PHARMACOLOGY OF THE CHOLINERGIC SYSTEM

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2019

LECTURE OUTLINE

- A brief overview of the cholinergic transmission & cholinergic receptors
- Pharmacology of the cholinomimetics
- Pharmacology of anticholinergics

CHOLINERGIC NEURON

Transmitter: ACh

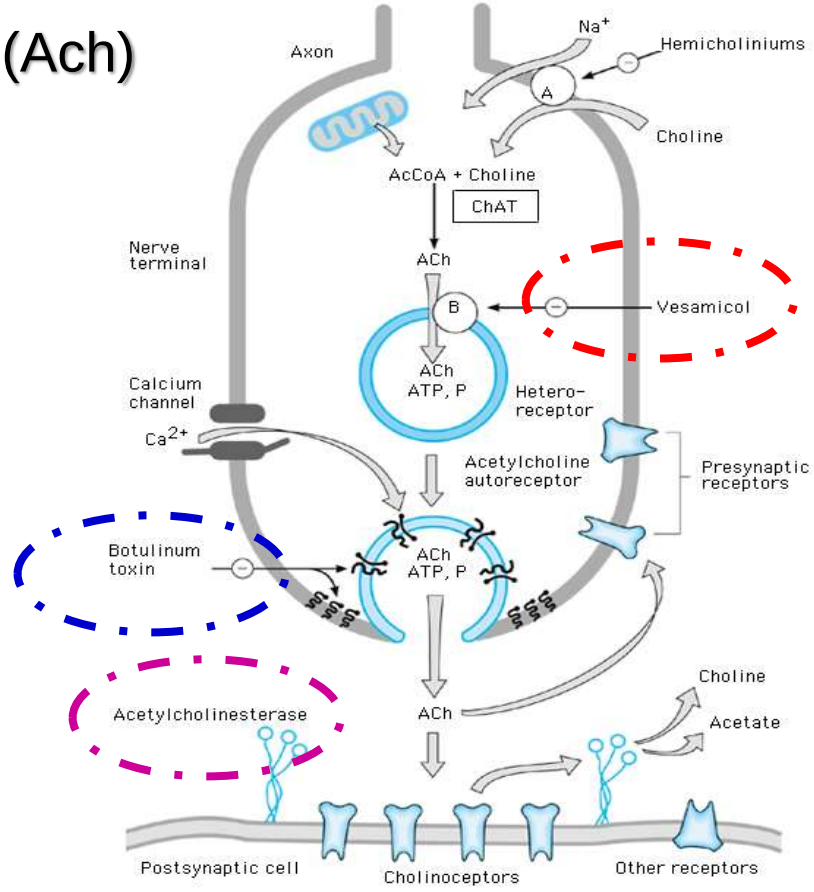
Acetylcholine (Ach)

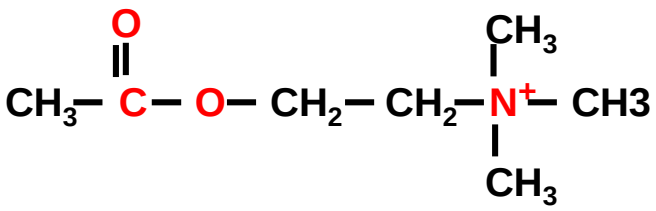
Synthesis

Storage

Release

Fate

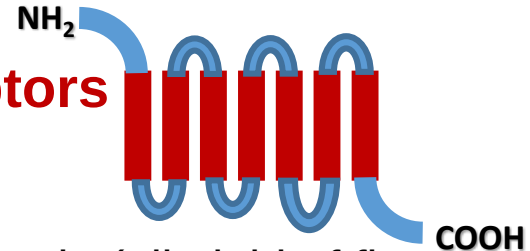




Acetylcholine

From B.G. Katzung's Basic and Clinical Pharmacology

CHOLINERGIC RECEPTORS (I)



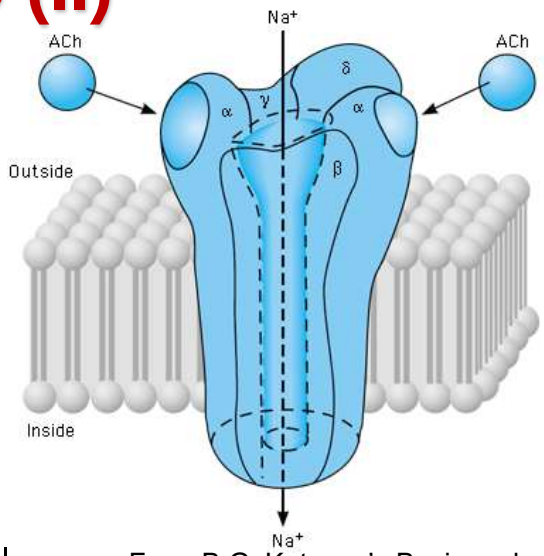
I- Muscarinic (M) receptors

- G protein coupled
- Have high affinity for muscarin (alkaloid of fly amanita, poison)

- Subtypes

- ❑ **M_1** (neuronal: CNS, gastric parietal cells; $G_{q/11,}$ ↑ IP3/DAG) ⇒ **Excitation**
- ❑ **M_2** (heart, nerves, smooth muscles; $G_{i/o}$, ↓ cAMP, ↑ K^+ channels) ⇒ **Inhibition**
- ❑ **M_3** (glands, smooth muscles, endothelium; $G_{q/11}$, ↑ IP3/DAG) ⇒ **Excitation**
- ❑ M_4 (CNS, lung; $G_{i/o}$, ↓ cAMP)
- ❑ M_5 (CNS; $G_{q/11}$)

