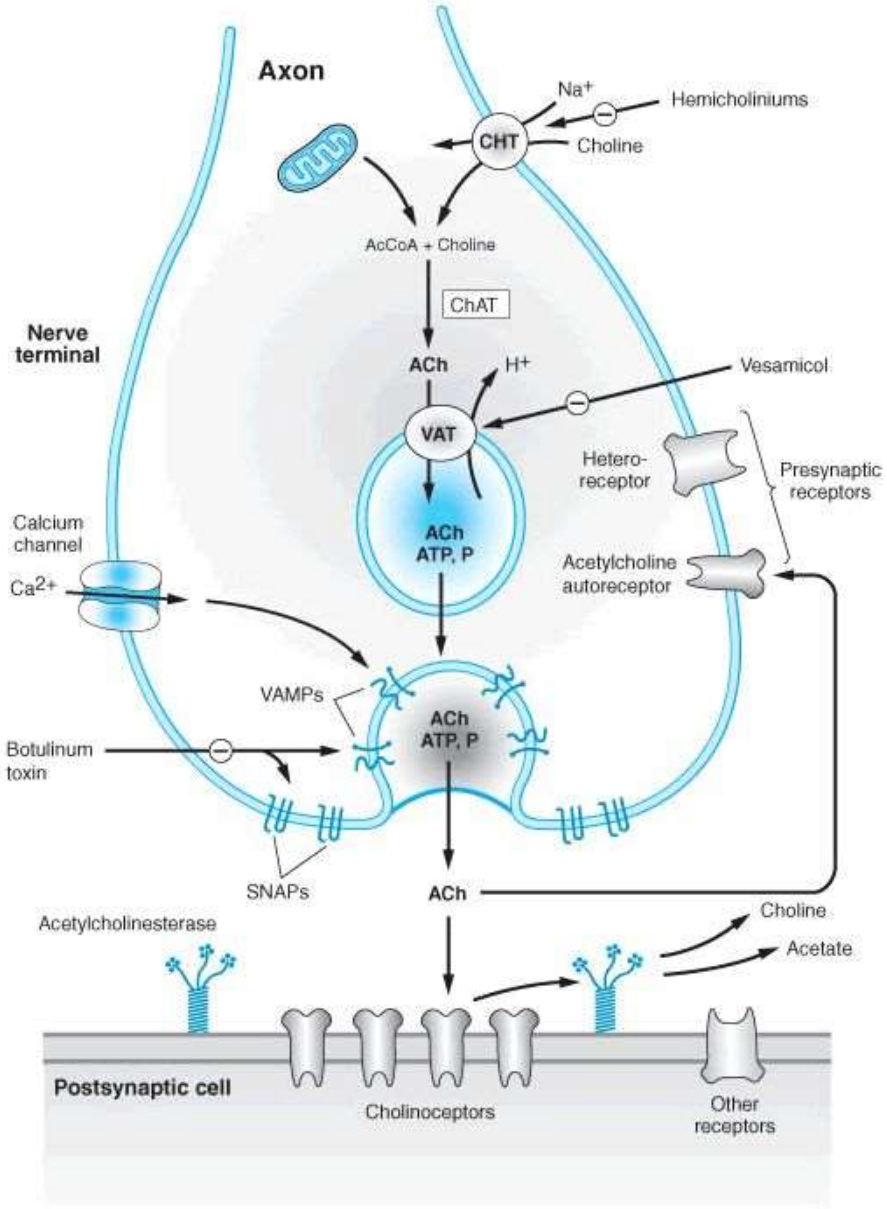
Cholinomimetic agents

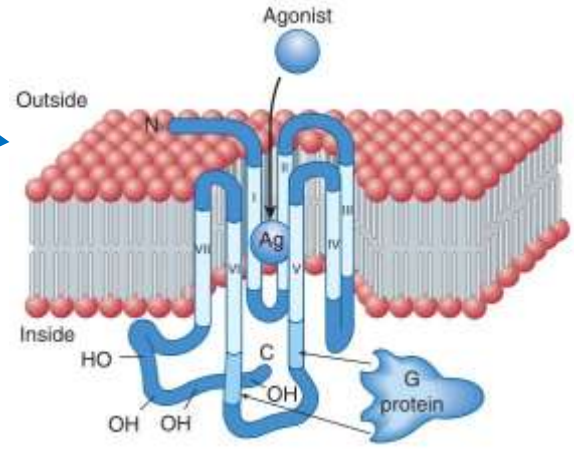
- mimic acetylcholine (ACh)
  - direct ↔ indirect
  - muscarinic ↔ nicotinic
- direct: binding to / activation of ACh rec.
- indirect: ↓ hydrolysis of endogenous ACh
  - no (sub)type selectivity
  - ACh receptors not only in ANS

