Topic 10 Drugs of the Nervous System

Ch 19,20 Patrick

Part VI- Nervous system -Corey

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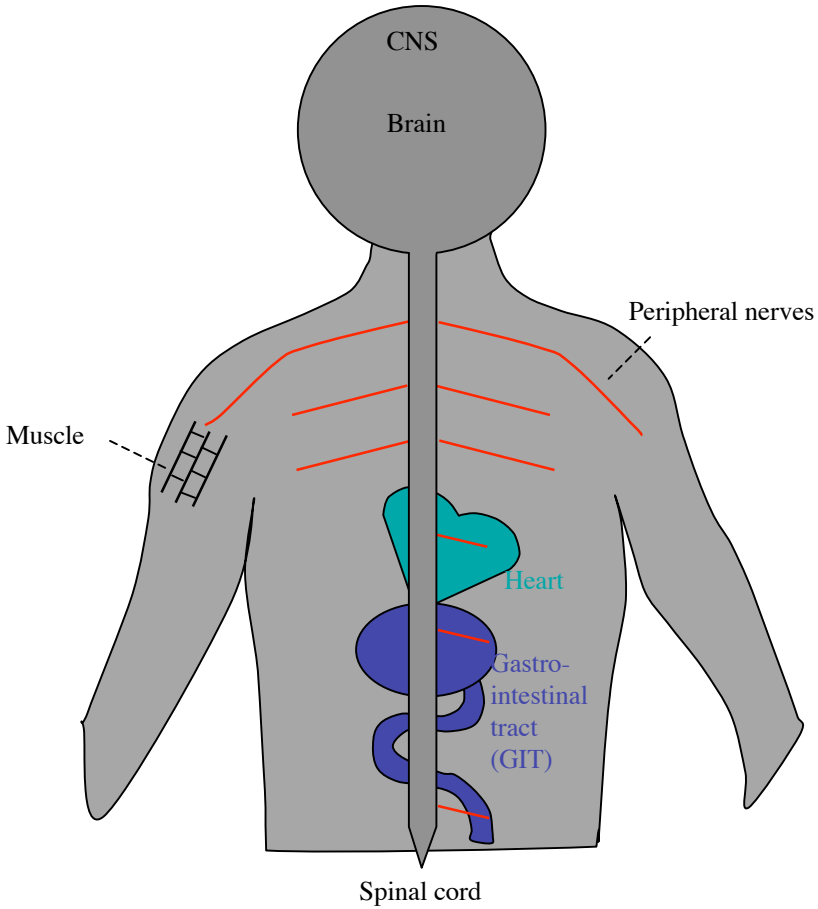
CHOLINERGIC NERVOUS SYSTEM

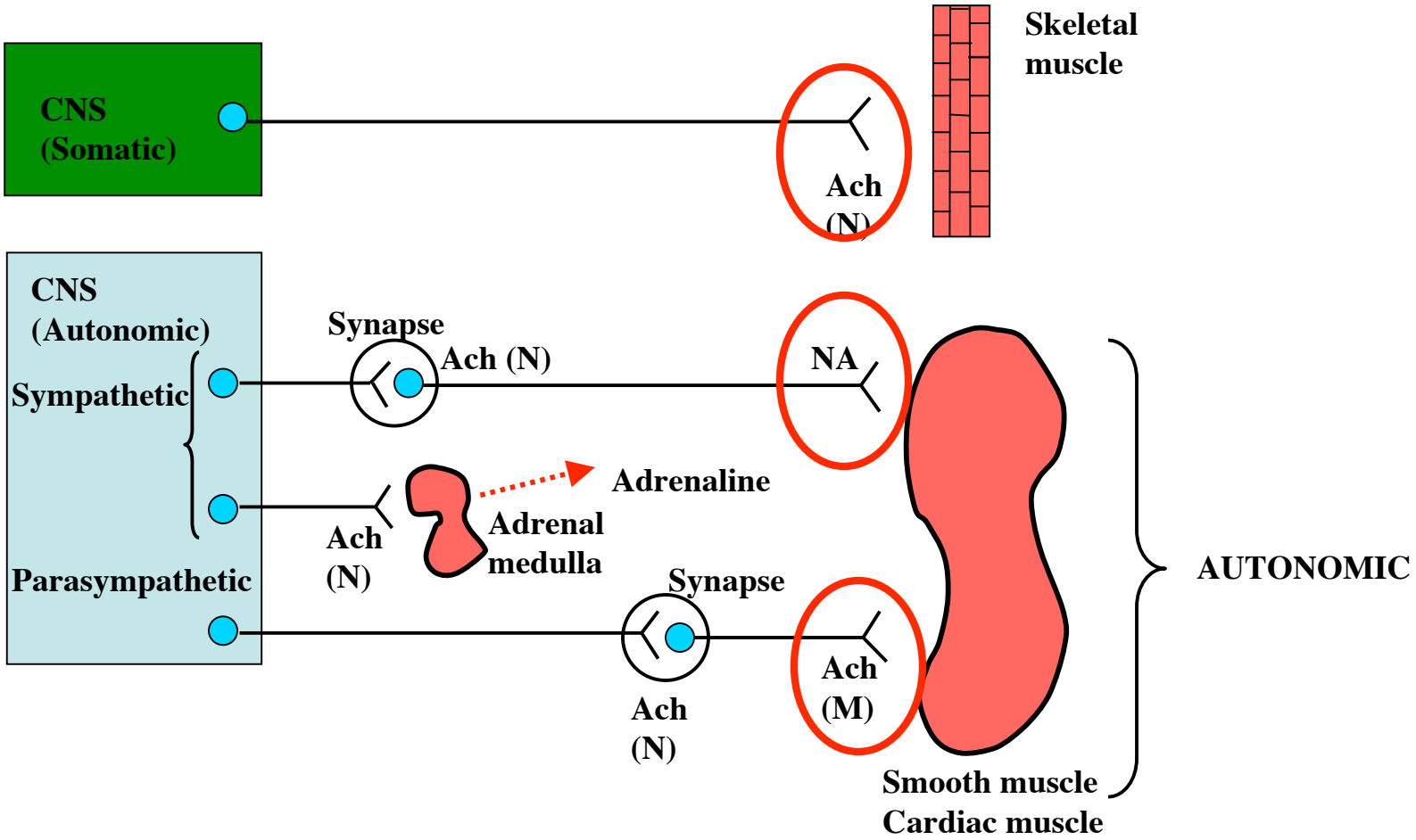
1. Nerve Transmission

Peripheral nervous system



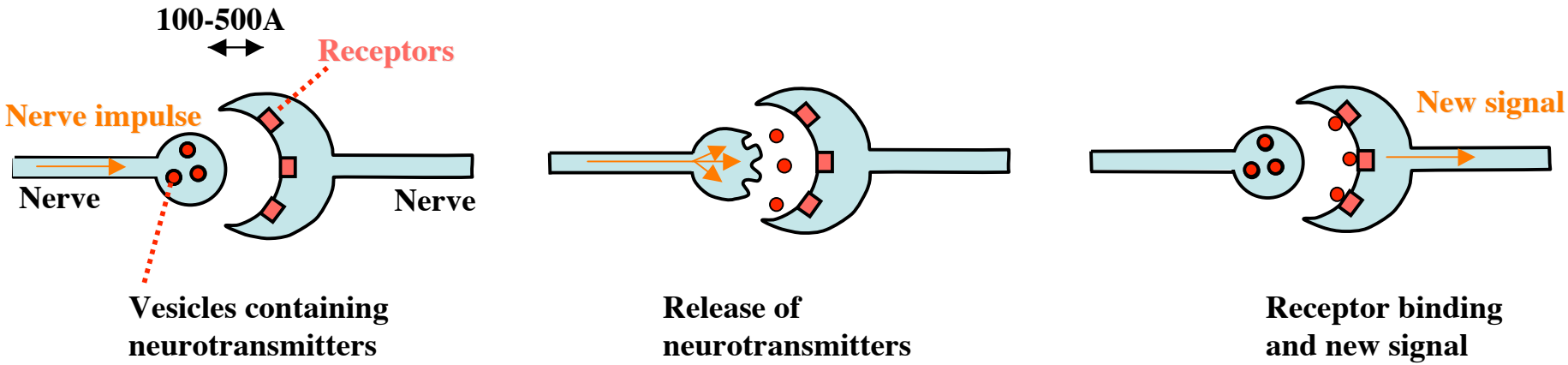
1. Nerve Transmission

Peripheral nervous system



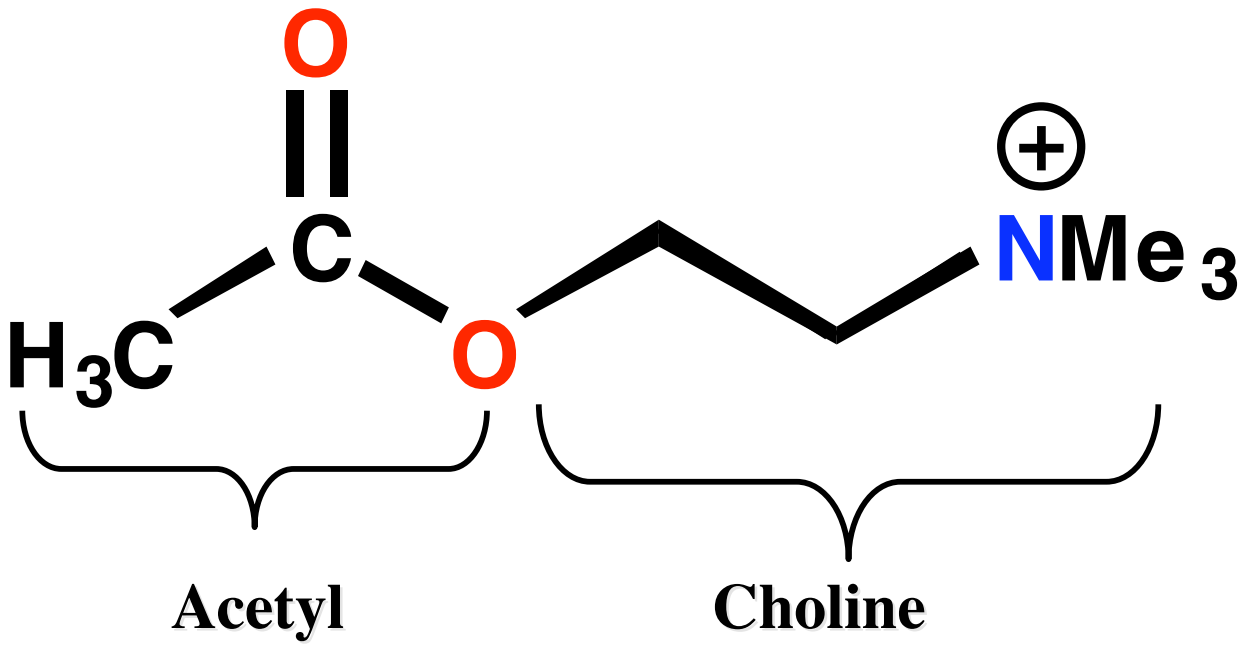
1. Nerve Transmission

Synapses



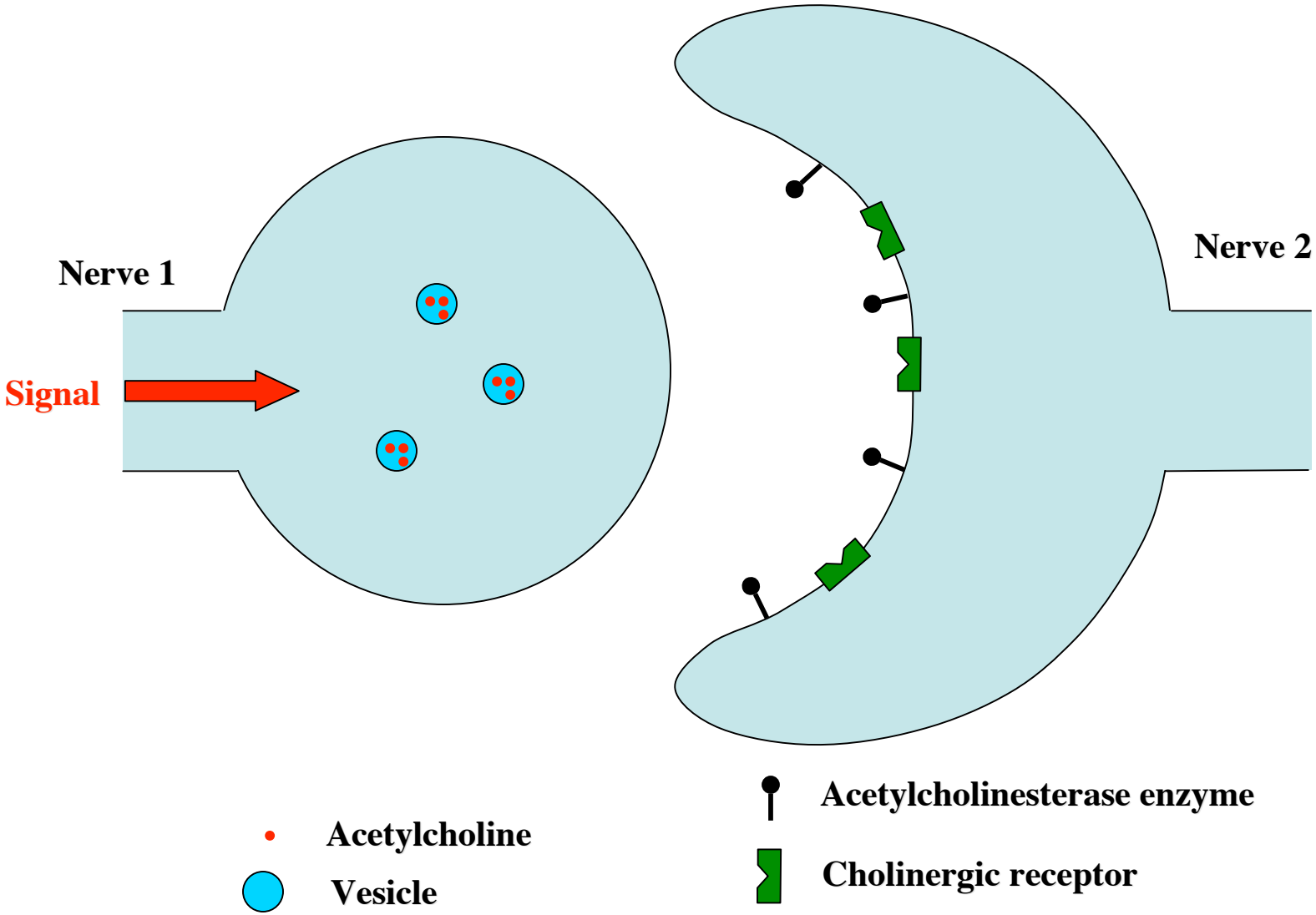
2. Neurotransmitter

Acetylcholine (Ach)