CHOLINERGIC RECEPTORS (II)



From B.G. Katzung's Basic and Clinical Pharmacology

II- Nicotinic receptors

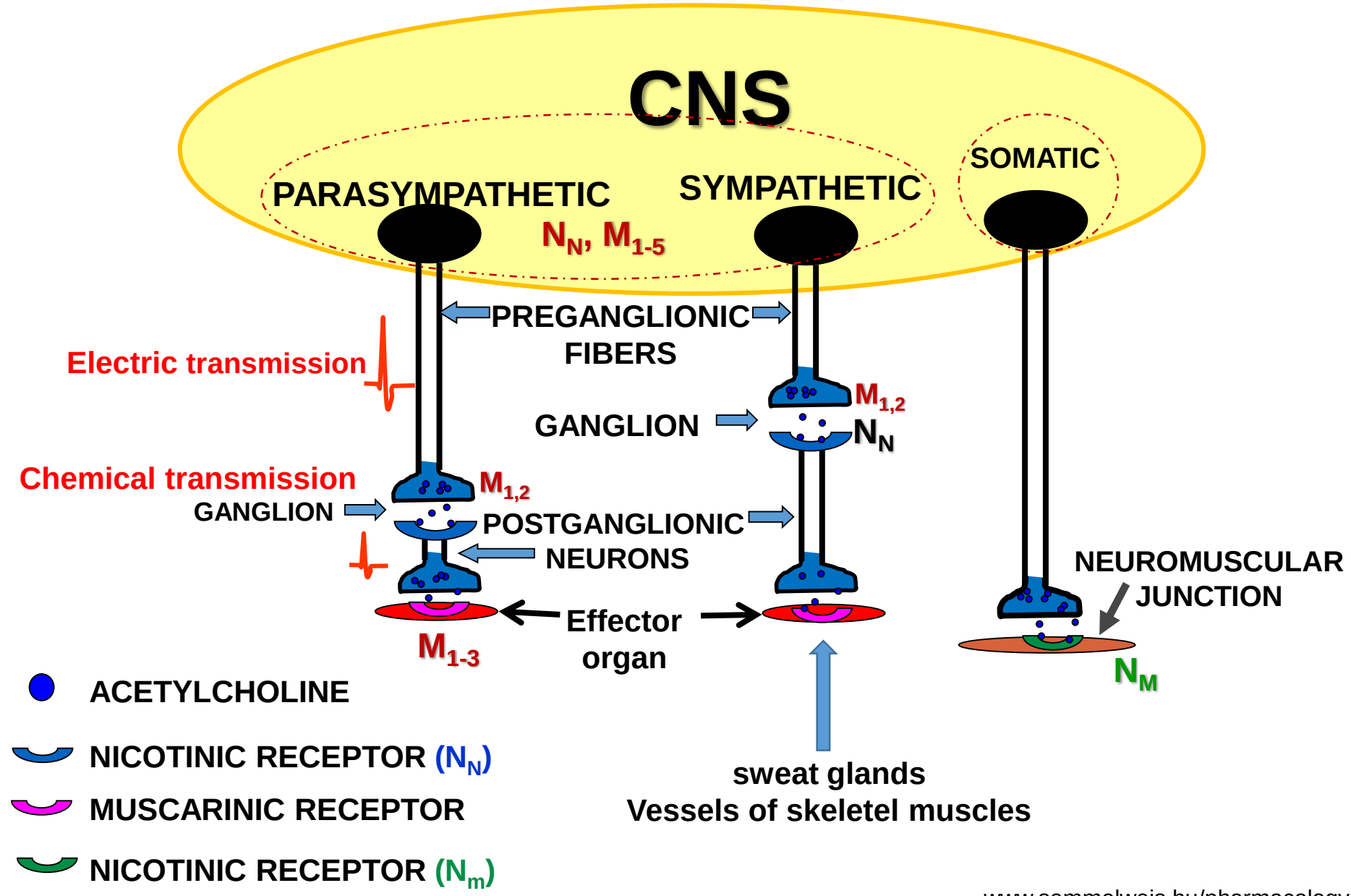
- Ligand-gated channel **(ionotropic).**
- Have high affinity for nicotine

  2 Ach molecules are needed to make conformational change and opening of Na channel.

- Subtypes

- Neuronal N receptors **(N_N):** α & β subunit only, <u>2 Ach molecules for activation</u>
- Muscular N receptors **(N_m)**: pentamer-$\alpha 2\beta\gamma\delta$, <u>2-5 Ach molecules for activation</u>

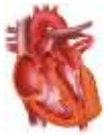
MAIN CHOLINERGIC TRANSMISSION SITES & RECEPTORS



MAIN CHOLINERGIC TRANSMISSION SITES AND RECEPTORS

Body part	Receptors
1. Central nervous system	M_1-M_5& N_N
2. Autonomic ganglion (both sympathetic and parasympathetic)	M_1-M_2& N_N
3. Neuromuscular junction	N_M
4. Parasympathetic postganglionic nerve	M_1-M_3
5. Certain sympathetic postganglionic nerves	M

Consequences of cholinergic system activation

Organ	The pharmacological effects	Receptor
	- Contraction m. sphincter pupillae - miosis m. ciliaris - accomodation - lacrimal gland - ↑ secretion	M_3
	- Salivary glands- activation	M_3
	- S. muscle contraction - bronchoconstriction - bronchial glands - ↑secretion	M_3
	- SA, AV: negative chronotropic, dromotropic effect - bradycardia - atrial contracting decreases (minimum ventricular effect!)	M_2
	- smooth muscle contraction - smooth muscle relaxation! - NO (endothelium) + NA ↓	M_3 M_3, $M_{2,4}$
	- smooth muscle contraction - stimulation of GI motility - relaxation of sphincters - increased secretion (eg gastric acid)	M_3, M_1
	- smooth muscle contraction (detrusor) - relaxation of sphincters	M_3