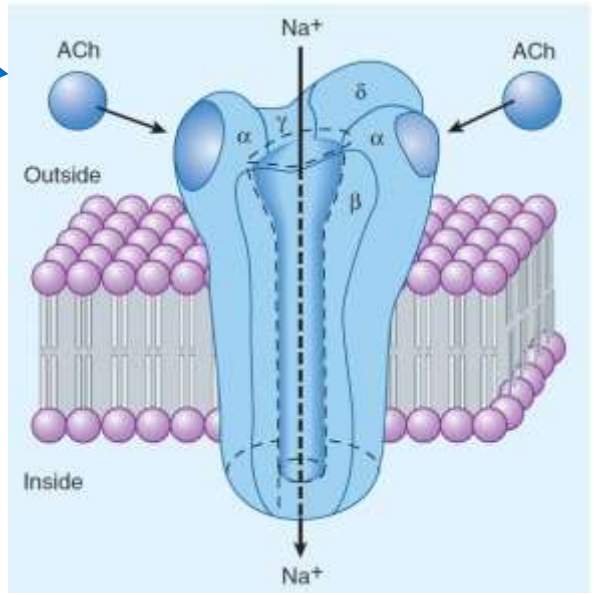
Cholinergic transmission



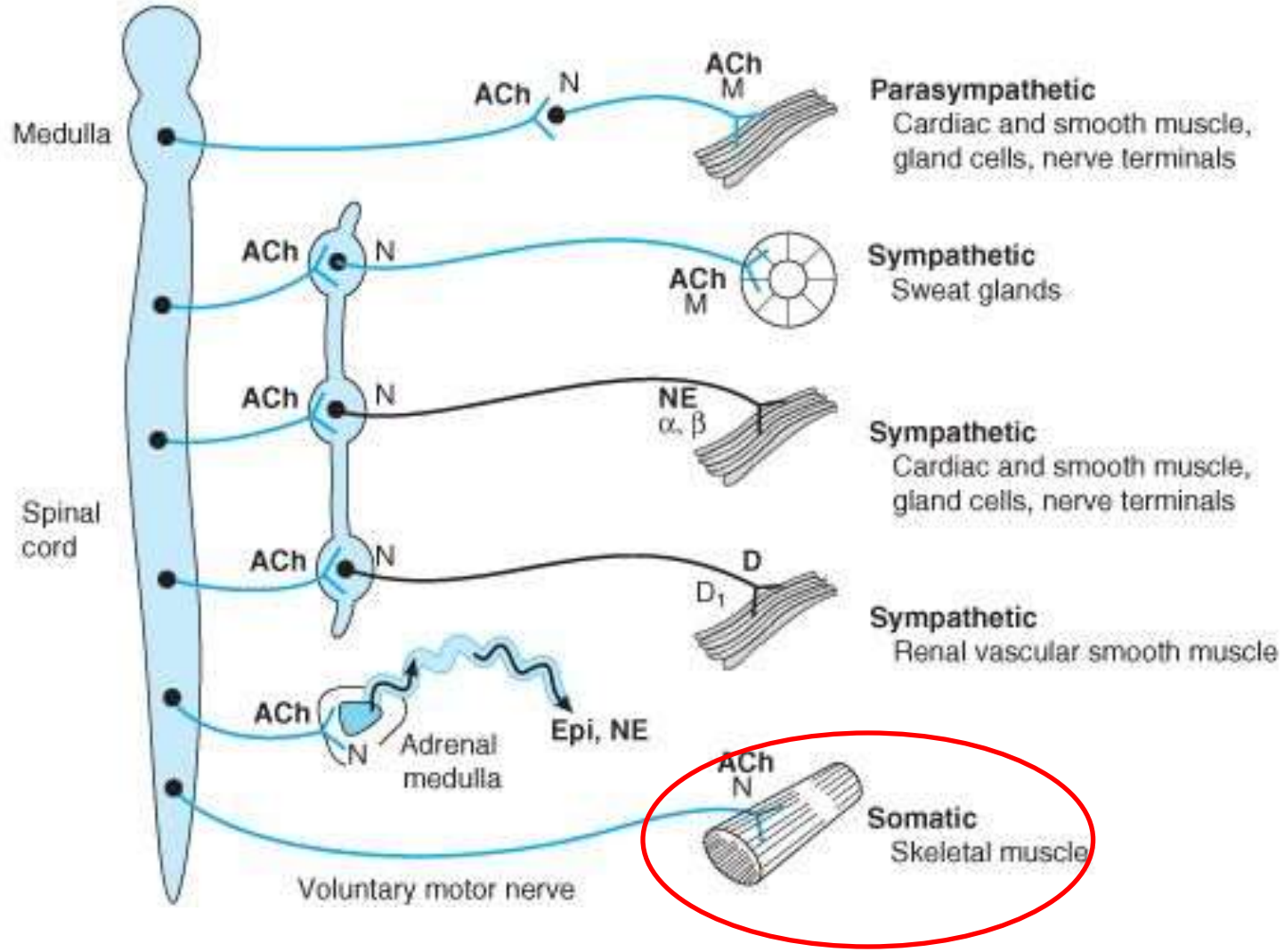
Acetylcholine receptors

- muscarinic
  - subtypes: M_1, M_2, M_3, M_4, M_5
  - second messenger
    - IP3-DAG-Ca: M_1, M_3, M_5
    - ↓ adenylyl cyclase / ↓ cAMP: M_2, M_4
- nicotinic
  - subtypes: N_N, N_M
- major sites
  - ANS, endothelium
  - neuromuscular junctions
  - CNS