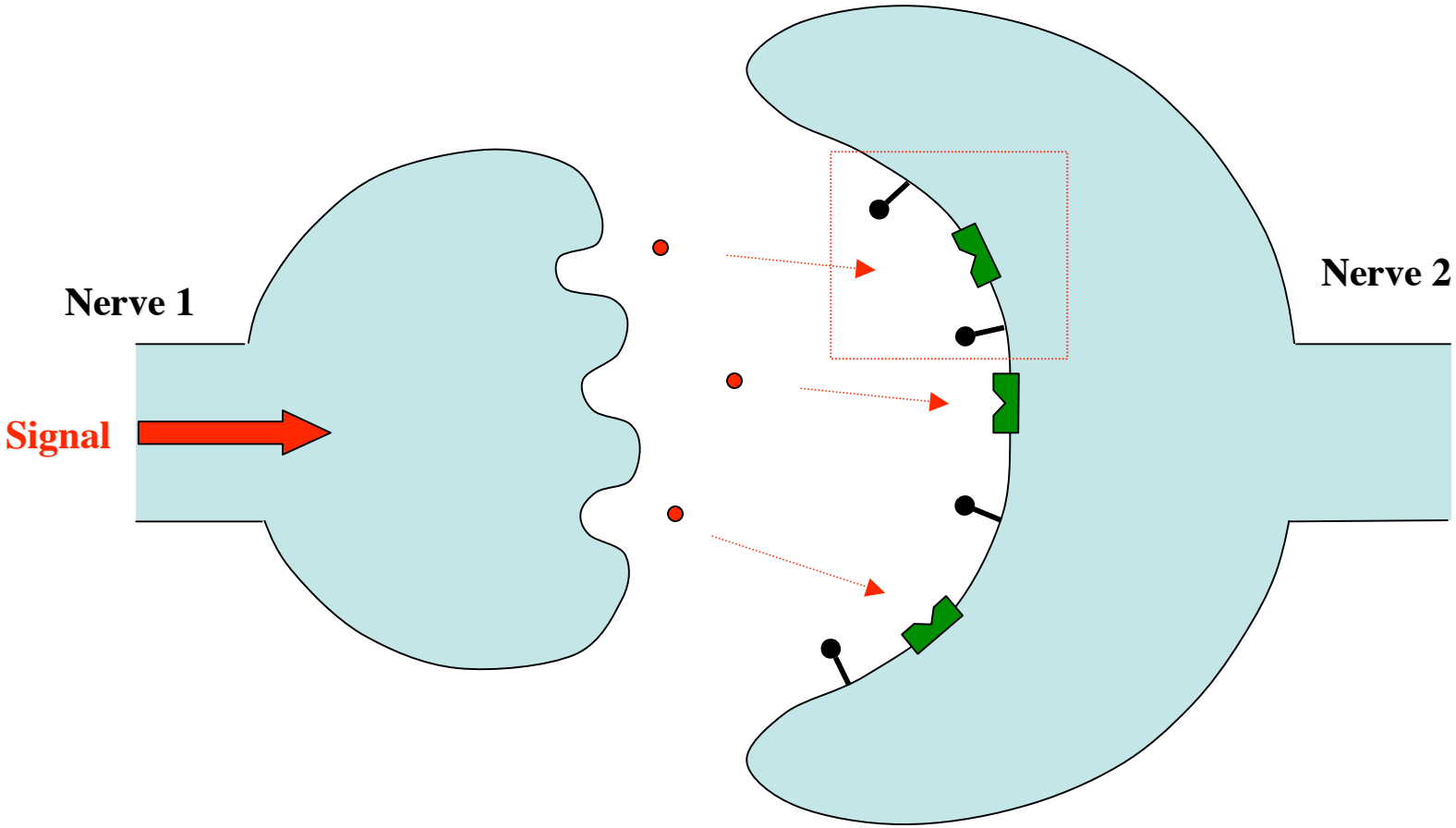
3. Transmission process

Signal in nerve 1

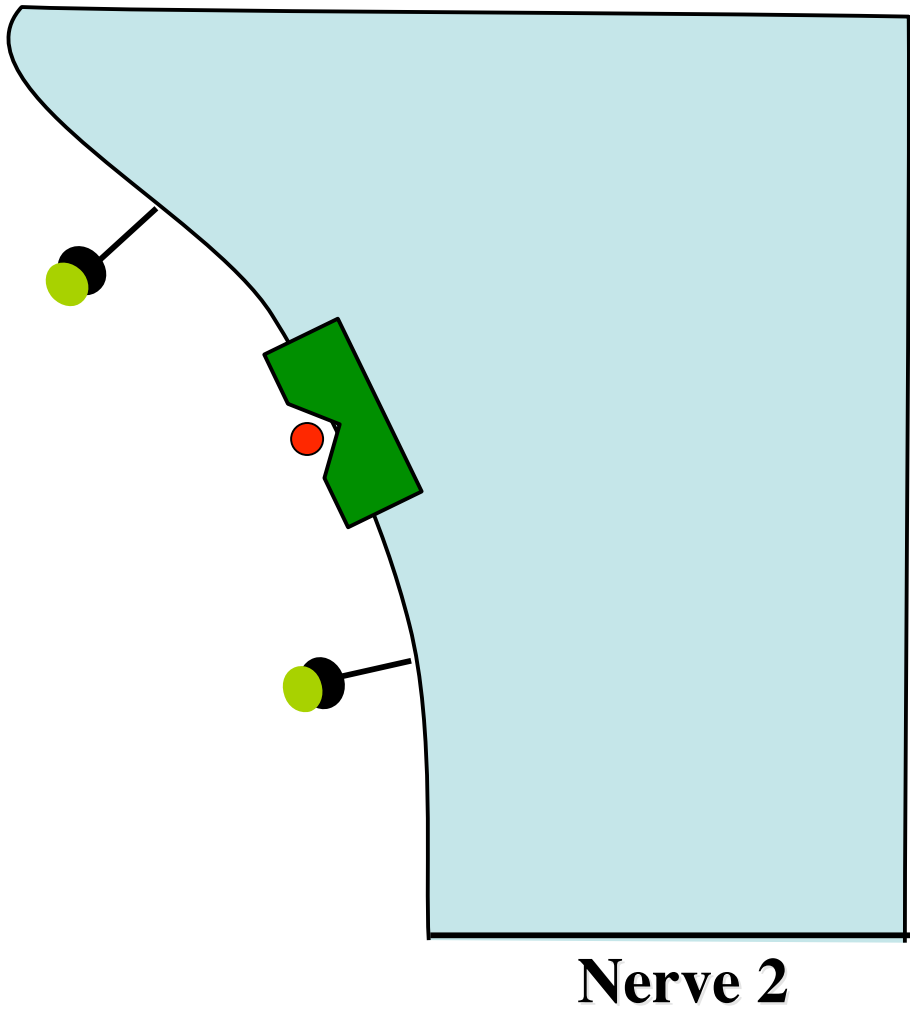


3. Transmission process

Vesicles fuse with membrane and release Ach

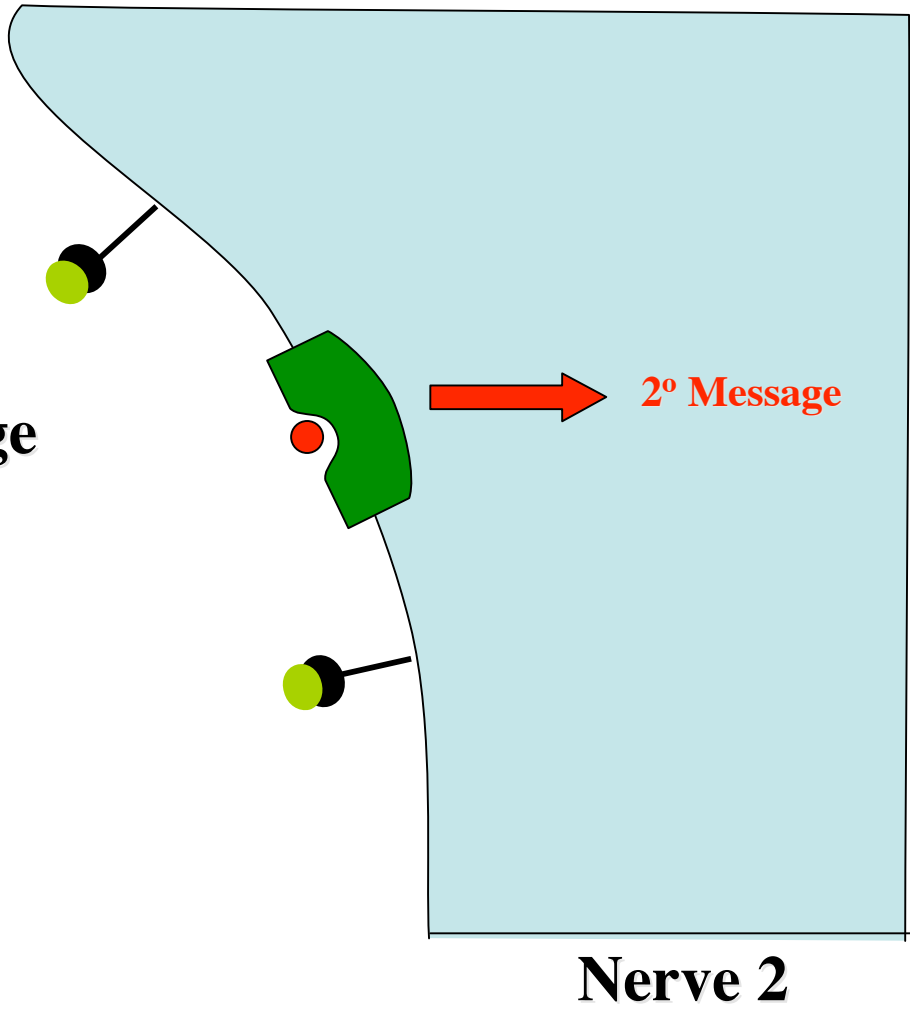


3. Transmission process



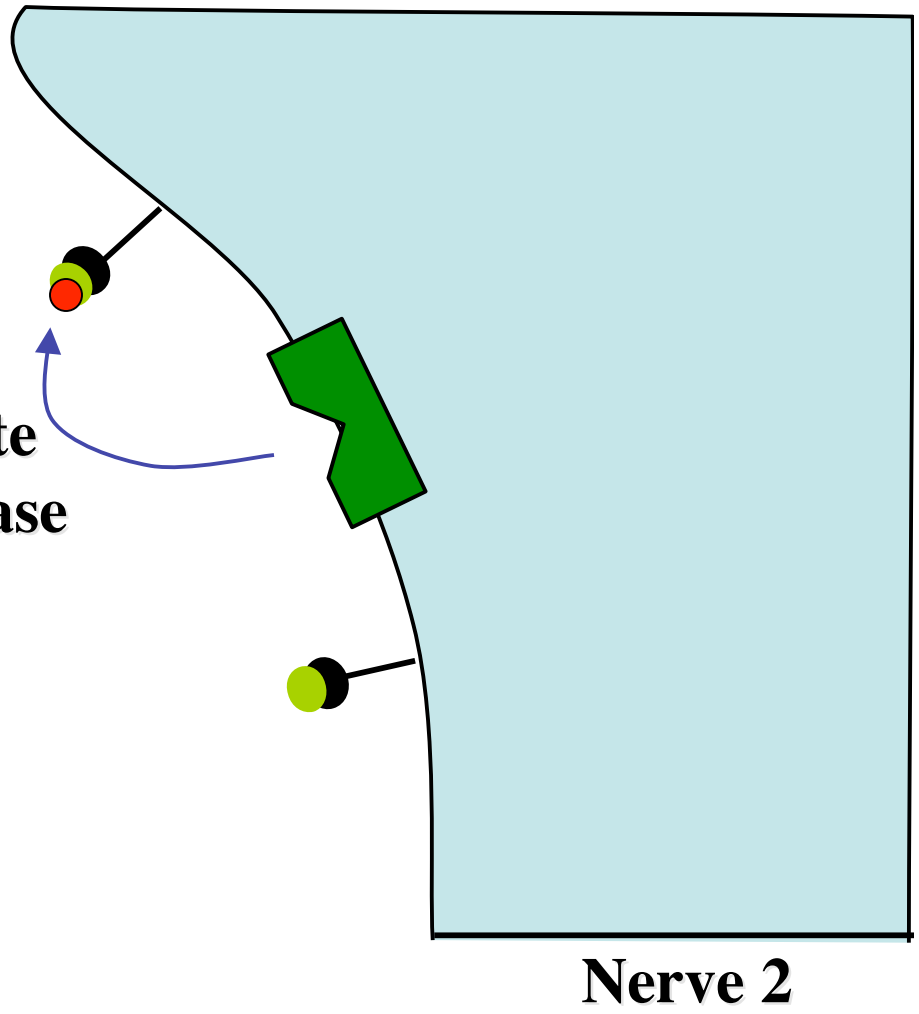
3. Transmission process

- Receptor binds Ach
- Induced fit triggers 2º message
- Triggers firing of nerve 2
- Ach undergoes no reaction



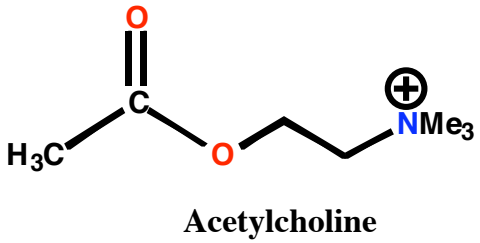
3. Transmission process

- Ach departs receptor
- Receptor reverts to resting state
- Ach binds to acetylcholinesterase