Consequences of cholinergic system activation

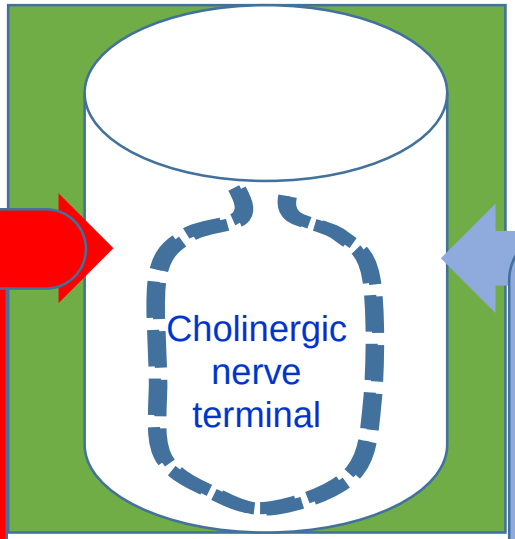
Organ	The pharmacological effects	Receptor
	- sweat glands - ↑secretion	M_3
	- cognitive functioning, modulation of mesolimbic DA release	$M_{1(2-5)}$
	- mesolimbic DA release (nicotine addiction), tremor, nausea	N_N $(\alpha_4)_2(\beta_2)_3$
	- cognitive function, modulation of pain sensation	N_N $(\alpha_7)_5$
	- inhibition of inflammatory cytokines (eg TNF-α, IL-1β)	N_N $(\alpha_7)_5$
	- stimulation of sympathetic and parasympathetic ganglions - mixed effects	N_N $\alpha_3\beta_{2/4}$ M_1
	- contraction of the skeletel muscle	N_M $(\alpha_1)_2\beta_1\delta\varepsilon$

POSSIBILITIES TO AFFECT CHOLINERGIC TRANSMISSION

Presynaptic stimulation Presynaptic inhibition	Drugs acting presynaptically
Postsynaptic stimulation	Direct and indirect cholinomimetics
Postsynaptic inhibition	Receptor antagonists

Presynaptic stimulation

- **K^+ channel blockers**
- **High Ca^{2+} conc.**
- **Latrotoxin**
- **Activation of stimulatory presynaptic receptors**



Presynaptic inhibition

- **Botulinum toxin („botox”)***
- **Hemicholin**
- **High Mg^{2+} concentration**
- **Tetrodotoxin, Vesamicol**
- **Aminoglycoside antibiotics (NMJ)**
- **Activation of presynaptic inhibitory receptors:e.g. M_2, α_2, D_2, opioid, adenosin**

4-aminopyridine (fampridine):
K^+ channel blockers – multiple sclerosis (MS)

*Local muscle spasms: blepharospasm, strabism)

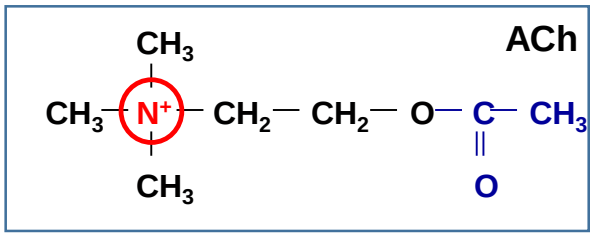
CHOLINERGIC TRANSMISSION:

POSTSYNAPTIC STIMULATION

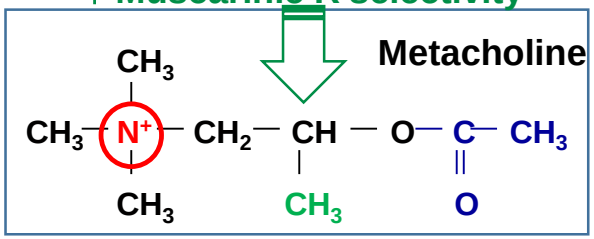
DRUGS		Molecular target
DIRECT ACTING	- Choline esters	M or M & N receptors
	- Alkaloids and others	M, M & N or N receptors
INDIRECT ACTING	- Alcohols	Acetylcholinestrase ↓ ↑ ACh M & N receptors
	- Carbamates	
	- Organophosphates	

M: Muscrinic; N:Nicotinic

DIRECT ACTING CHOLINOMIMETICS: CHOLINE ESTERS

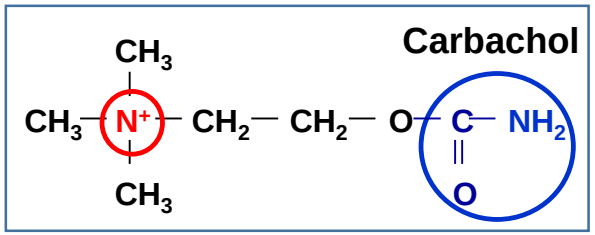


↑ Muscarinic R selectivity

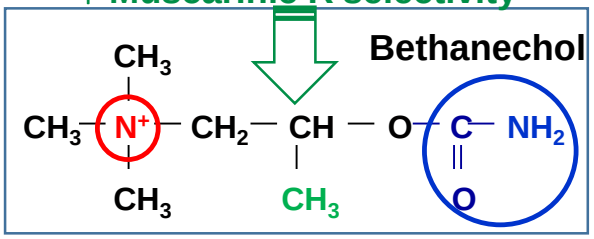


Carbamoyl group

↑ Cholinesterase resistance



↑ Muscarinic R selectivity

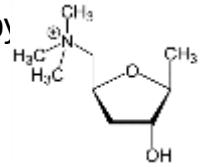
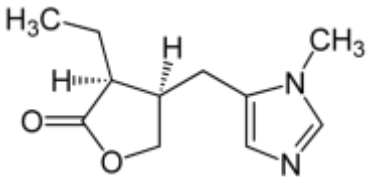