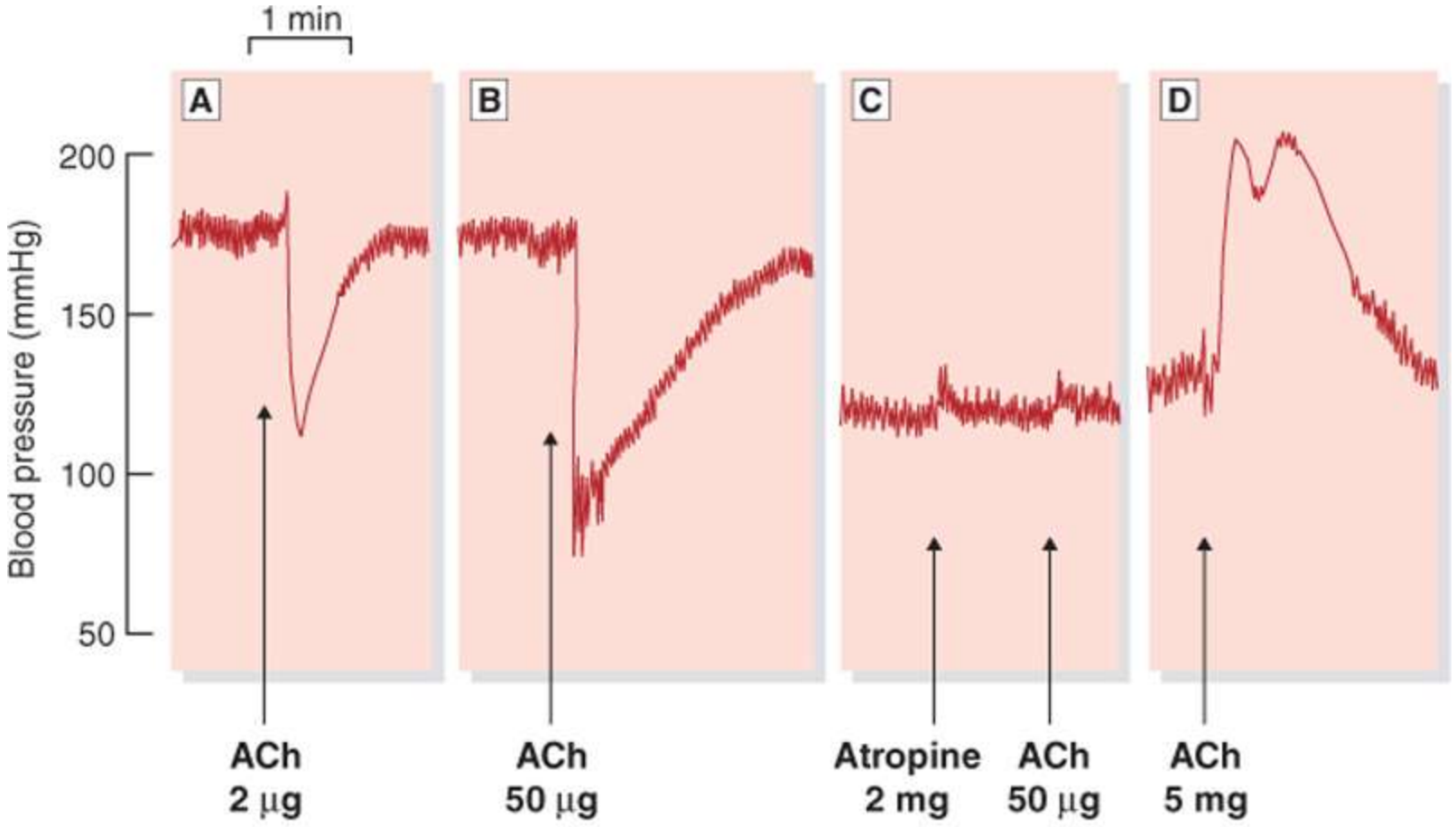


Anatomic aspects of the ANS



+ ENS = enteric nervous system

Dale's experiment



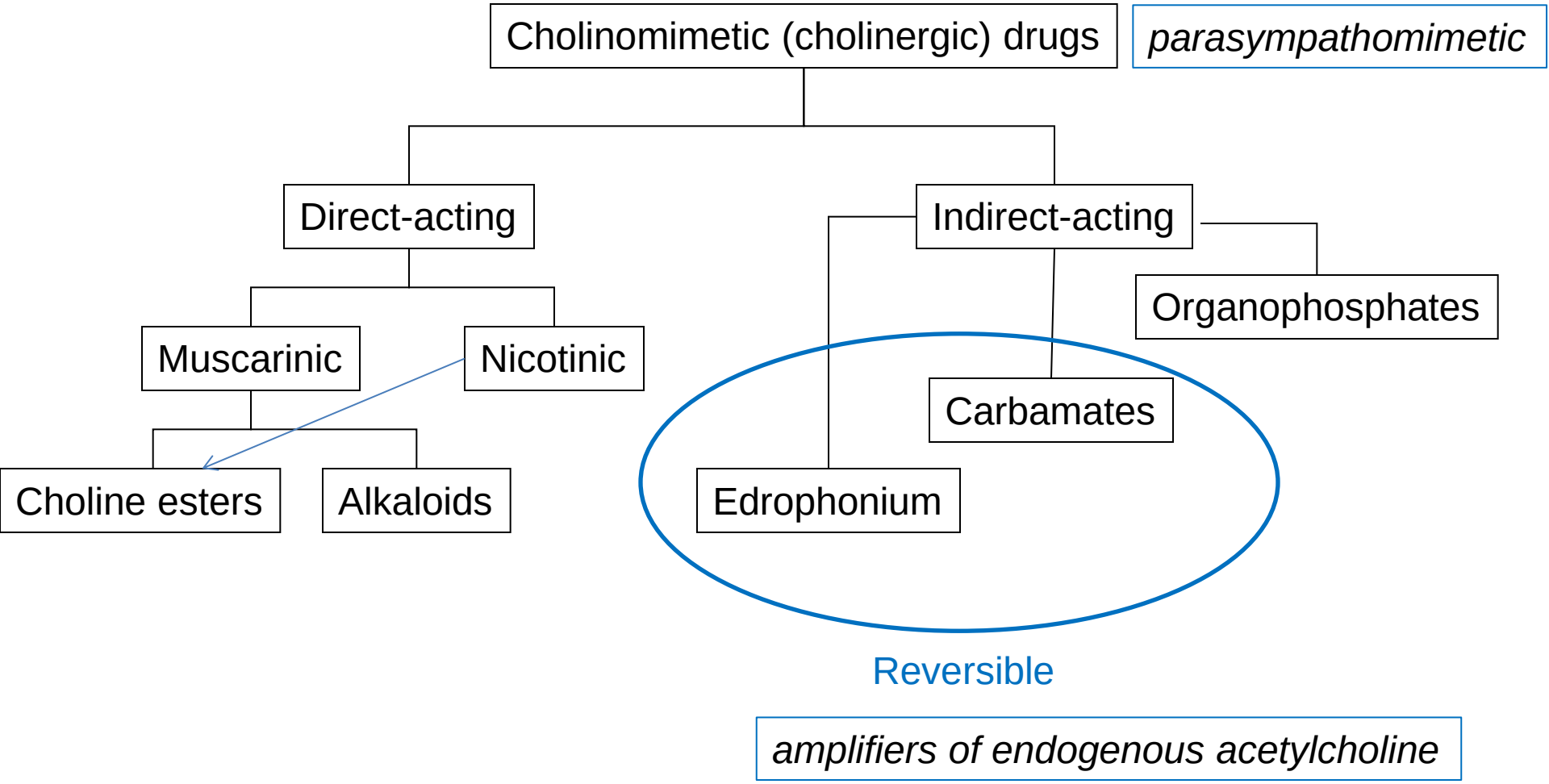
non-innervated endothelial M_3 receptors

Cholinoceptor subtypes

Receptor Type	Other Names	Location	Structural Features	Postreceptor Mechanism
M_1		Nerves	Seven transmembrane segments, $G_{q/11}$ protein-linked	IP_3, DAG cascade
M_2	Cardiac M_2	Heart, nerves, smooth muscle	Seven transmembrane segments, $G_{i/o}$ protein-linked	Inhibition of cAMP production, activation of K^+ channels
M_3		Glands, smooth muscle, endothelium	Seven transmembrane segments, $G_{q/11}$ protein-linked	IP_3, DAG cascade
M_4		CNS	Seven transmembrane segments, $G_{i/o}$ protein-linked	Inhibition of cAMP production
M_5		CNS	Seven transmembrane segments, $G_{q/11}$ protein-linked	IP_3, DAG cascade
N_M	Muscle type, end plate receptor	Skeletal muscle neuromuscular junction	Pentamer[1] $[(\alpha1)_2\beta1\delta\gamma)]$	Na^+, K^+ depolarizing ion channel
N_N	Neuronal type, ganglion receptor	CNS, postganglionic cell body, dendrites	Pentamer[1] with α and β subunits only, eg, $(\alpha4)_2(\beta2)_3$ (CNS) or $\alpha3\alpha5(\beta2)_3$ (ganglia)	Na^+, K^+ depolarizing ion channel

receptors not only on effector cells (M) → modulate ANS

Classification



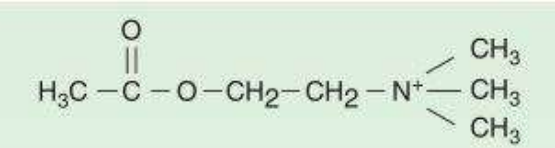
Direct-acting cholinomimetics

- direct
  - muscarinic
    - choline esters
      - acetylcholine (M+N!), methacholine (M) – hydrolysis +
      - carbachol (M+N!), **betanechol** (M) – hydrolysis -
    - alkaloids
      - muscarine / pilocarpine
  - nicotinic
    - nicotine, lobeline