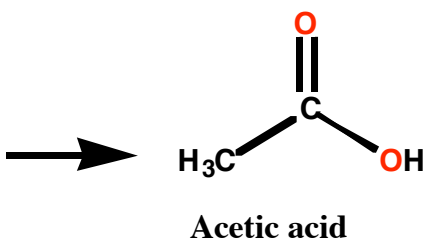


3. Transmission process

Ach hydrolysed
by acetylcholinesterase

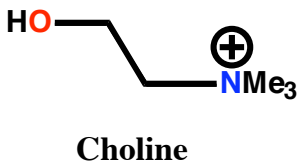


Acetylcholine

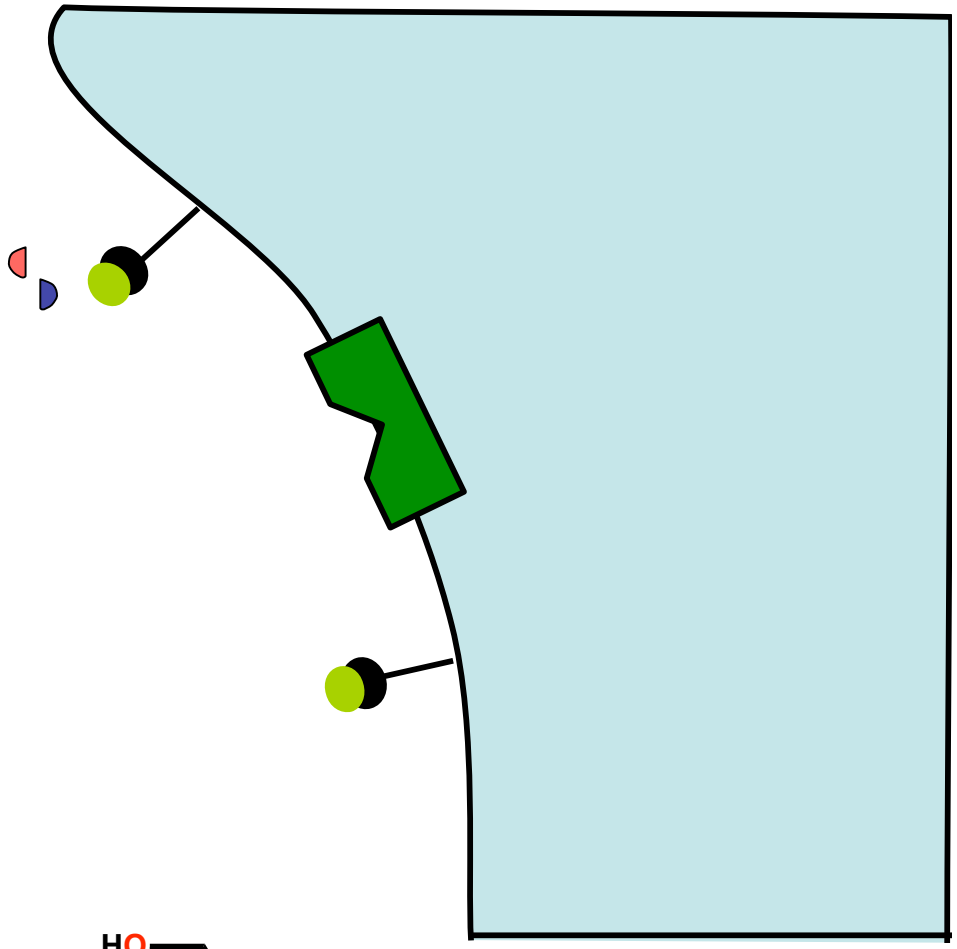


Acetic acid

+

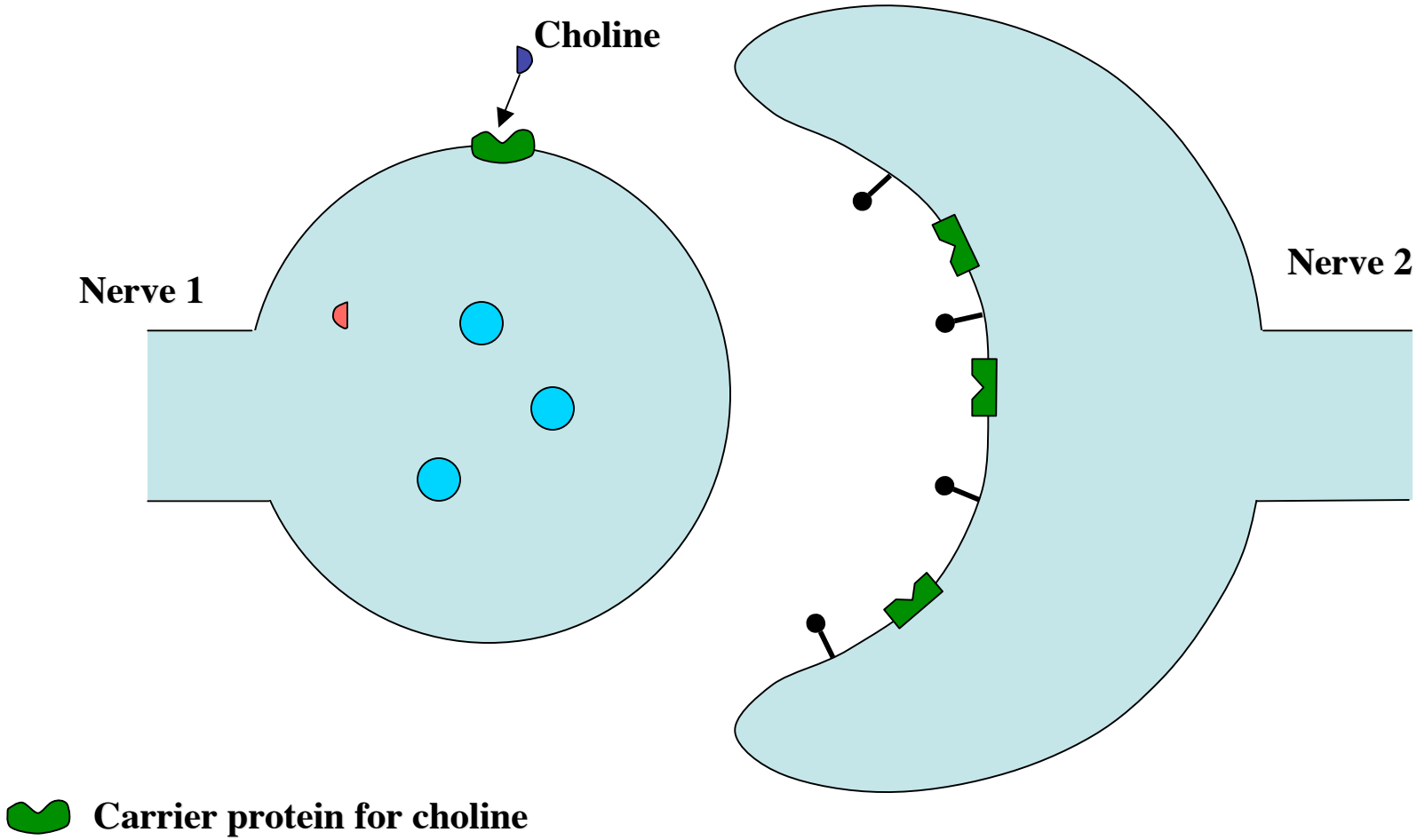


Choline



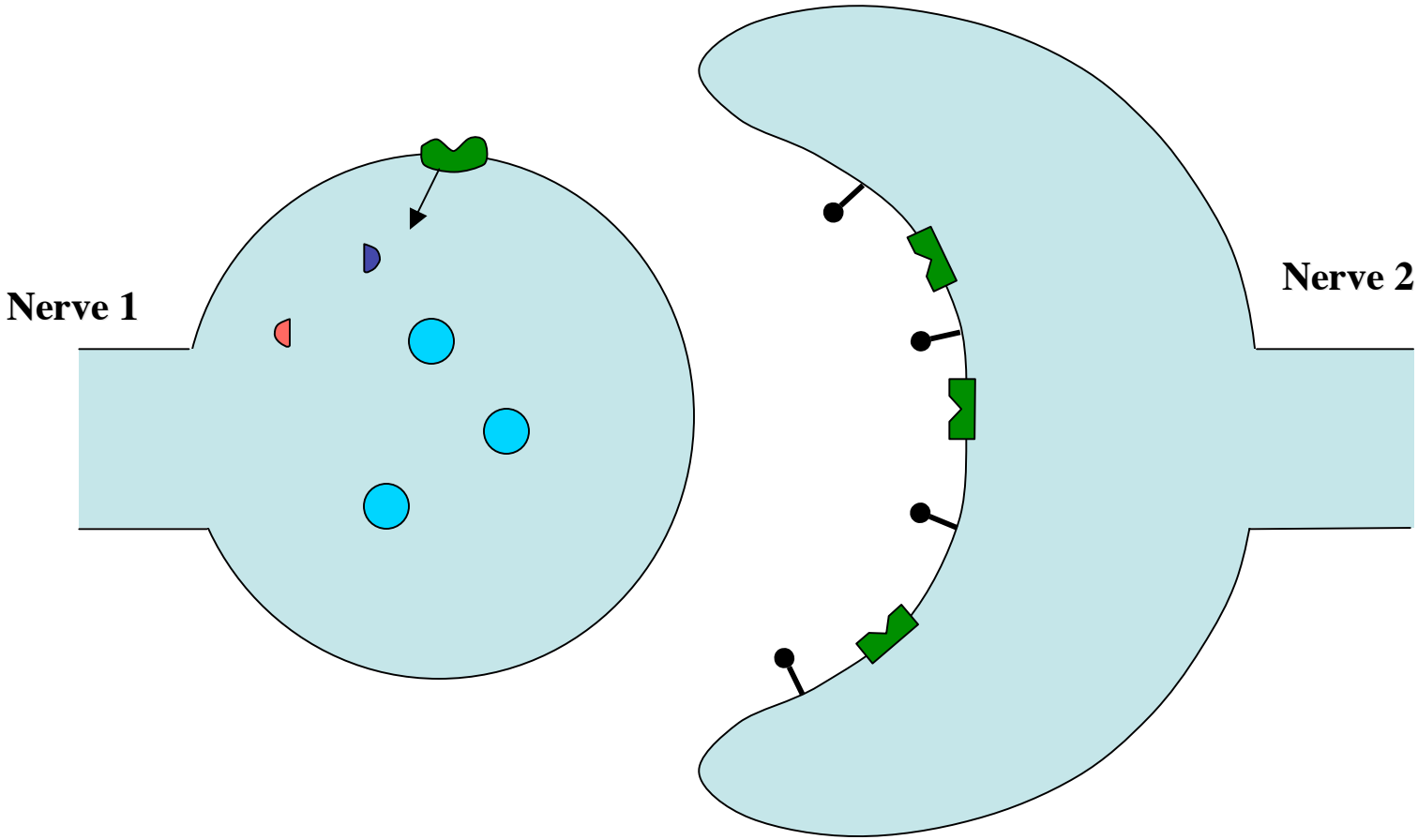
3. Transmission process

Choline binds to carrier protein



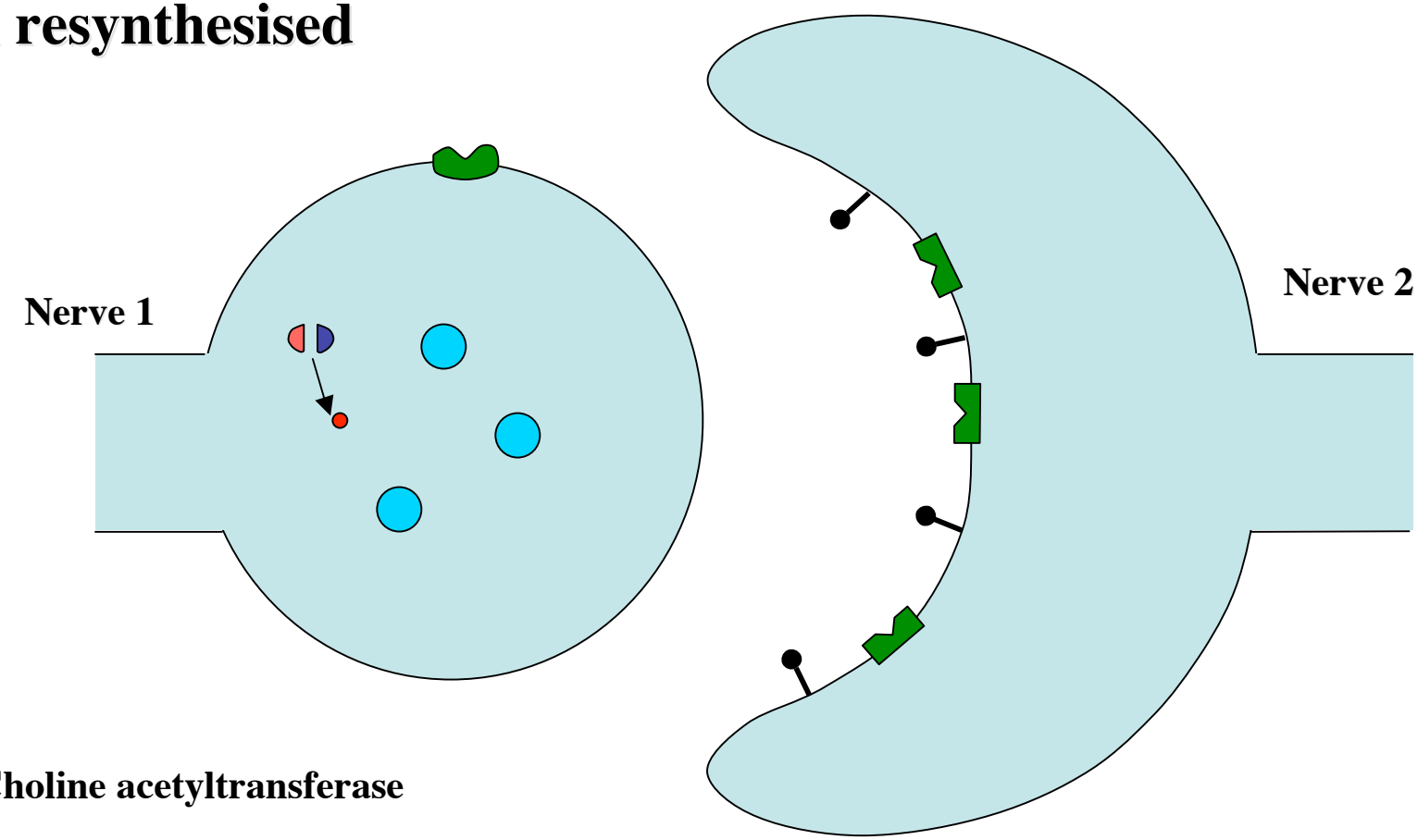
3. Transmission process

Choline transported into nerve

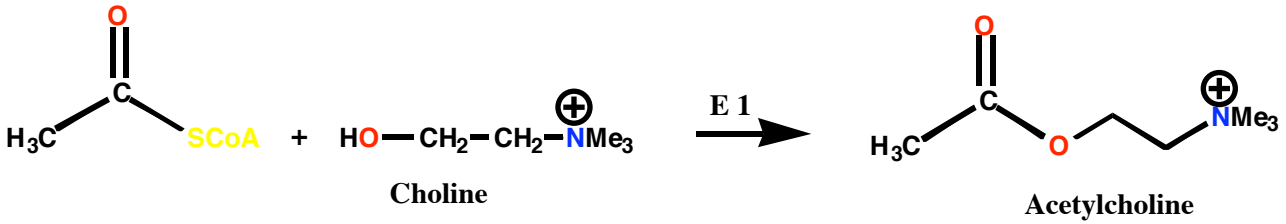


3. Transmission process

Ach resynthesised

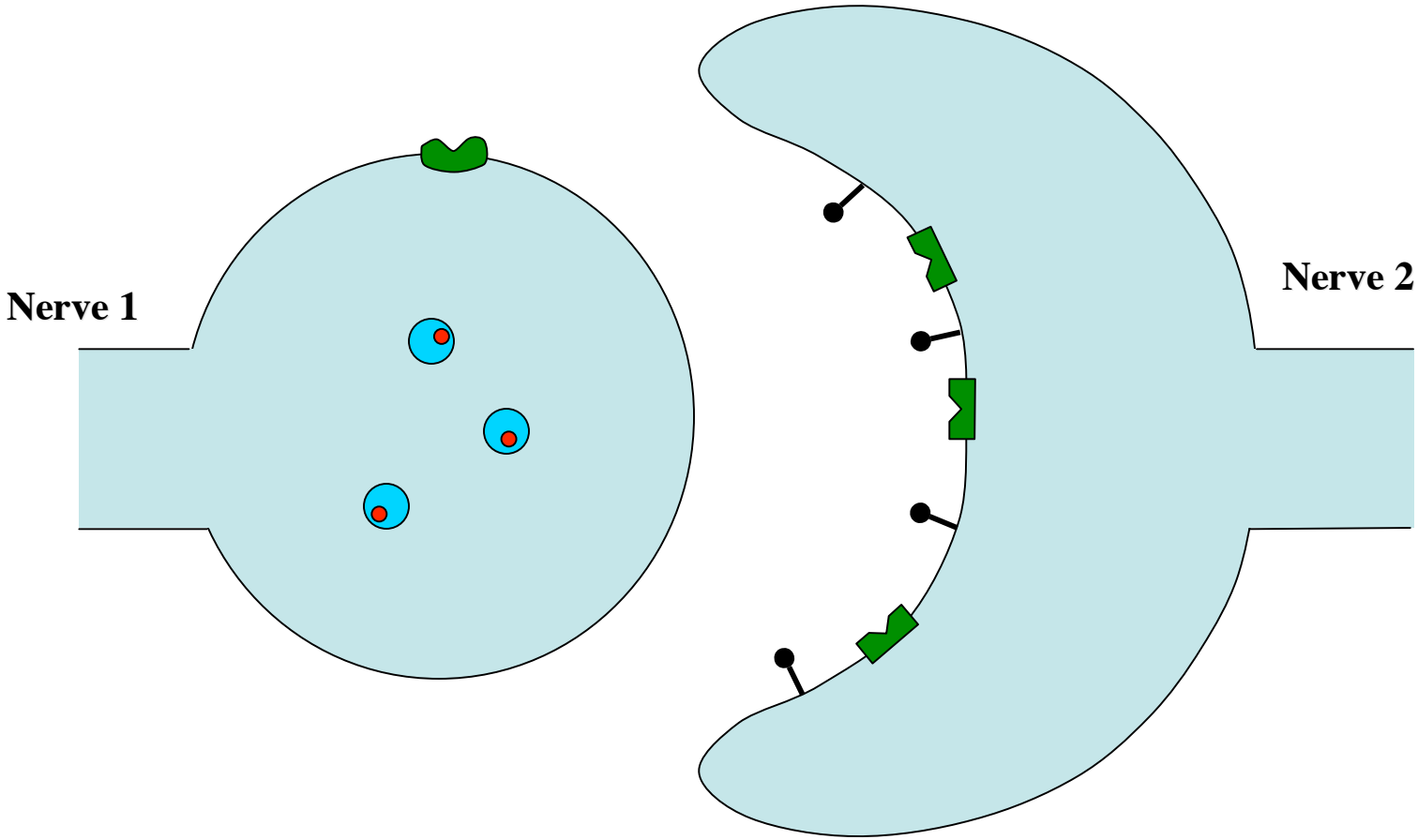


E 1 = Choline acetyltransferase