Drug	Cholinesterase sensitivity	M effect	N effect	Indication
ACh	+++	+++	+++	- only in opthalology
Methacholine	+	+++	Ø	- diagnosis of bronchial hyperreactivity
Carbachol	Ø	++	+++	- glaucoma, eye surgery
Bethanechol	Ø	++	Ø	- gastrointestinal atony, bladder atony, peri-operative urinary retention- (p.o., s.c.)

All are quaternary amines
Poor GI absorbtion & CNS penetration
Excretion: kidney

M: Muscrinic; N:Nicotinic

DIRECT ACTING CHOLINOMIMETICS: ALKALOIDS

Drug	Chemic. Struct.	M effect	N effect	Indication
Muscarine	quaternary amine (non ester - not hydrolysed by cholinesterase) 	**+++**	**Ø**	- poison, experimental use.  Amanita muscaria (poisonous mushroom)
Pilocarpine	tertiary amine 	**+++**	(+)	- Glaucoma (Pilocarpin 1-2% sol.) - xerostomia (dry mouth) caused by radiotherapy, p.os tabl. - Sjogren's syndrome (xerostomia, xerophthalmia), p.os tabl.
Arecolin	tertiary amine	**++**	**++**	-euphoric effect 
SYNTHETIC COMPOUNDS				
Cevimeline	tertiary amine	**M3 mid M1**		- Sjogren's syndrome

M: Muscrinic receptor; N:Nicotinic receptor

CHOLINOMIMETICS: NICOTINIC RECEPTOR AGONISTS

Drug	Struct.	M effect	N effect	Indication	Note
ALKALOIDS					
Nicotine	tertiary amine	**Ø**	**+++**	poison, smoking cessation 	ganglionic stimulant (small dose)
SYNTHETIC COMPOUNDS					
Varenicline	Cytisine analog	**Ø**	$(\alpha_4)_2(\beta_2)_3$ N_NR partial agonist	smoking cessation	ganglionic stimulant
Suxamethonium or Succinylcholine	quaternary amine	**Ø**	**N_M**	endotracheal intubation (general anesthesia)	depolarizing skeletal muscle relaxant*

M: Muscrinic receptor; N:Nicotinic receptor

***** Pharmacology of skeletal muscle lecture

TAKE HOME MESSAGE-1

THERAPEUTICAL USE OF MUSCARINIC RECEPTOR AGONISTS

- Eye surgery
- Glaucoma
- Xerostomia
- Gastrointestinal atony, bladder atony, peri-operative urinary retention

THERAPEUTICAL USE OF NICOTINIC RECEPTOR AGONISTS

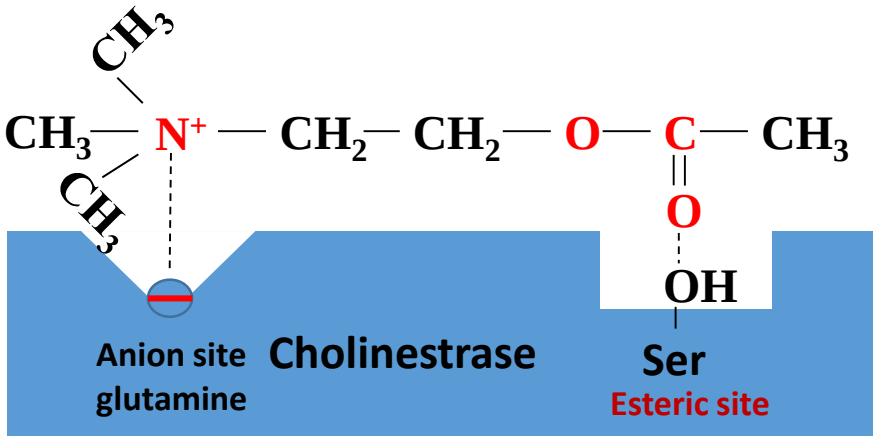
- Smoking cessation
- Endotracheal intubation

INDIRECT ACTING CHOLINOMIMETICS

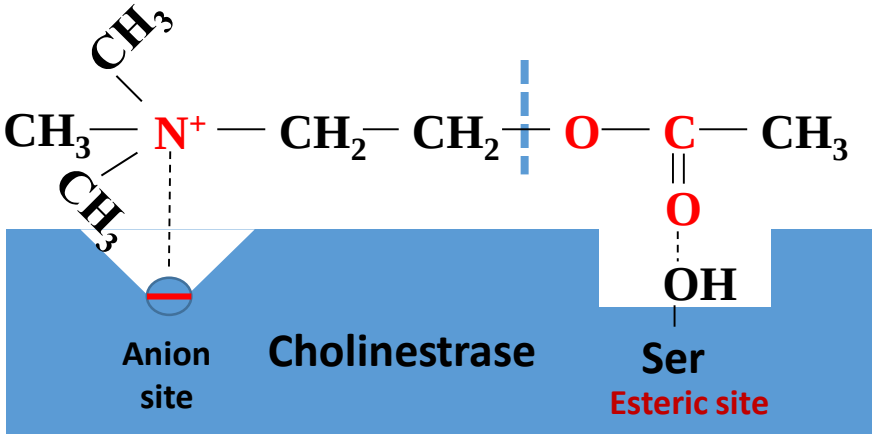
(ACETYLCHOLINESTRASE INHIBITORS)