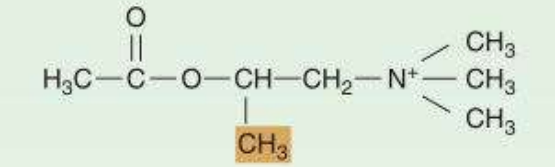
no receptor subtype selectivity (but see cevimeline)

significant stereoselectivity – 1000x potency: (S)-bethanechol > (R)-bethanechol

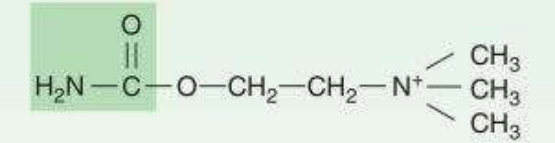
Choline esters



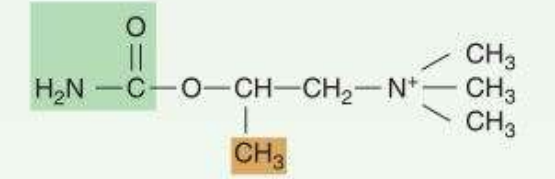
Acetylcholine



Methacholine
(acetyl-β-methylcholine)



Carbachol
(carbamoylcholine)



Bethanechol
(carbamoyl-β-methylcholine)

Choline Ester	Susceptibility to Cholinesterase	Muscarinic Action	Nicotinic Action
Acetylcholine chloride	++++	+++	+++
Methacholine chloride	+	++++	None
Carbachol chloride	Negligible	++	+++
Bethanechol chloride	Negligible	++	None

quaternary N → hydrophilic → absorption / distribution
differences in hydrolysis → duration

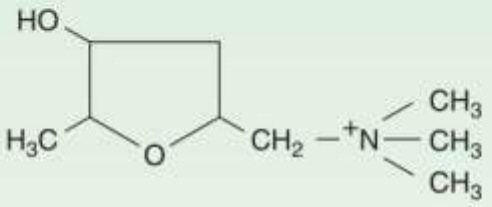
Alkaloids

Amanita muscaria

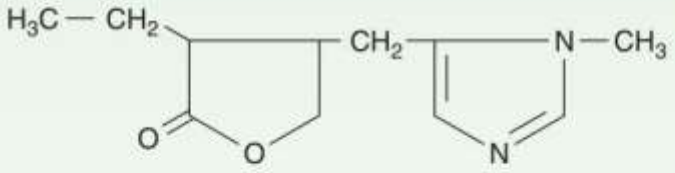
Inocybe erubescens

Pilocarpus microphyllus

Action chiefly muscarinic

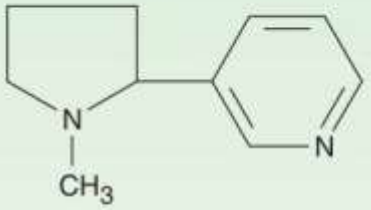


Muscarine

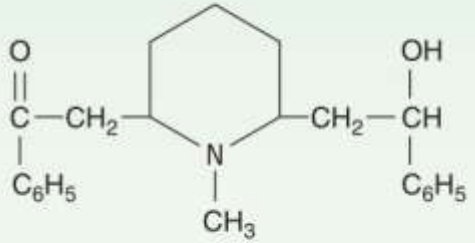


Pilocarpine

Action chiefly nicotinic



Nicotine



Lobeline

tertiary N → lipid soluble → good absorption
quaternary N → worse absorption (but see mushroom poisoning)

Effects of direct-acting cholinoceptor stimulants

M

Organ	Response
Eye	
Sphincter muscle of iris	Contraction (miosis)
Ciliary muscle	Contraction for near vision
Heart	
Sinoatrial node	Decrease in rate (negative chronotropy)
Atria	Decrease in contractile strength (negative inotropy). Decrease in refractory period
Atrioventricular node	Decrease in conduction velocity (negative dromotropy). Increase in refractory period
Ventricles	Small decrease in contractile strength
Blood vessels	
Arteries, veins	Dilation (via EDRF). Constriction (high-dose direct effect)
Lung	
Bronchial muscle	Contraction (bronchoconstriction)
Bronchial glands	Stimulation
Gastrointestinal tract	
Motility	Increase
Sphincters	Relaxation
Secretion	Stimulation
Urinary bladder	
Detrusor	Contraction
Trigone and sphincter	Relaxation
Glands	
Sweat, salivary, lacrimal, nasopharyngeal	Secretion