3. Transmission process

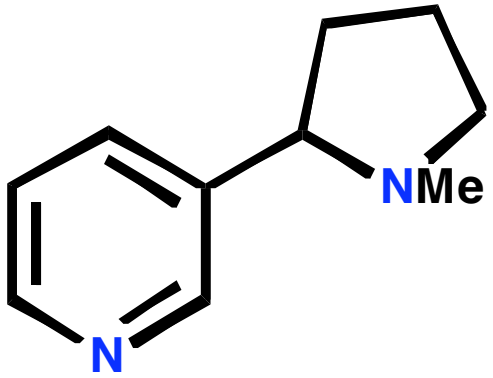
Ach repackaged in vesicles



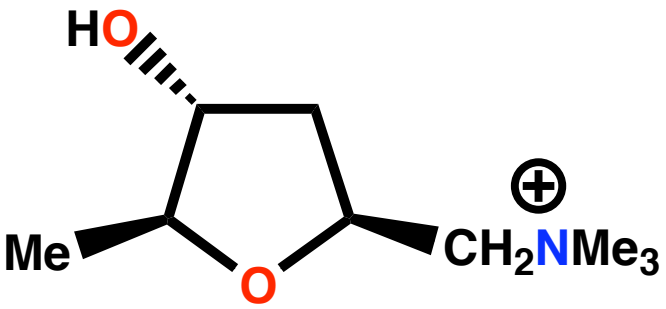
4. Cholinergic receptors

Receptor types

- Not all cholinergic receptors are identical
- Two types of cholinergic receptor - nicotinic and muscarinic
- Named after natural products showing receptor selectivity



Nicotine



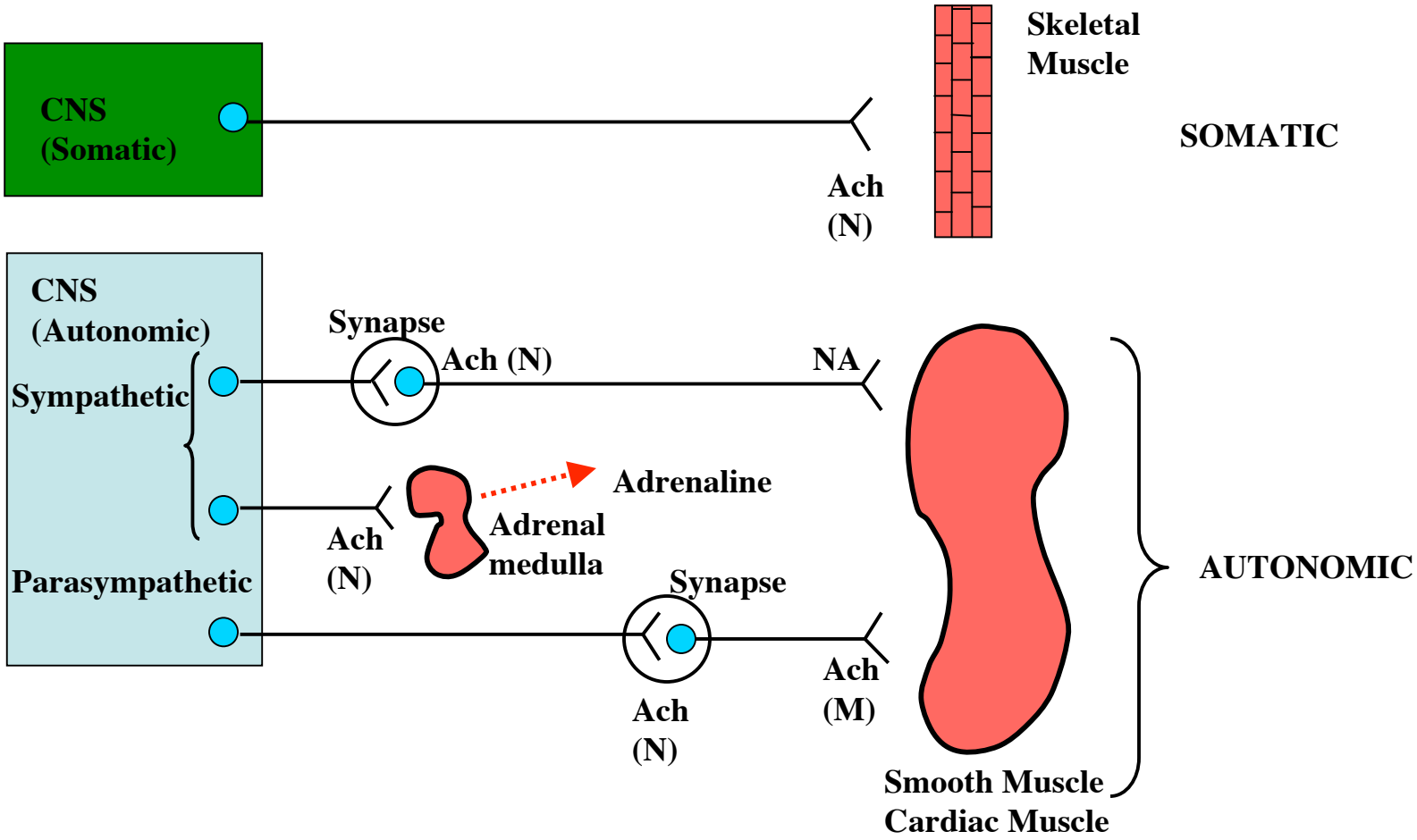
L-(+)-Muscarine

Activates cholinergic receptors at nerve synapses and on skeletal muscle

Activates cholinergic receptors on smooth muscle and cardiac muscle

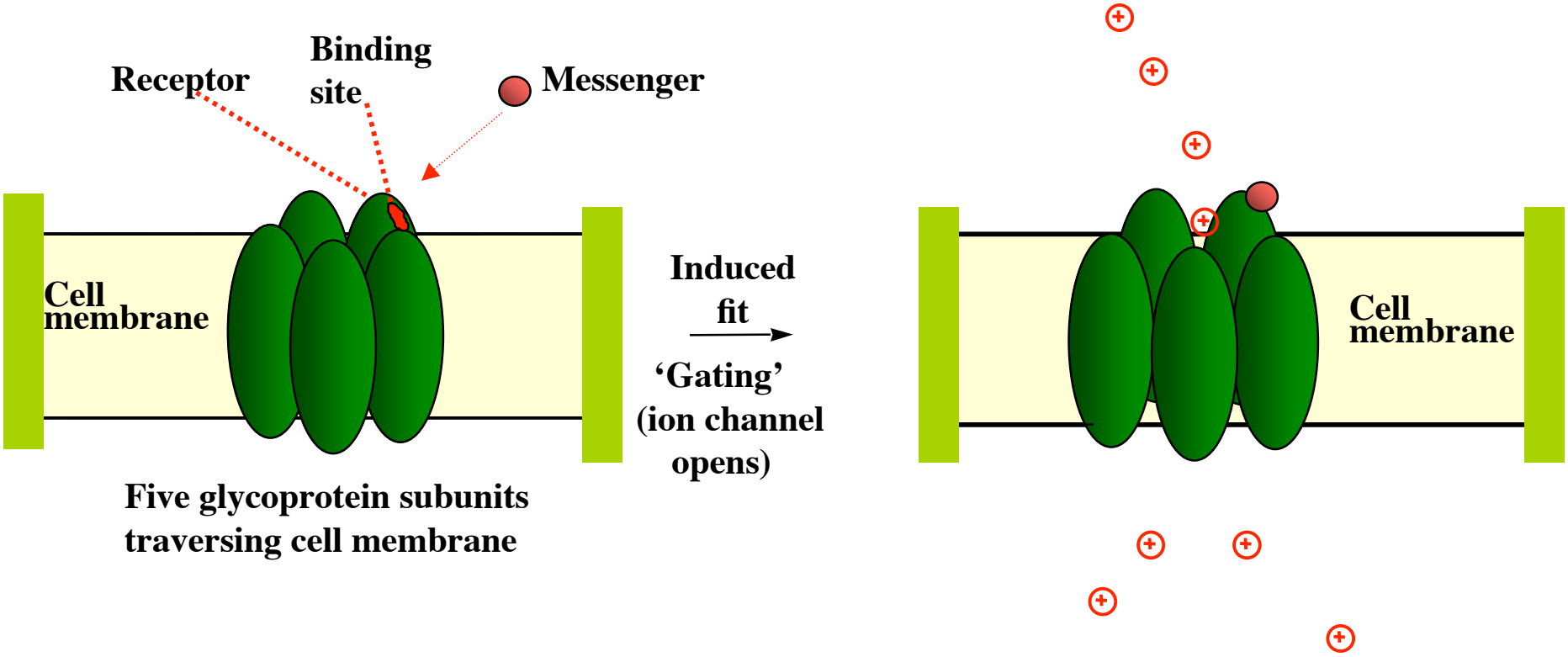
Acetylcholine is natural messenger for both receptor types