Group	Note
- Alcohols & other struct.	Reversible, competitive
- Carbamates	Noncompetitive
- Organophosphates	Irreversible inhibition

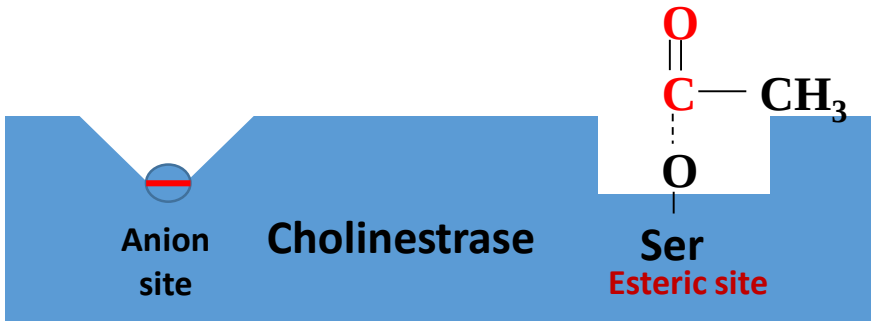
MECHANISM OF ACETYLCHOLINESTERASE



ACh binds to the active center



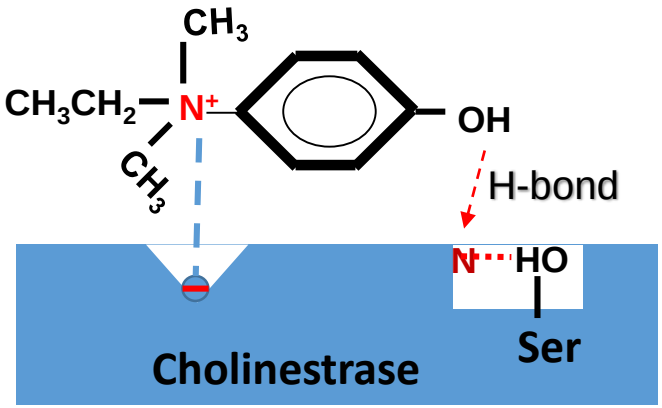
The enzyme cuts the ester bond in ACh



The enzyme becomes acetylated and choline leaves

The acetyl group leaves the enzyme by spontaneous hydrolysis (addition of H_2O) (150μs)

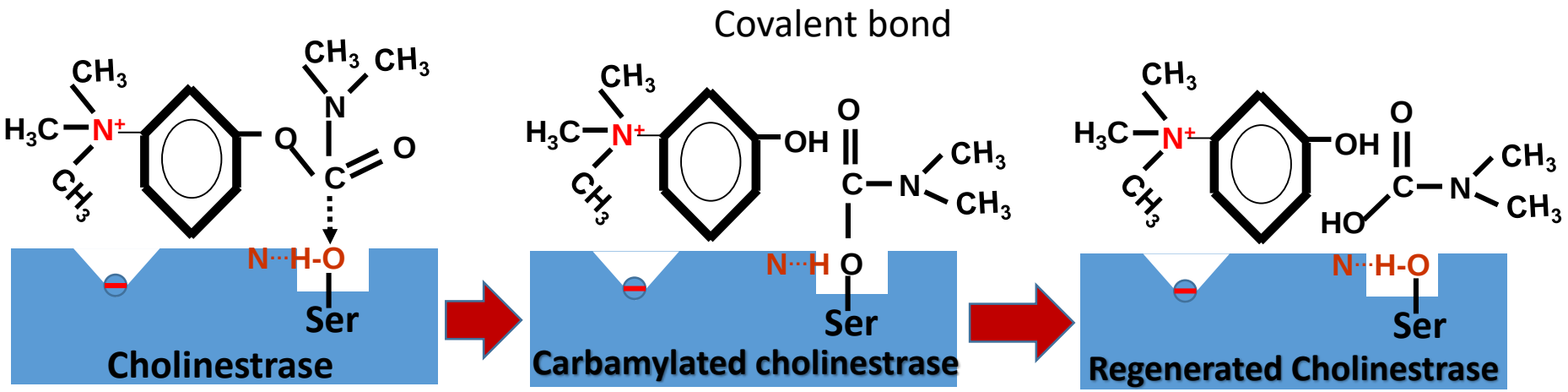
REVERSIBLE CHOLINESTRASE INHIBITORS:
Competitive inhibitors (no covalent bond)



EDROPHONIUM: limits the acetylcholine access

Agent	Struct.	Half life	Indication	Note
Edrophonium	Alcohol, quaternary amine, Water soluble	0.5 – 2h (5-15min)	- myasthenia gravis diagnosis ("Tensilon test", i.v./ i.m.) - Overcome the effect of non-depol. muscle relaxants (i.v.)	
Tacrine	TC-amine, Lipid soluble		Alzheimer's disease	hepatotoxic
Donepezil	Lipid soluble	58-90h (1 tabl./day)	Alzheimer's disease	Hepatic metabolism
Galantamine	Lipid soluble	5-7h	Alzheimer's disease	Hepatic~75% metabolism

REVERSIBLE CHOLINESTRASE INHIBITORS:
Carbamates (noncompetitive, Carbamoylating Inhibitors)



In the presence of Histadine

Carbamylated cholinestrase is slowly hydrolized (covalent bond)

Duration of action largely based on the stability of drug-enzyme complex and not on metabolism or excretion.