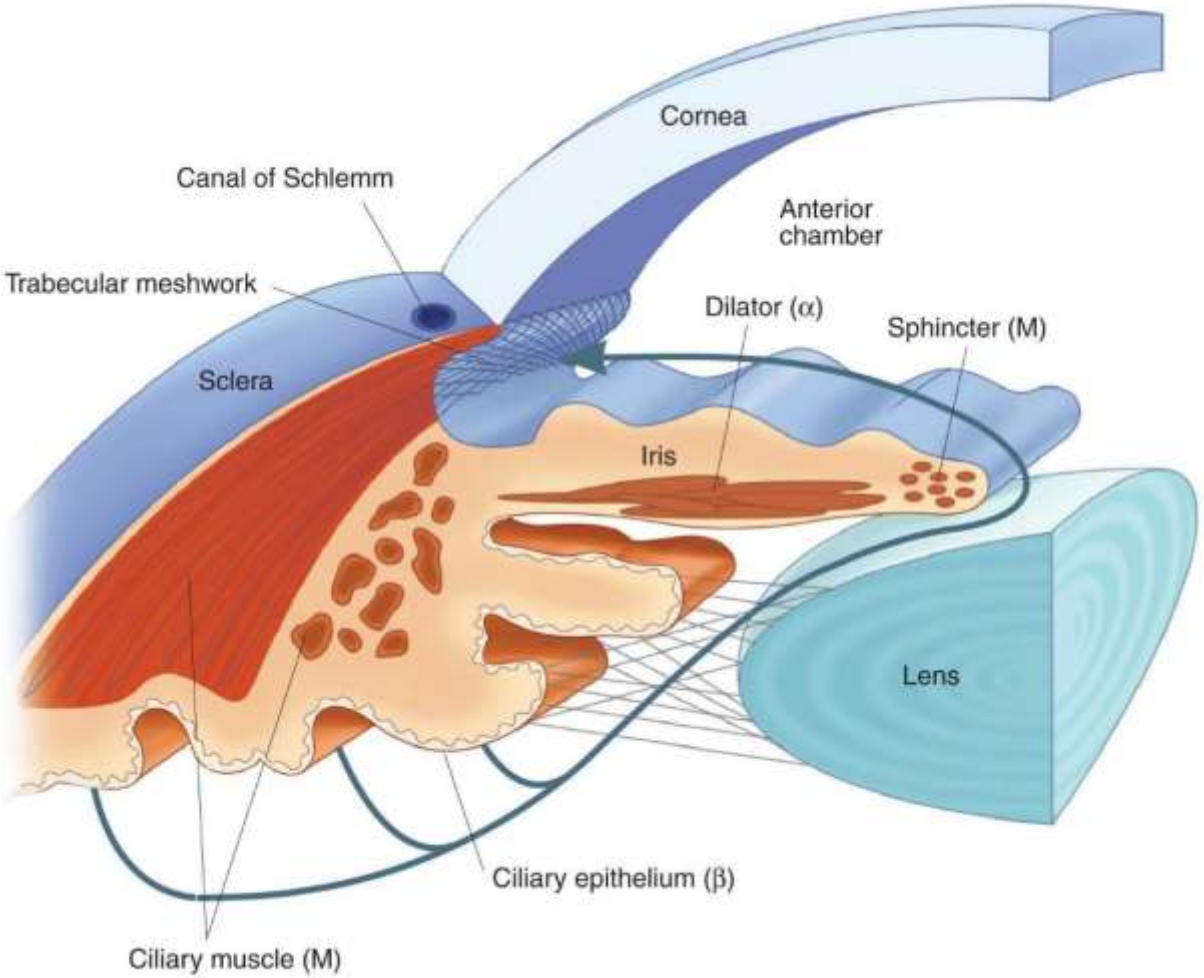
but see homeostatic reflexes

N

CNS
brain: M>N / spinal cord: N>M
M knockout – cognition / appetite
see nicotine CNS effects

ganglia
simultaneous discharge of PNS and SNS

neuromuscular junction
initial contraction→depolarization blockade



cholinomimetics
α agonists
β blockers
prostaglandin F2α analogs
diuretics

+

prostaglandin E2
marijuana

Nicotine (PK)

- lipid soluble natural alkaloid
  - tobacco / insecticides
- skin absorption / CNS penetration
  - limited absorption from the stomach (base!)
- metabolism
  - primarily liver (cotinine)
  - slow hydrolysis in synapse (see depolarization block)
- excretion
  - kidney (metabolites too)
- relatively short half-life (≈ 2 hours)

Nicotine (PD)

- agonist at N ACh receptors ($N_N > N_M$)
- brain, ganglia, nm junction
  - brain: transmitter release modulation
    - mesolimbic dopamin ↑ → addiction, ↑ alertness
    - high cc: tremor, emesis, respiratory center ↑ → convulsions, coma, death
  - ganglia
    - parasympathetic and sympathetic
    - CV effects: hypertension, alternating tachy- and bradycardia
    - GI/urinary: nausea, vomiting, diarrhea, voiding of urine
  - nm junction
    - disorganized **fasciculations** → strong contraction
    - depolarization blockade

Nicotine toxicity 1.

- acute
  - lethal dose ≈ 40 mg (1 drop / 2 cigarettes)
  - effects
    - vomiting – limit oral absorption, nausea, diarrhea
    - CNS: convulsions, coma, respiratory arrest
    - muscle: depol. blockade, respiratory paralysis
    - CV: hypertension, cardiac arrhythmias
  - treatment
    - **symptomatic**
    - atropin / diazepam
    - urinary excretion ↓ in alkaline urine