Peripheral nervous system



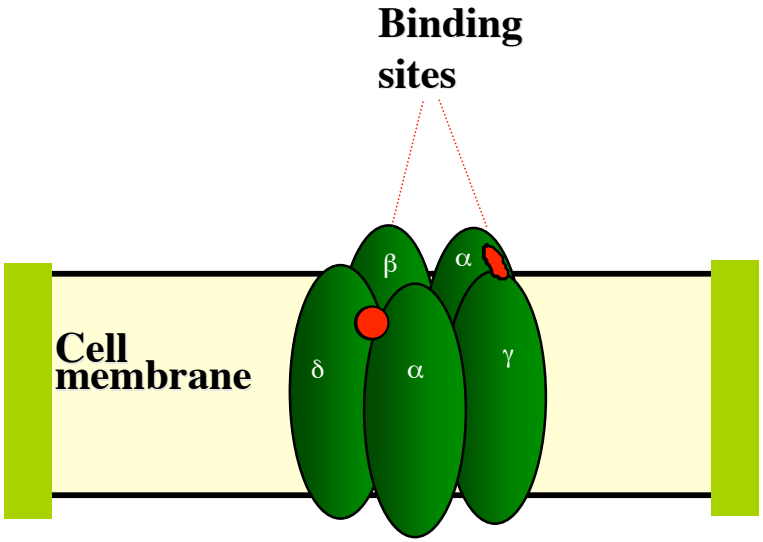
4.1 Nicotinic receptor

Control of Cationic Ion Channel:

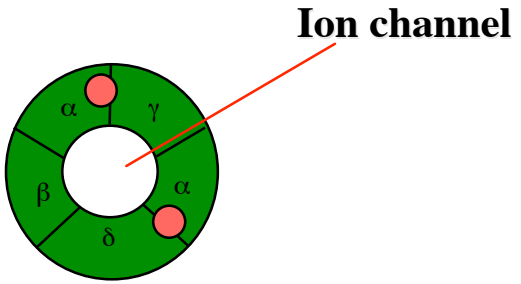


4.1 Nicotinic receptor

The binding sites



2xα, β, γ, δ subunits

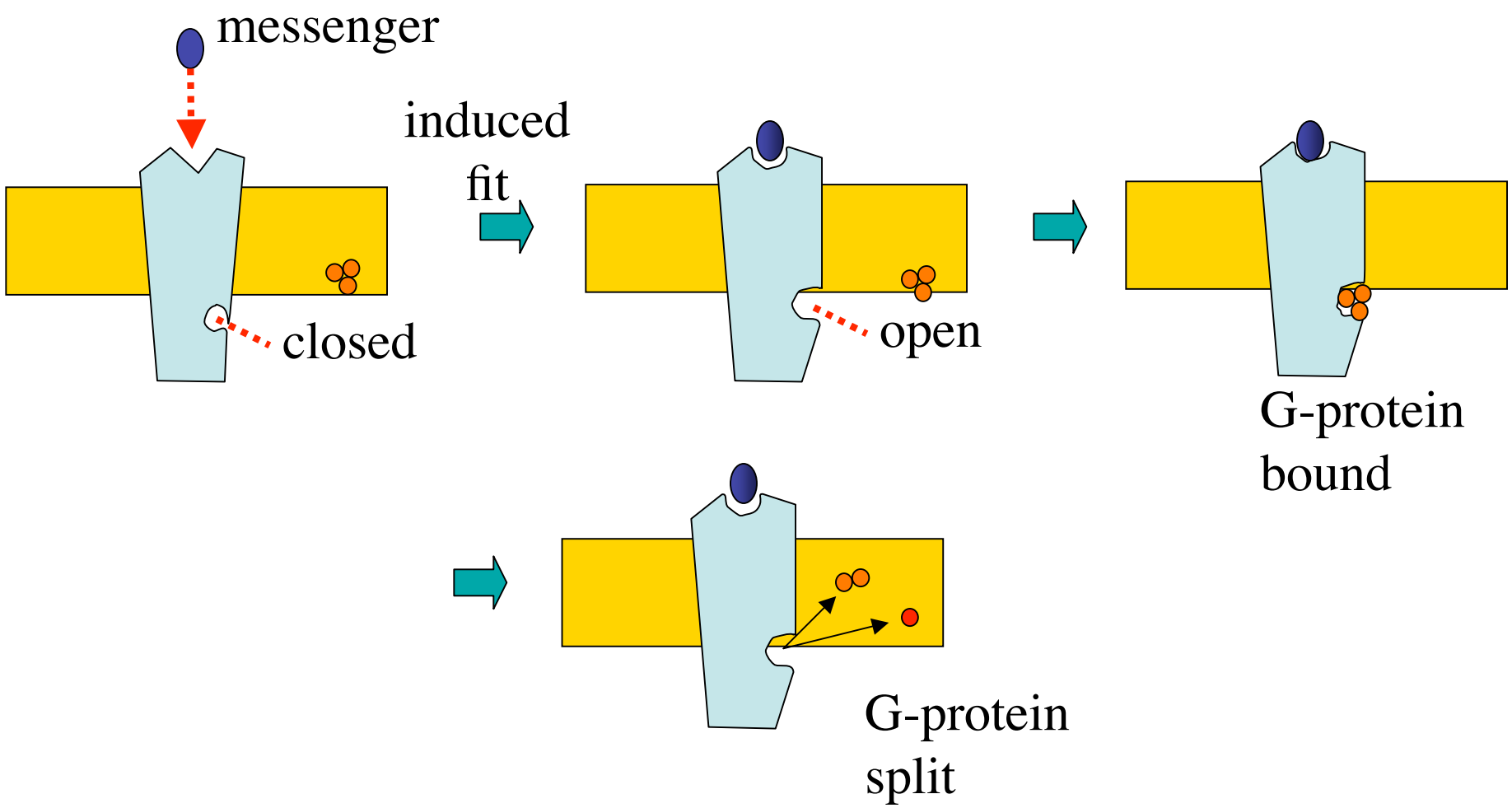


Two ligand binding sites mainly on α-subunits

4.2 Muscarinic receptor - G Protein coupled receptor

Activation of a signal protein

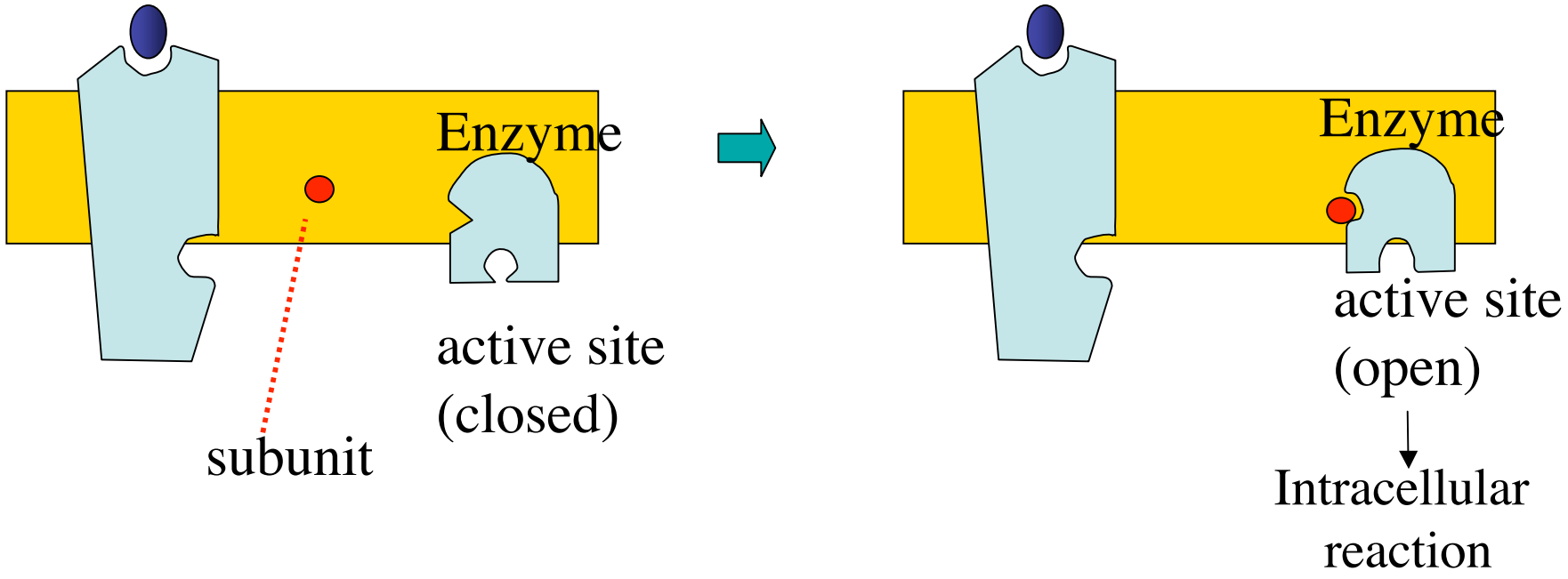
- **Receptor binds messenger leading to an induced fit**
- **Opens a binding site for a signal protein (G-protein)**



4.2 Muscarinic receptor - G Protein coupled receptor

Activation of membrane bound enzyme

- **G-Protein is split and subunit activates a membrane bound enzyme**
- **Subunit binds to an allosteric binding site on enzyme**
- **Induced fit results in opening of an active site**
- **Intracellular reaction is catalysed**

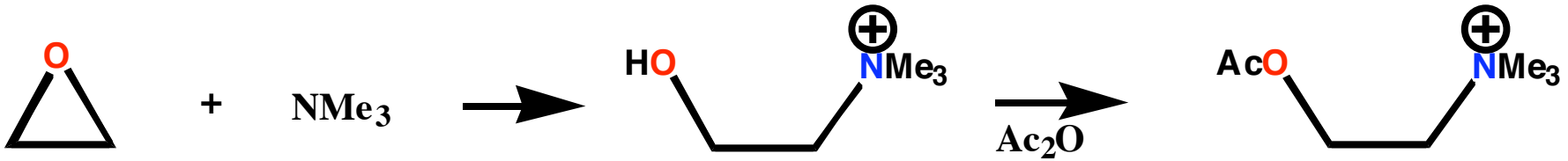


5. Cholinergic agonists

5.1 Acetylcholine as an agonist

Advantages

- Natural messenger
- Easily synthesized



Disadvantages

- Easily hydrolysed in stomach (acid catalysed hydrolysis)
- Easily hydrolysed in blood (esterases)
- No selectivity between receptor types
- No selectivity between different target organs

5. Cholinergic agonists

5.2 Nicotine and muscarine as cholinergic agonists

Advantages

- More stable than Ach
- Selective for main cholinergic receptor types
- Selective for different organs

Disadvantages

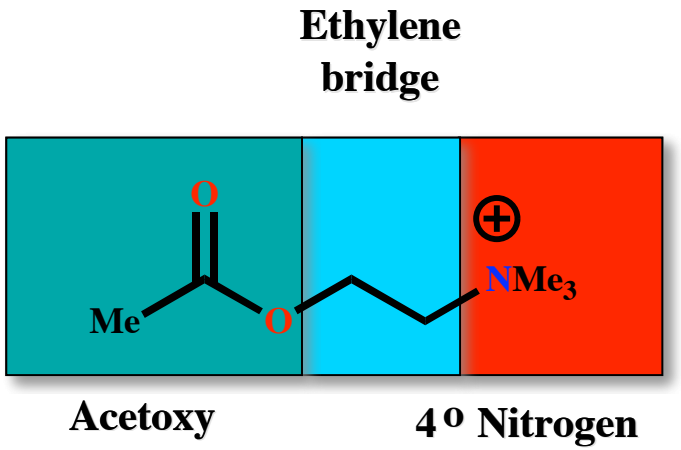
- Activate receptors for other chemical messengers
- Side effects

5. Cholinergic agonists

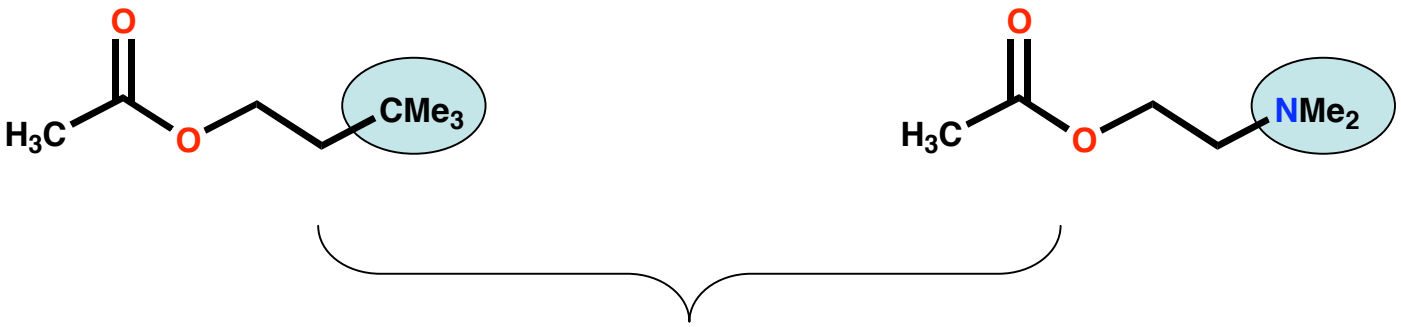
5.3 Requirements for cholinergic agonists

- **Stability to stomach acids and esterases**
- **Selectivity for cholinergic receptors**
- **Selectivity between muscarinic and nicotinic receptors**
- **Knowledge of binding site**
- **SAR for acetylcholine**