REVERSIBLE CHOLINESTRASE INHIBITORS: Carbamates

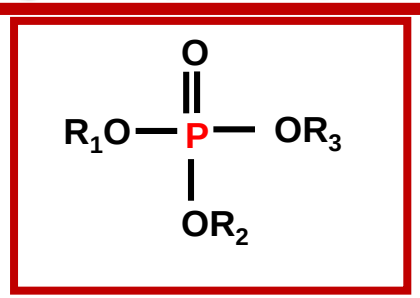
Agents	Duration of action (h)	Indication	Note
Physostigmine (Eserin)	**0.5-2**	- glaucoma - atropine poisoning (i.v.)	Tertiary amine, Lipid soluble
Rivastigmine*	**9**	- Alzheimer's disease or dementia (transdermal patch, p.os).	Lipid soluble, is metabolized by AChE and BChE
Neostigmine	**0.5-2**	- intestine, bladder atony (s.c., i.m., i.v.) - myasthenia gravis (s.c., i.m., i.v.) - antagonizing the effect of non-depolarizing muscle relaxants. - atonic obstipation, meteorism, postoperative gastrointestinal atonia and urinary retention (s.c., i.m., i.v.).	Quaternary amine, Water soluble
Pyridostigmine	**3-6**	- myasthenia gravis psuedoparalytica (p.os.) - intestinal atony, atonic obstipation (p.os.)	Quaternary amine, Water soluble
Ambenonium	**4-8**	- myasthenia gravis (p.os.)	Quaternary amine, Water soluble
Demecarium	**4-6**	- glaucoma	Quaternary amine, Water soluble

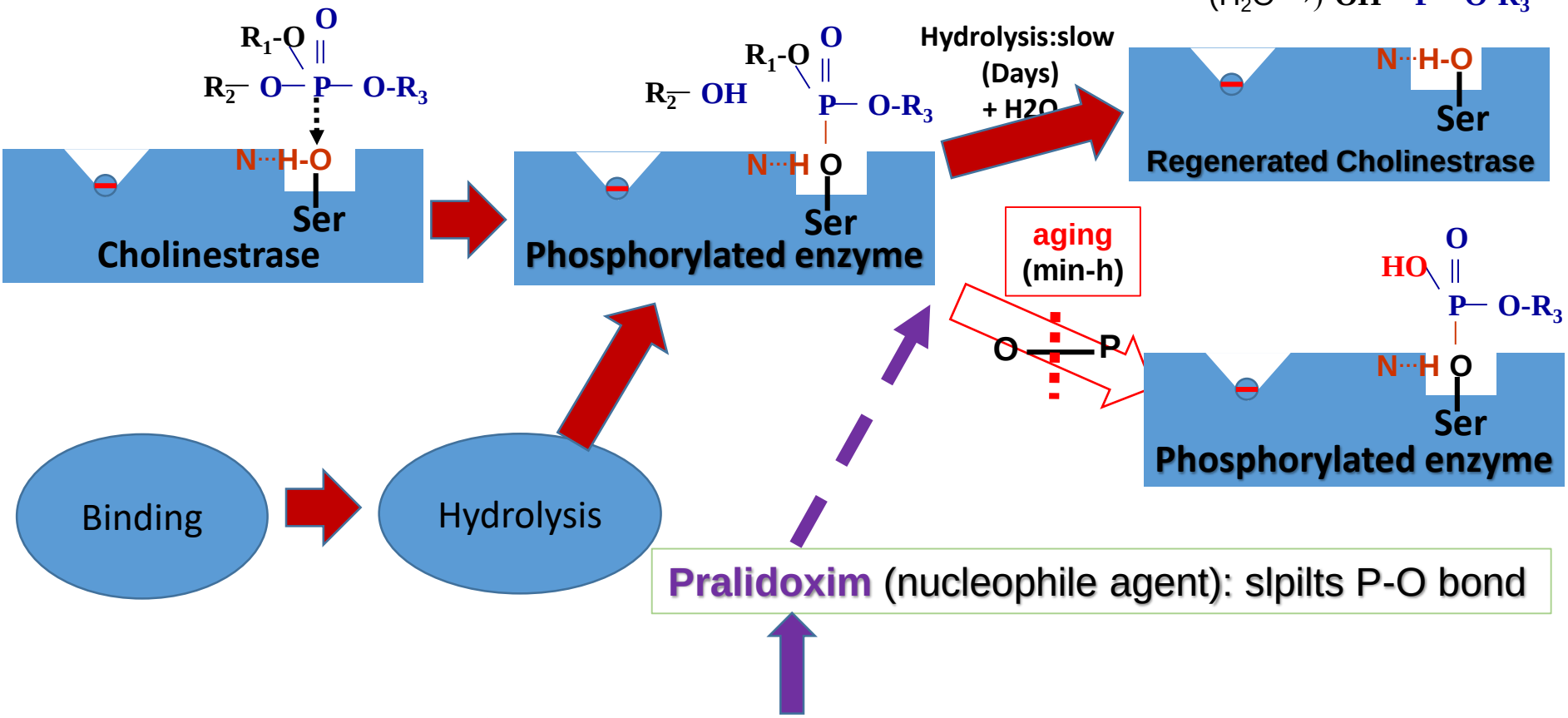
TAKE HOME MESSAGE-2

THERAPEUTICAL USE OF REVERSIBLE ACHE INHIBITORS (competitive or noncompetitive)

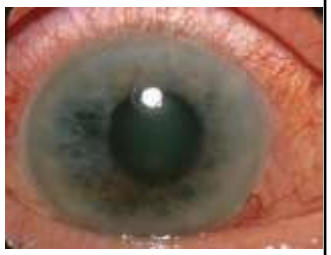
- **Myasthenia gravis (**diagnostic and/or treatment)
- **Alzheimer's disease**
- **Post-operative ileus**
- **Bladder distention**
- **Glaucoma**
- **Antidote to anticholinergic overdose**
- **Reversing the action of neuromuscular blocking agents**

