3)
  - **Ipratropium**

- **LAMA** (Long-Acting Muscarinic Antagonists)
  - **Aclidinium** – cca 12h

- **U-LAMA** (Ultra-Long-Acting Muscarinic Antagonists) (cca 24 h)
  - **Tiotropium, Glycopyrronium, Umeclidinium**
  - ↑ selectivity to M_3 receptors

Parasympatholytics

Quaternary amine parasympatolytics – Urinary system

⟶ **Overactive bladder syndrome**

Trospium, Propiverine, Oxybutinin

– Non-selective

Solifenacine, Darifenacin, Fesoterodine, Tolterodine

– Selective to M_3 receptors
– ↓ adverse effects

→ inhibition of detrusor function, ↓ perception of bladder filling and improve symptoms as urgency, frequency, nocturia and incontinence

– Adverse effects: ↓ salivation, accommodation disorders, constipation

Parasympatholytics

Quaternary amine parasympatolytics

Peptic ulcer therapy

Pirenzepine

- Selective antagonist of M_1 receptors

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Thank you for your attention