6. SAR for acetylcholine

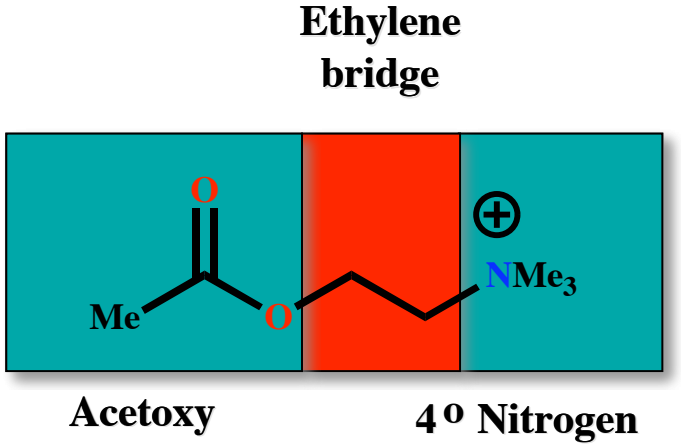


Quaternary nitrogen is essential

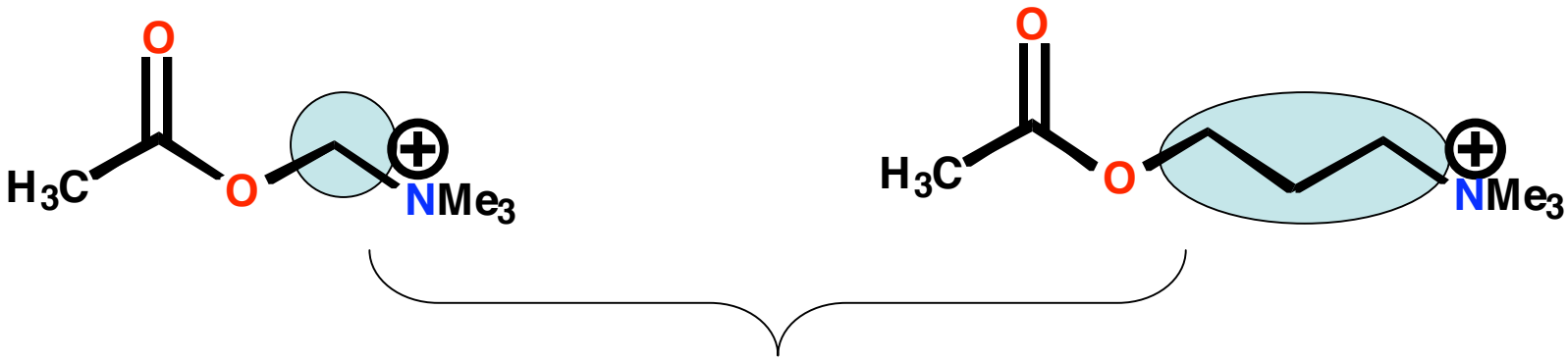


Bad for activity

6. SAR for acetylcholine

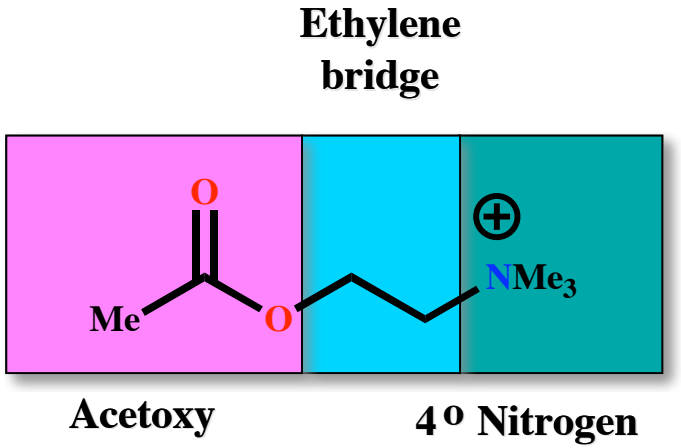


- Distance from quaternary nitrogen to ester is important
- Ethylene bridge must be retained