Alkyl phosphates (Organophosphates)





IRREVERSIBLE CHOLINESTRASE INHBITOTS: (ORGANOPHOSPHATES)

Agent	Indication
Ecothiophate	- Glaucoma 
Tabun, Soman, Sarin, VX (nerve agent)	War gases (nerve agents)
Parathion, Malathion, Diazinon, Dimethoate	Insecticides

TAKE HOME MESSAGE-3

Drug	Mechanism of action
Edrophonium	selective, reversible AChE inhibitor
Donepezil	selective, reversible AChE inhibitor
Rivastigmine	Noncompetitive-reversible carbamate inhibitor inhibits both BuChE and AChE
Galantamine (alkaloid)	selective, competitive, reversible AChE inhibitor
Physostigmine (alkaloid)	Noncompetitive-reversible carbamate inhibitor, tertiary amine
Neostigmine Pyridostigmine Ambenonium Demecarium	Noncompetitive-reversible, quaternary amine, carbamate analogs
Ecothiophate Parathion, Malathion, Diazinon, Dimethoate	Irreversible AChE

SUMMARY: THERAPEUTICAL USE OF CHOLINOMIMETICS

- Glaucoma
- Postoperative and neurogenic ileus, urinary retention
- Myasthenia gravis
- Reversing the action of neuromuscular blocking agents
- Alzheimer’s disease
- Sjögren’s syndrom

THE ADVERSE EFFECTS OF CHOLINOMIMETICS

Diarrhea	**D**
Urination	**U**
Miosis	**M**
Bronchospasm	**B**
Bradycardia	**B**
Excitation (CNS & skeletal muscles	**E**
Lacrimation	**L**
Secretion (Salivation & Sweating)	**S**

POSTSYNAPTIC INHIBITION

Anticholinergic agents

1. Muscarin receptor antagonists

(Parasympatholytics)

- Tropeins
- Non-tropeins

2. Nicotine receptor antagonists

- Ganglionic blockers
  - Quaternary compounds [N^+] (tetraethylammonium, hexamethonium)
  - Tertiary compounds [N] (mecamylamine, trimetaphan)
- Skeletal muscle relaxants*

***** Pharmacology of skeletal muscle lecture

Atropine

Source	Potato family (Solanaceae): eg. Atropa belladonna, Datura stramonium
Structure	Tertiary
Duration of action	~ 2-3 h (mydriasis: 7-10 days!)
Single dose	0.3 - 0.5 mg
Lethal dose	~ 100 mg (infants: 2 mg!)
Indication	- eye drops (0.5 - 1%): mydriasis, cycloplegia, pupil dilation (in inflammatory iris conditions), amblyopia therapy. - bradycardia, grade I AV block - GI / bladder / urinary cramps - cholinomimetic poisoning: (alkylphosphate, inocybe mushrooms)

THE EFFECTS OF ATROPINE

Peripheral

- Mydriasis (wide pupils)
- Loss of accomodation
- Dry mouth
- Bronchodilation
- Tachycardia
- Decreased gastric acid secretion
- Constipation
- Dysuria
- Dry skin (atropine fever in children)

CNS

- Antiemetic effect (for motion sickness)
- Restlessness
- Extrapyramidal symptoms (dyskinesia)
- Raging
- Hallucinations
- Epileptiform convulsions
- Coma, death

Signs of atropine overdose:hot as a hare, blind as a bat, dry as a bone, red as a beet and mad as a hatter.

SCOPOLAMINE (HYOSCIN)

Source	Potato family (Solanaceae): eg. Frowning belts (Hyoscyamus niger) Datura stramonium
Structure	tertiary amine (→ large distribution, CNS- sedation, amnesia)
Duration of action	~ 2-3 hours (mydriasis: 3-7 days!)
Single dose	0.2 - 0.4 mg
Lethal dose	~ 500 mg
Indication	- antiemetic (per os, i.v., transdermal patch)

MUSCARINIC RECEPTOR ANTAGONISTS

Drug	Structure	Character	Indication
Homatropine	tertiary amine, tropein (semisynthetic)	4-6 x weaker than atropine, 2-5 %, 12-24 h	- eye examination internal Stereoscopic view
Tropicamide	tertiary amine	0,5 - 1 %, 6 h	
Cyclopentolate	tertiary amine	0,5 - 2 %, 3-6 h	
Oxybutynin	tertiary amine		overactive bladder with symptoms of urge urinary incontinence
Darifenacin	tertiary amine	„M3 selective” (10-20 x)	
Solifenacin	tertiary amine	„M3 selective” (2-3 x)	
Tolterodine	tertiary amine		
Fesoterodine	tertiary amine		
Trospium	quaternary amine		
Pirenzepine	tertiary amine	„M_1 selective” (20-30 x)	- peptic ulcer
Telenzepine	tertiary amine	„M_1 selective” (20-30 x)	

MUSCARINIC RECEPTOR ANTAGONISTS

Drug	Structure	Character	Indication
Benz(a)tropine	tertiary amine, tropein		- Parkinson's syndrome
Biperiden	tertiary amine		
Procyclidine	tertiary amine		
Propantheline	quaternary amine		- smooth muscle spasms
Butyl-scopolamine (Hyoscine-Butylbromide)	quaternary amine, tropein (félszintetikus)		
Ipratropium	quaternary amine, tropein		- COPD, asthma
Tiotropium	quaternary amine, tropein	„M_3-selective”, inhaled aerosol	
Aclidinium	quaternary amine	„M_3-selective”, inhaled aerosol	
Umeclidinium	quaternary amine	„M_3-selective”, inhaled aerosol	

TAKE HOME MESSAGE-4

Anticholinergic agents

- Cause pupil dilation and inhibit salivation & sweating.
- Inhibit bronchial smooth muscle contraction & secretion.
- Cause tachycardia (M2 blockade).
- Inhibits gastric acid secretion and GI motility.
- Inhibit the urination.
- Inhibit the action of cholinomimetics (at M and/or N receptors) in the periphery and CNS (these effects depend on the selectivity and pharmacokinetic profiles).