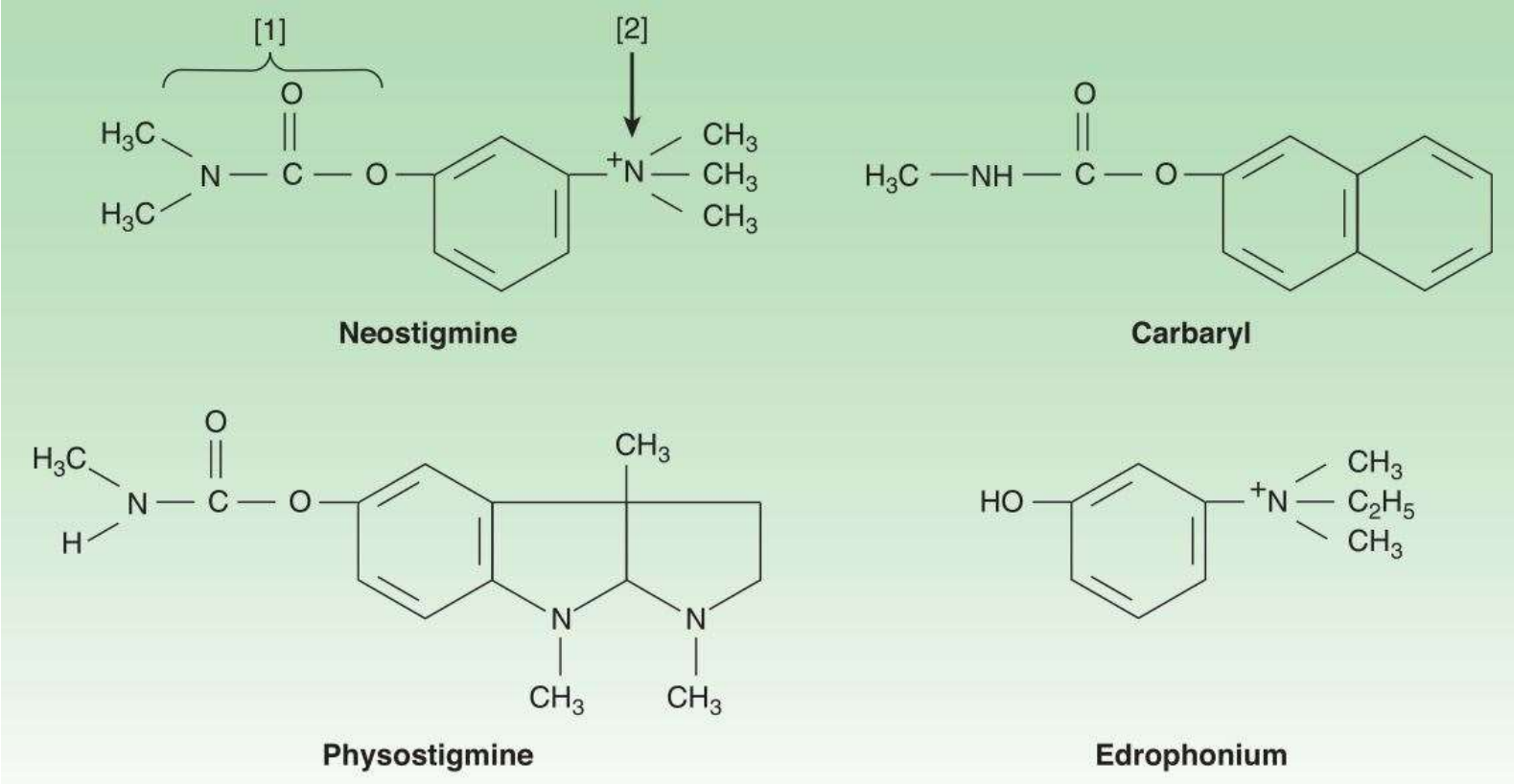
Nicotine toxicity 2.

- chronic
  - "cigarette smoking is clearly the largest single preventable cause of illness and premature death"
    - but delayed onset of diseases
  - nicotine's role in
    - addiction +
    - other diseases ? (vascular disease, sudden coronary death, peptic ulcer)
  - therapy (smoking cessation)
    - nicotine replacement therapy
    - varenicline (agonist at α4β2)
    - bupropion