Bad for activity

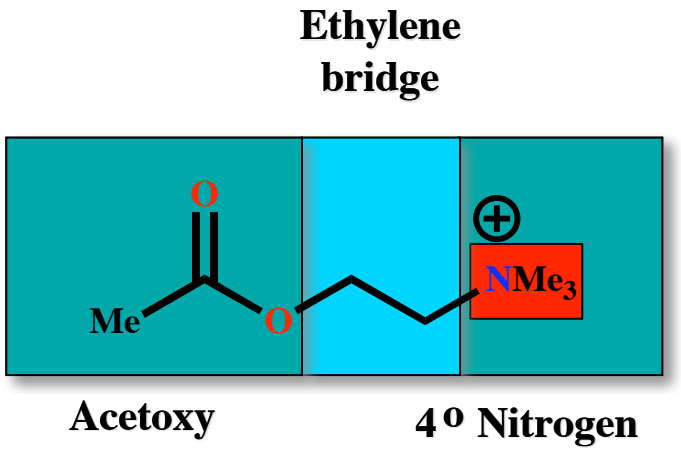
6. SAR for acetylcholine



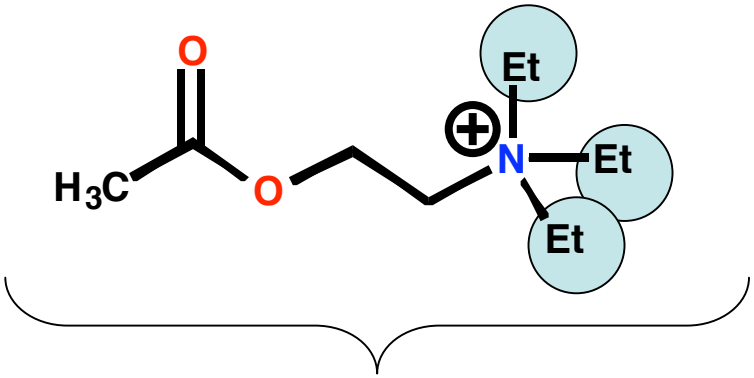
Ester is important

Bad for activity

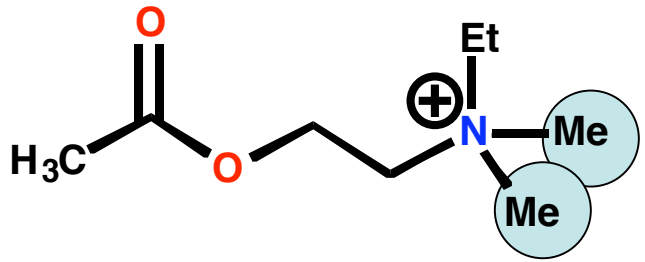
6. SAR for acetylcholine



Minimum of two methyl groups on quaternary nitrogen

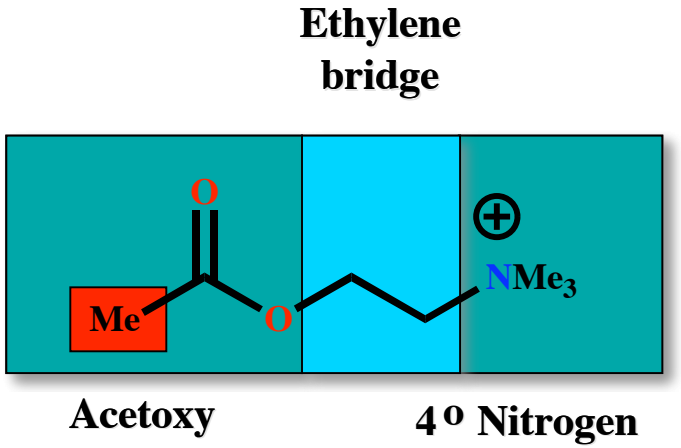


Bad for activity

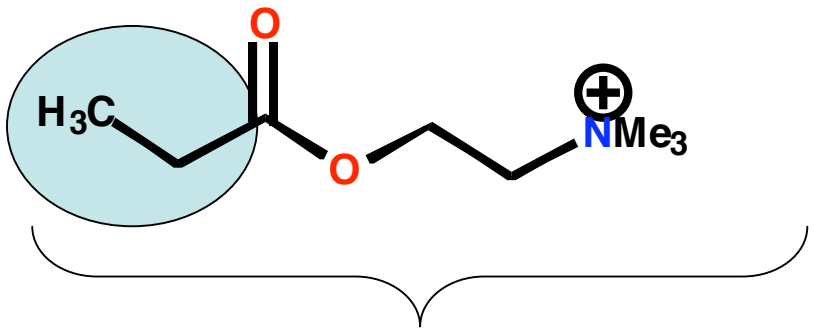


Active

6. SAR for acetylcholine

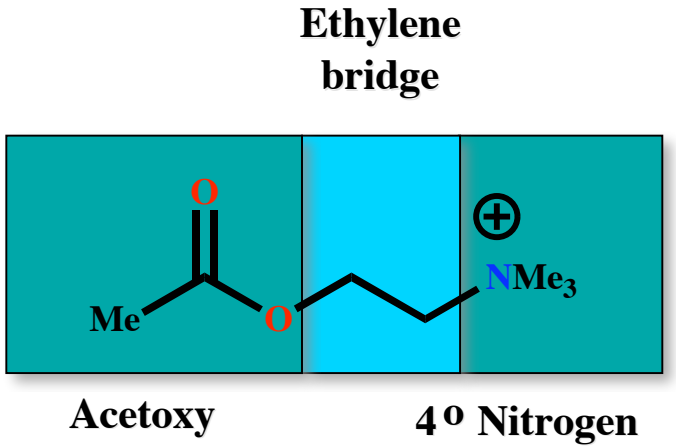


Methyl group of acetoxy group cannot be extended



Bad for activity

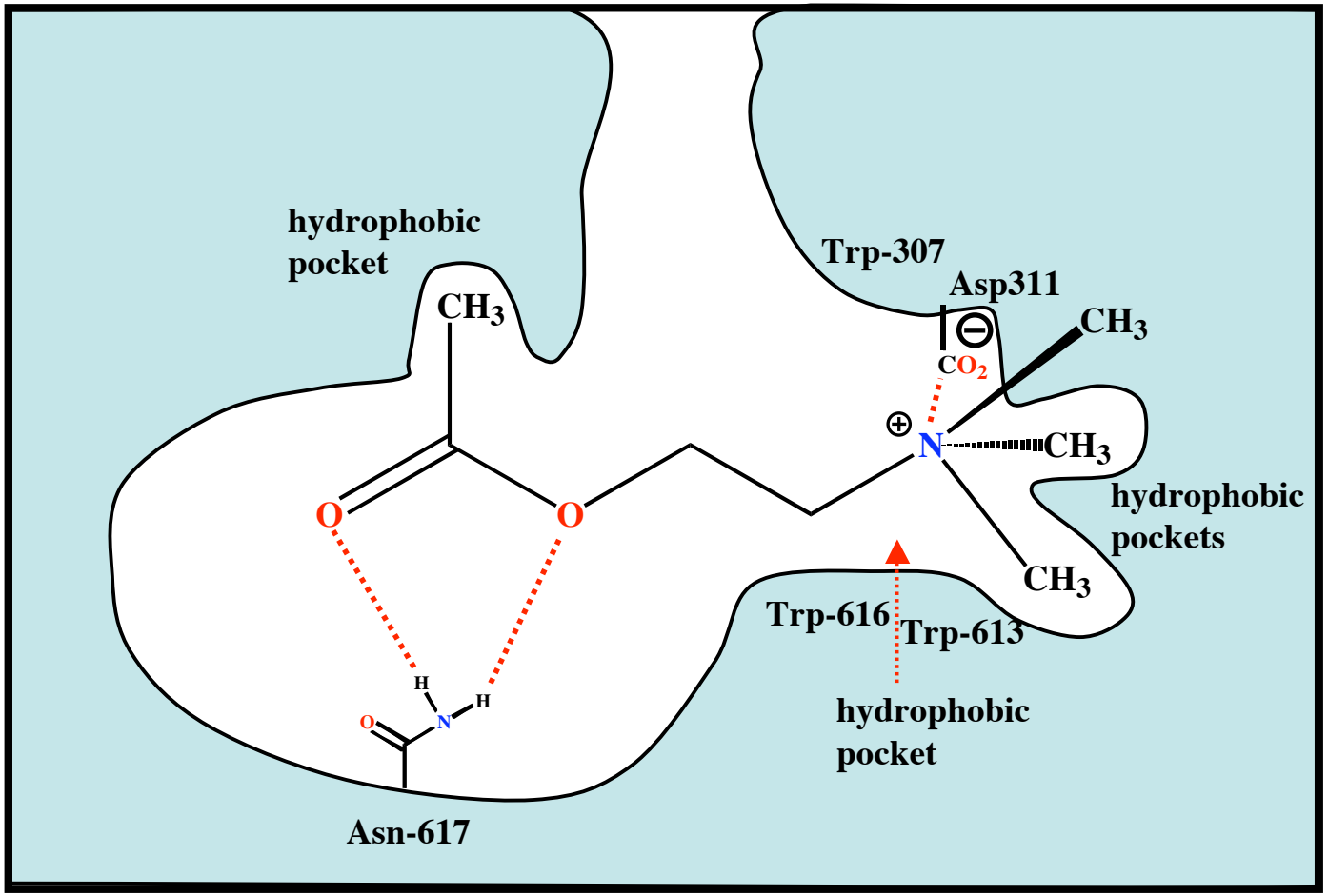
6. SAR for acetylcholine



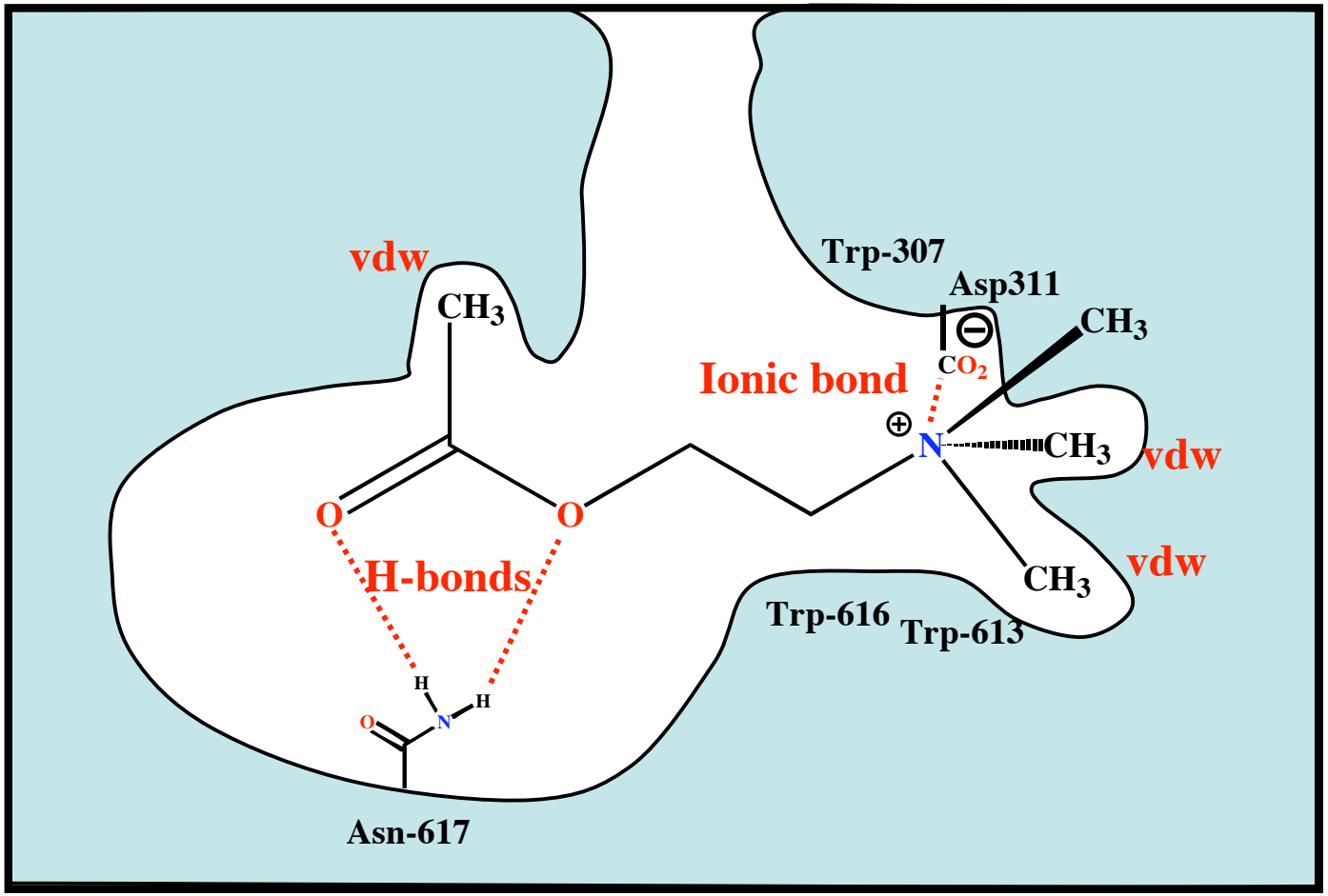
Conclusions:

- Tight fit between Ach and binding site
- Methyl groups fit into small hydrophobic pockets
- Ester interacting by H-bonding
- Quaternary nitrogen interacting by ionic bonding

7. Binding site (muscarinic)

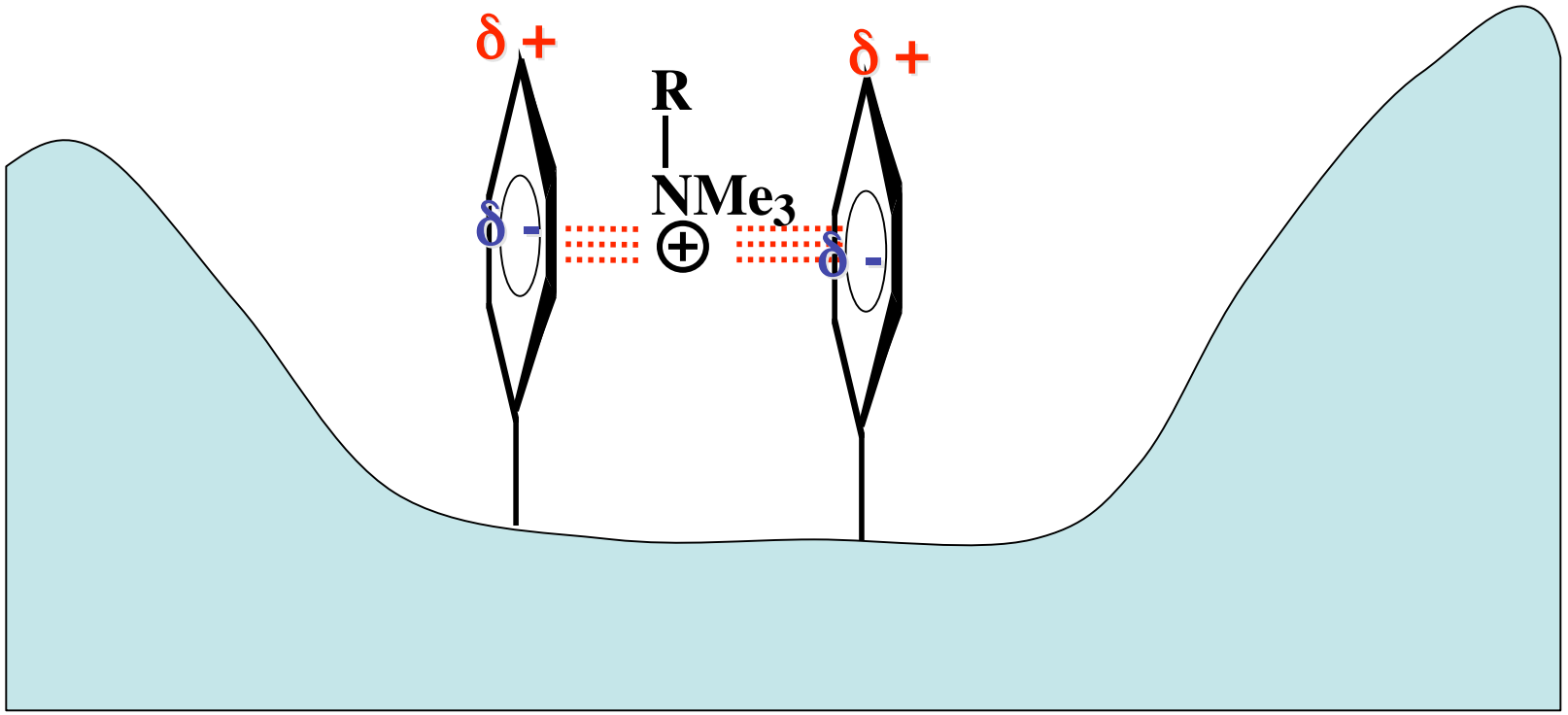


7. Binding site (muscarinic)

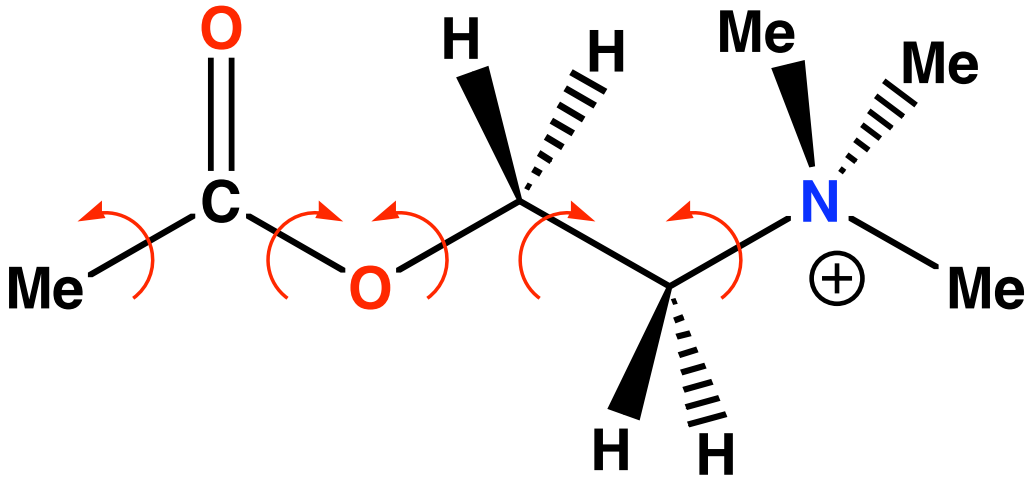


7. Binding site (muscarinic)

- **Possible induced dipole dipole interaction between quaternary nitrogen and hydrophobic aromatic rings in binding site**
- **N^+ induces dipole in aromatic rings**



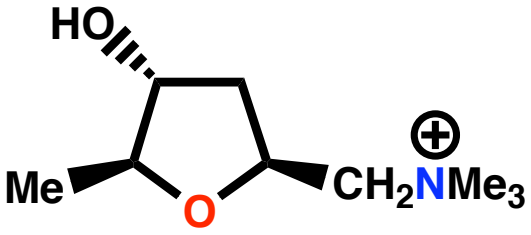
8. Active conformation of acetylcholine



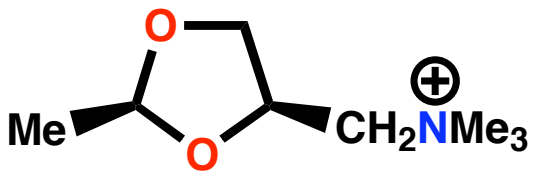
- **Several freely rotatable single bonds**
- **Large number of possible conformations**
- **Active conformation does not necessarily equal the most stable conformation**

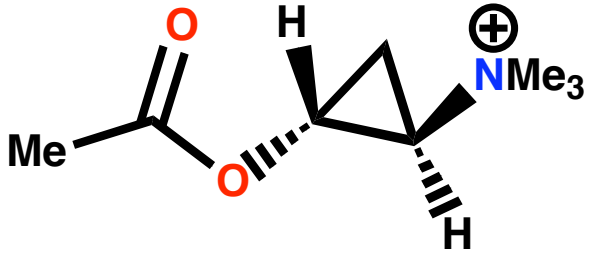
8. Active conformation of acetylcholine

Rigid Analogues of acetylcholine

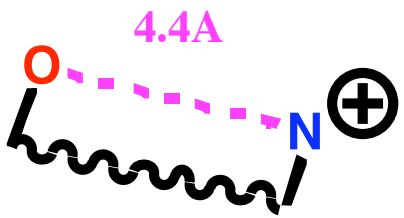


MUSCARINE

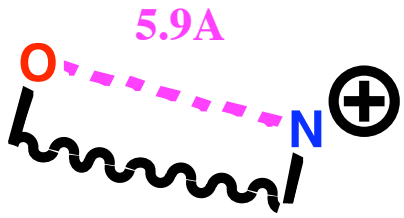




- **Rotatable bonds 'locked' within ring**
- **Restricts number of possible conformations**
- **Defines separation of ester and N**

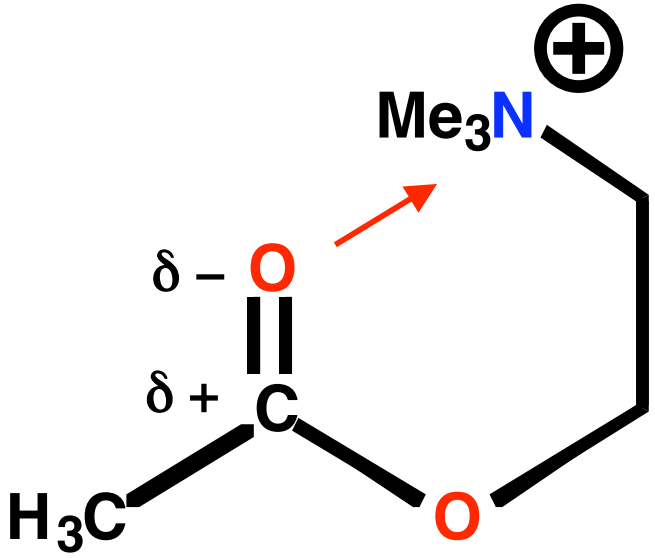


Muscarinic receptor



Nicotinic receptor

9. Instability of acetylcholine



- **Neighbouring group participation**
- **Increases electrophilicity of carbonyl group**
- **Increases sensitivity to nucleophiles**

10. Design of cholinergic agonists

Requirements

- **Correct size**
- **Correct pharmacophore - ester and quaternary nitrogen**
- **Increased stability to acid and esterases**
- **Increased selectivity**

10. Design of cholinergic agonists

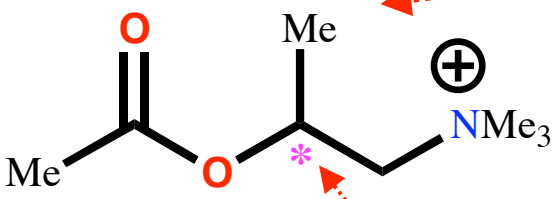
Use of steric shields

Rationale

- **Shields protect ester from nucleophiles and enzymes**
- **Shield size is important**
- **Must be large enough to hinder hydrolysis**
- **Must be small enough to fit binding site**

10. Design of cholinergic agonists

Methacholine

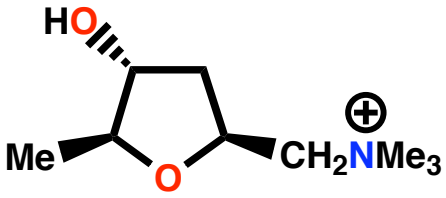


hinders binding to esterases and provides a shield to nucleophilic attack

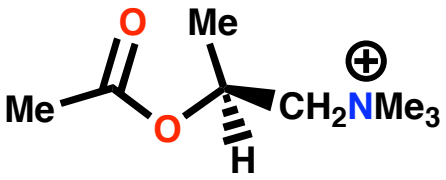
asymmetric centre

Properties

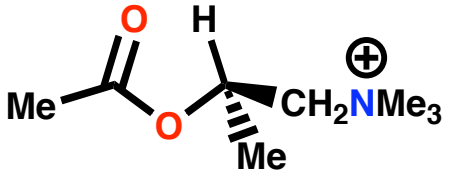
- **Three times more stable than acetylcholine**
- **Increasing the shield size increases stability but decreases activity**
- **Selective for muscarinic receptors over nicotinic receptors**
- ***S*-enantiomer is more active than the *R*-enantiomer**
- **Stereochemistry matches muscarine**
- **Not used clinically**



MUSCARINE



(*S*)