Summary: Clinical use of parasympatholytics I

- For diagnostic & therapeutic purposes (pupil dilation, refraction of light).
- COPD, Bronchial asthma (ipratropium spray).
- Bradycardia, 1st grade AV-block.
- Pre- or intraoperative medication (antagonizing the vagostimulant effects of certain anesthetics).
- To antagonize the parasympathomimetic effects of cholineterase inhibitors in the case of reversing the effect of curare type skeletal muscle relaxants.

Summary: Clinical use of parasympatholytics II

- Peptic ulcer (pirenzepine)
- Incontinence
- Diarrhea (with an opioid)
- Abdominal cramps (with painkillers and smooth muscle relaxants)
- Parkinson’s syndrome (centrally acting)
- Organophosphate poisoning

THE ADVERSE EFFECTS OF PARASYMPATHOLYTICS

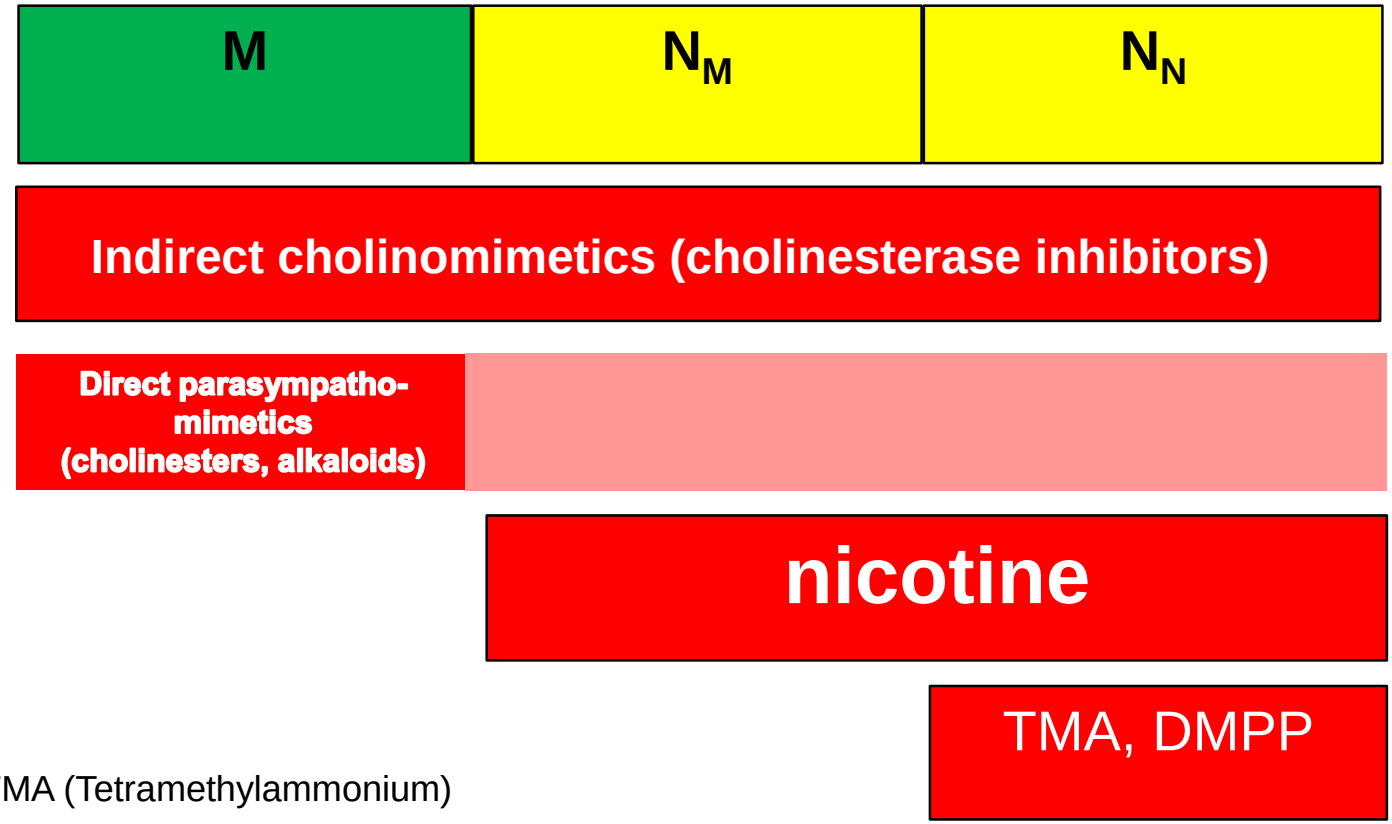
Atropine fever	**A**
Blurred vision	**B**
Constipation	**C**
Dryness	**D**

Thank you for your attention

EXTRA SLIDES:

Drugs affecting cholinergic transmission (postsynaptically)

stimulation



TMA (Tetramethylammonium)

DMPP (1,1-dimethyl-4-phenyl piperazinium)

Drugs affecting cholinergic transmission (Postsynaptically)

Inhibition