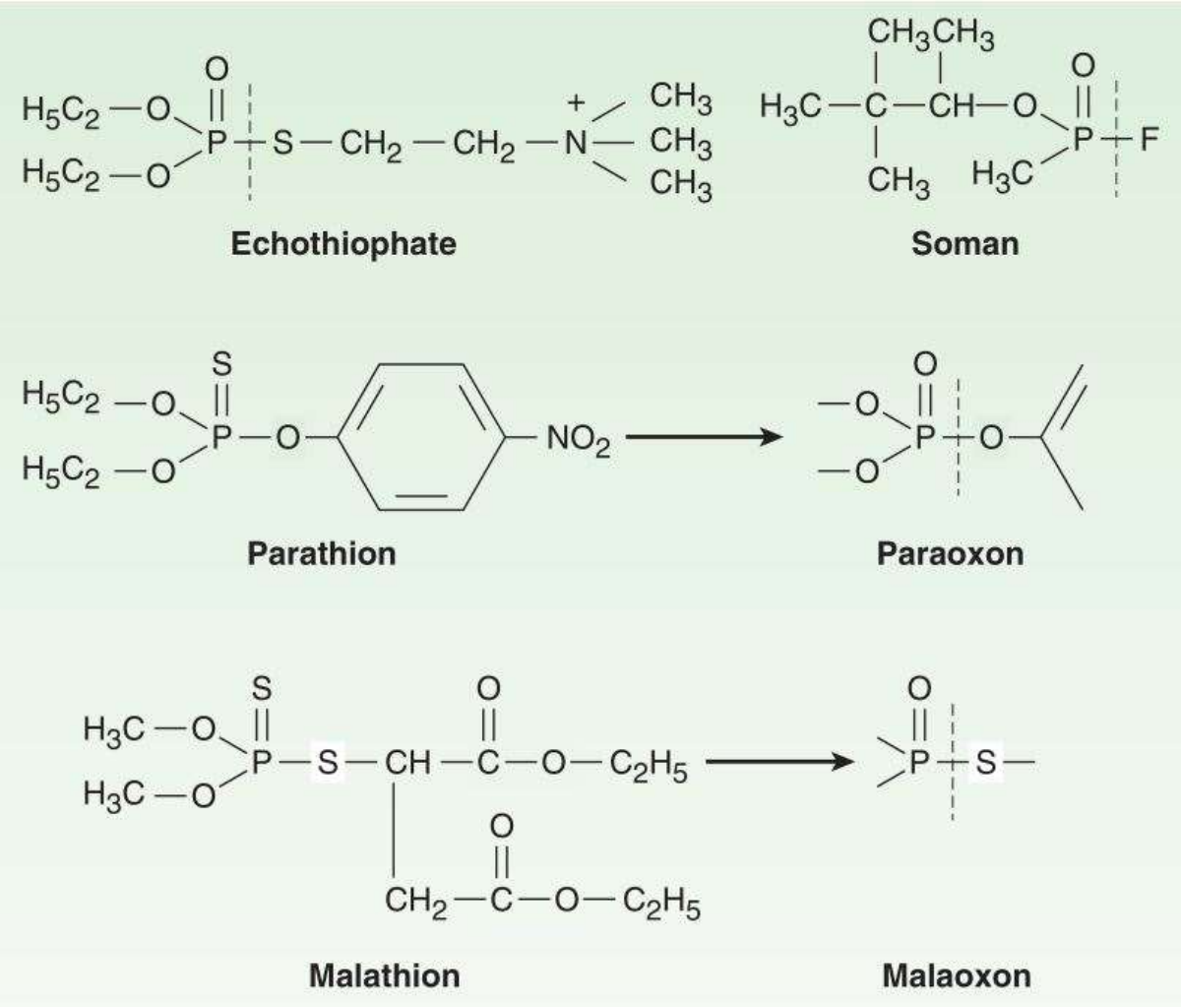
Indirectly acting cholinomimetics

- Reversible
  - edrophonium
  - carbamates
    - neostigmine / pyridostigmine / physostigmine
  - used in Alzheimer's disease
    - tacrine, donepezil, galantamine, rivastigmine
- Irreversible
  - organophosphates
    - echothiophate
    - malathion, parathion
    - sarin

Reversible indirectly acting cholinomimetics



Irreversible indirectly acting cholinomimetics



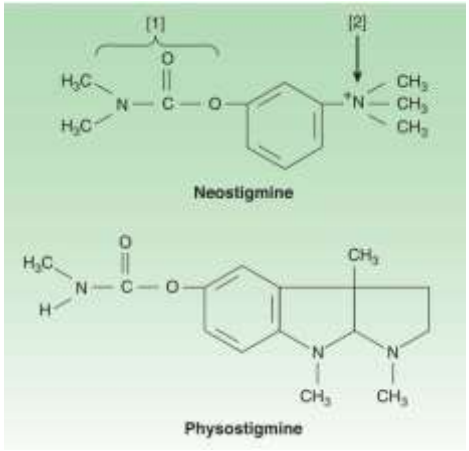
Edrophonium

- short duration of action
- myasthenia gravis diagnosis

Edrophonium

Carbamates

- neostigmine, pyridostigmine, physostigmine
- clinical use
  - myasthenia gravis treatment
  - glaucoma
  - postoperative ileus / urinary retention



Organophosphates

- insecticids
  - malathion / parathion
- chemical warfares
  - sarin / tabun / soman
- was used in glaucoma
  - echothiophate
- lipid solubility
- aging
- delayed neuropathy + demyelination of axons

Indirect-acting cholinomimetics for Alzheimer's disease

- tacrine, **donepezil, rivastigmine, galantamine**
- oral, penetrate BBB
- modest clinical benefit
- adverse effects
  - nausea and vomiting + peripheral cholinomimetic effects

Clinical use of major cholinomimetics

Drug	Clinical Applications	Action
Direct-acting agonists		
Bethanechol	Postoperative and neurogenic ileus and urinary retention	Activates bowel and bladder smooth muscle
Carbachol	Glaucoma[a]	Activates pupillary sphincter and ciliary muscles of eye
Pilocarpine	Glaucoma,[a] Sjögren's syndrome	Activates pupillary sphincter and ciliary muscles of eye; stimulates salivation
Nicotine	Smoking deterrence (patch, chewing gum)	Replaces rapid-onset actions (cigarette) with slower action
ndirect-acting agonists		
Neostigmine	Postoperative and neurogenic ileus and urinary retention	Amplifies endogenous acetylcholine
Neostigmine, pyridostigmine, edrophonium	Myasthenia gravis, reversal of neuromuscular blockade	Amplifies endogenous acetylcholine; ↑ strengt
Physostigmine, echothiophate	Glaucoma[a]	Amplifies effects of ACh

cevimeline – Sjögren's syndrome
varenicline – smoking cessation