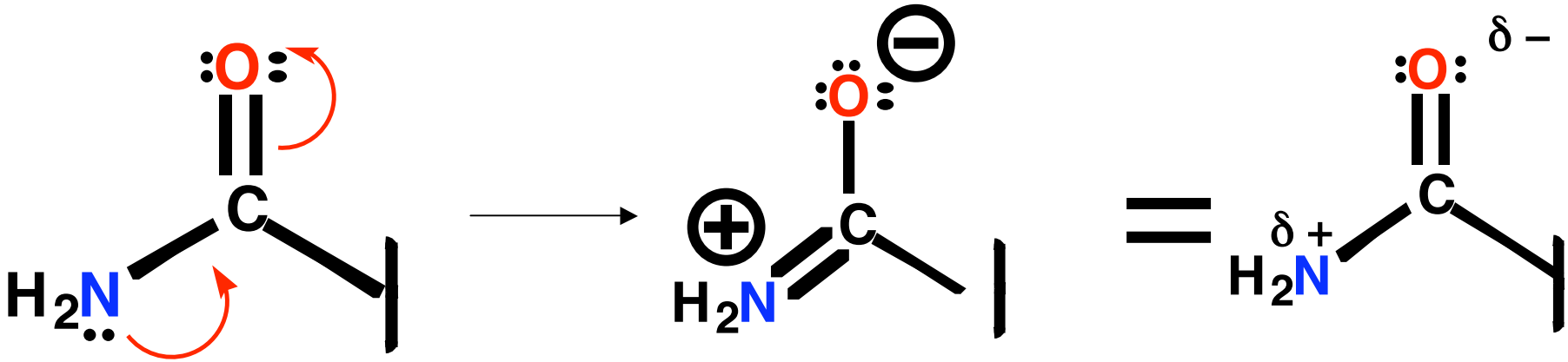


(*R*)

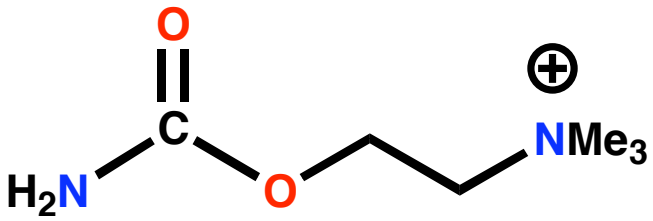
10. Design of cholinergic agonists

Use of electronic factors

- **Replace ester with urethane**
- **Stabilises the carbonyl group**



10. Design of cholinergic agonists



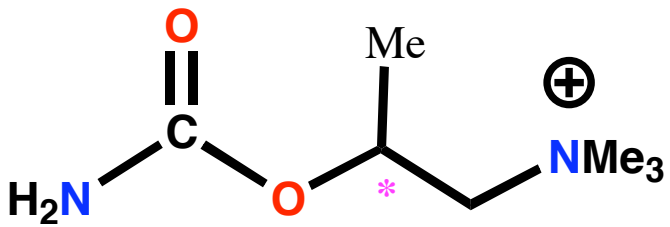
Carbachol

Properties

- **Resistant to hydrolysis**
- **Long lasting**
- **NH_2 and CH_3 are equal sizes. Both fit the hydrophobic pocket**
- **NH_2 = bio-isostere**
- **Muscarinic activity = nicotinic activity**
- **Used topically for glaucoma**

10. Design of cholinergic agonists

Steric + Electronic factors



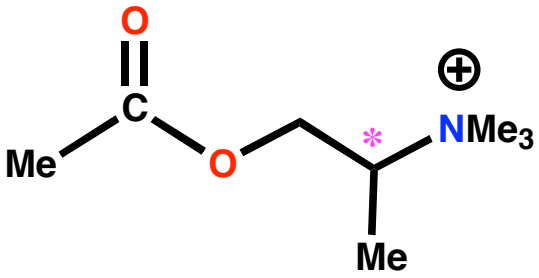
Bethanechol

Properties

- **Very stable**
- **Orally active**
- **Selective for the muscarinic receptor**
- **Used to stimulate GI tract and urinary bladder after surgery**

10. Design of cholinergic agonists

Nicotinic selective agonist



* asymmetric centre

11. Uses of cholinergic agonists

Nicotinic selective agonists

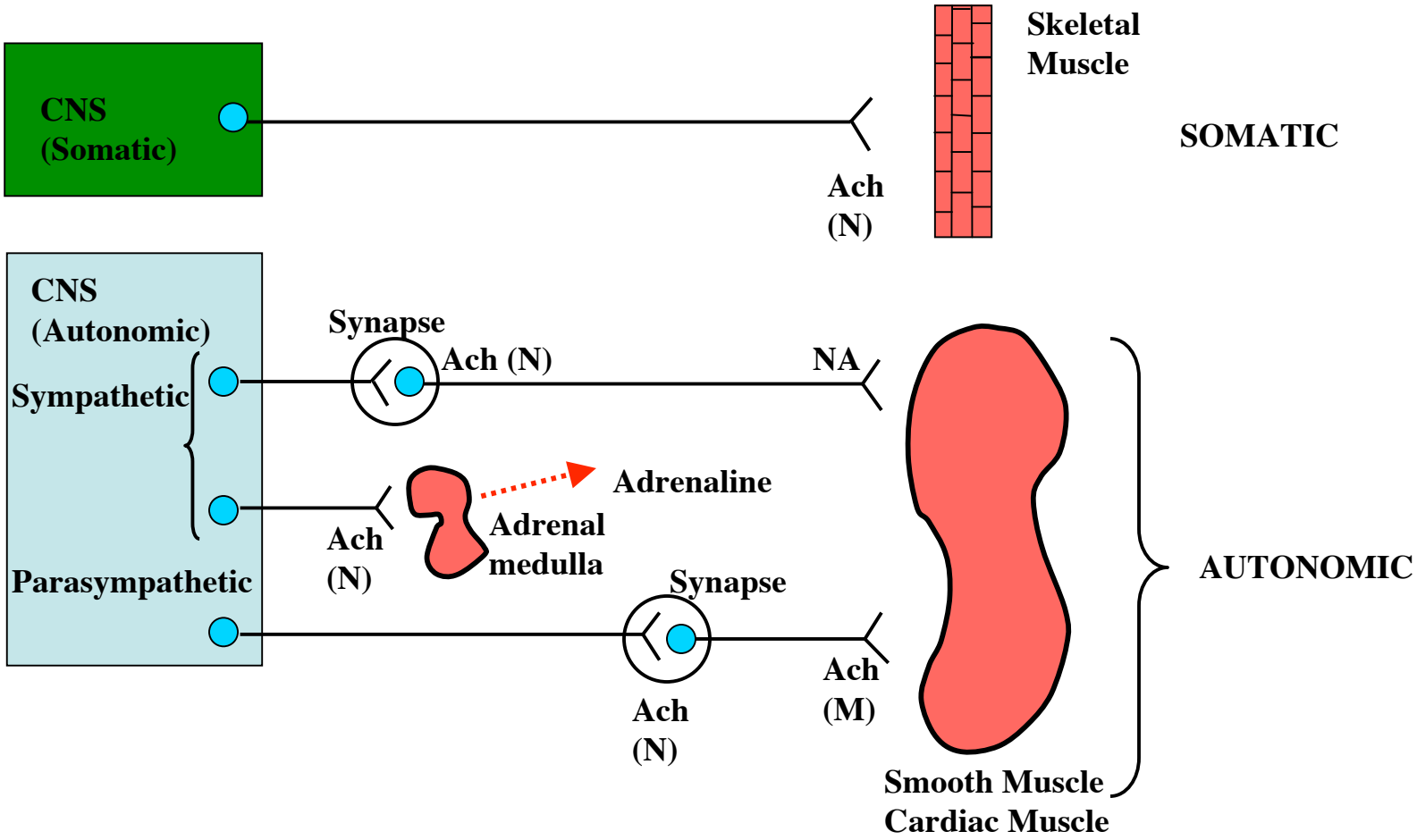
Treatment of myasthenia gravis

- lack of acetylcholine at skeletal muscle causing weakness

Muscarinic selective agonists

- **Treatment of glaucoma**
- **Switching on GIT and urinary tract after surgery**
- **Treatment of certain heart defects. Decreases heart muscle activity and decreases heart rate**

Peripheral nervous system



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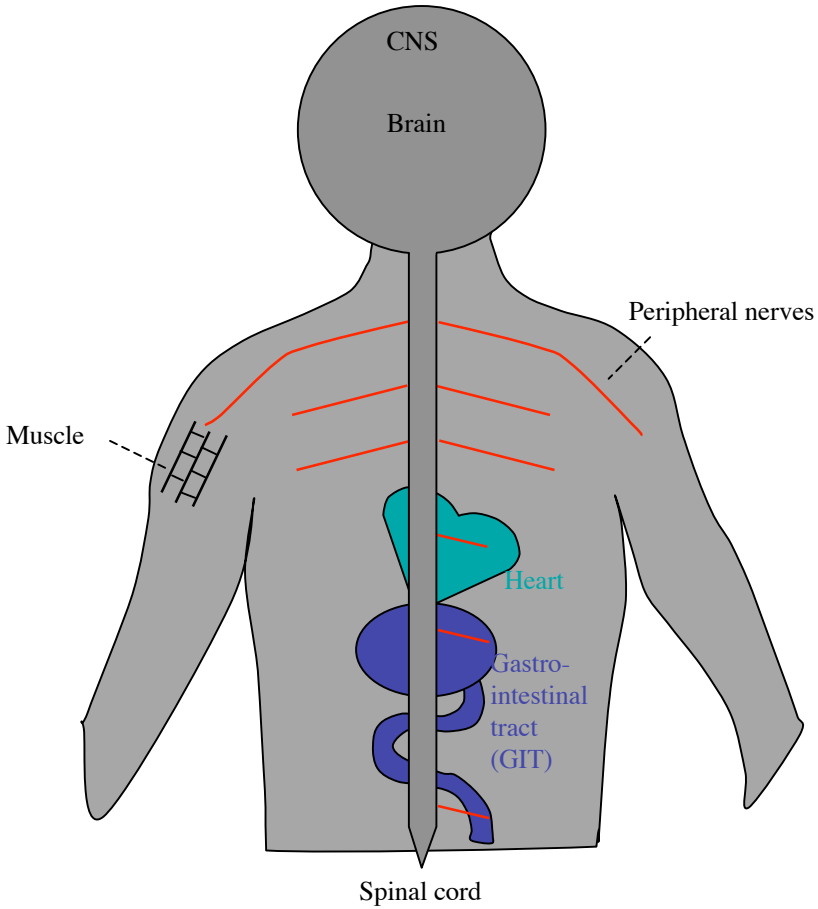
8. Active conformation of acetylcholine
9. Instability of acetylcholine
10. Design of cholinergic agonists
11. Uses of cholinergic agonists

CHOLINERGIC NERVOUS SYSTEM

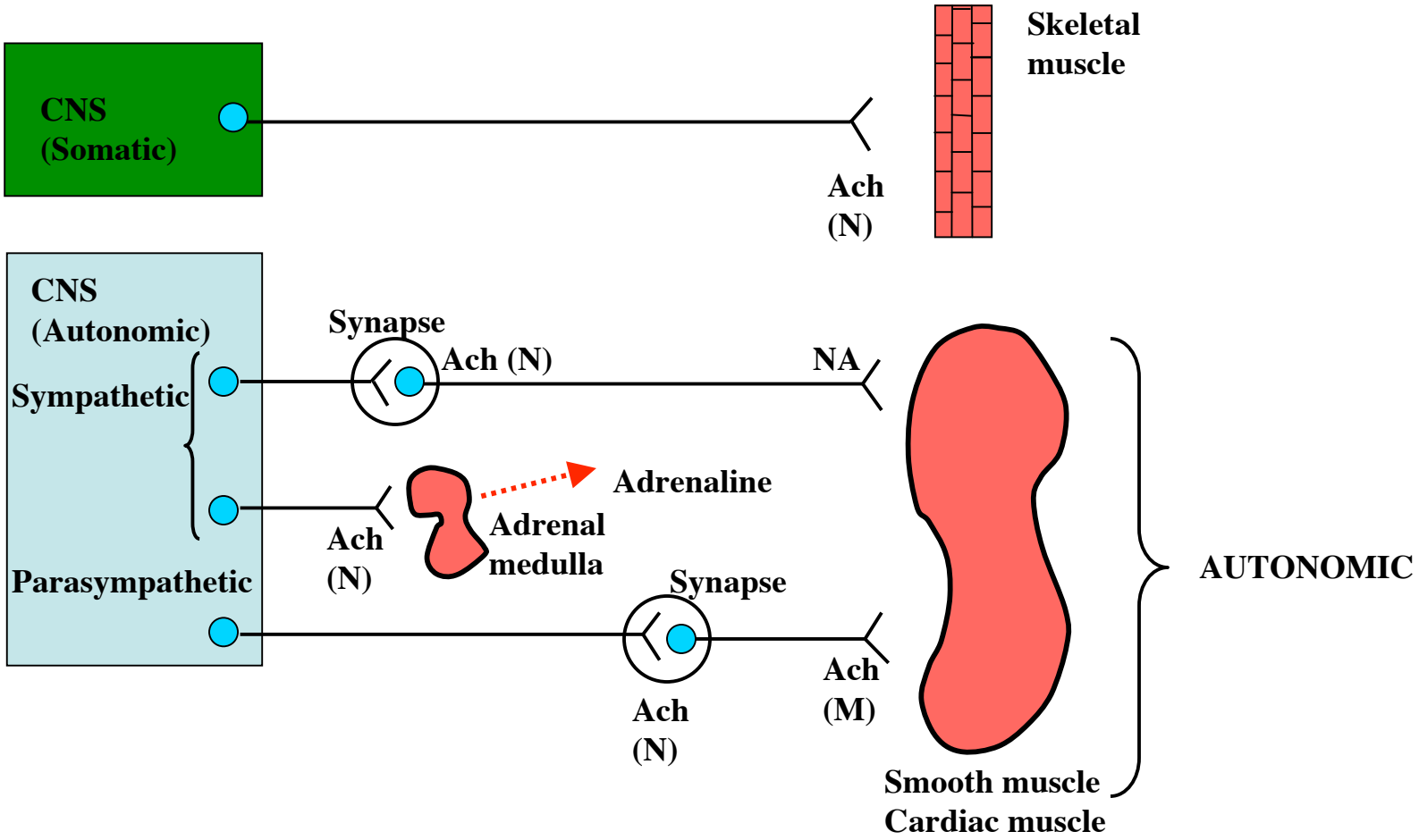
1. Nerve Transmission

Peripheral nervous system



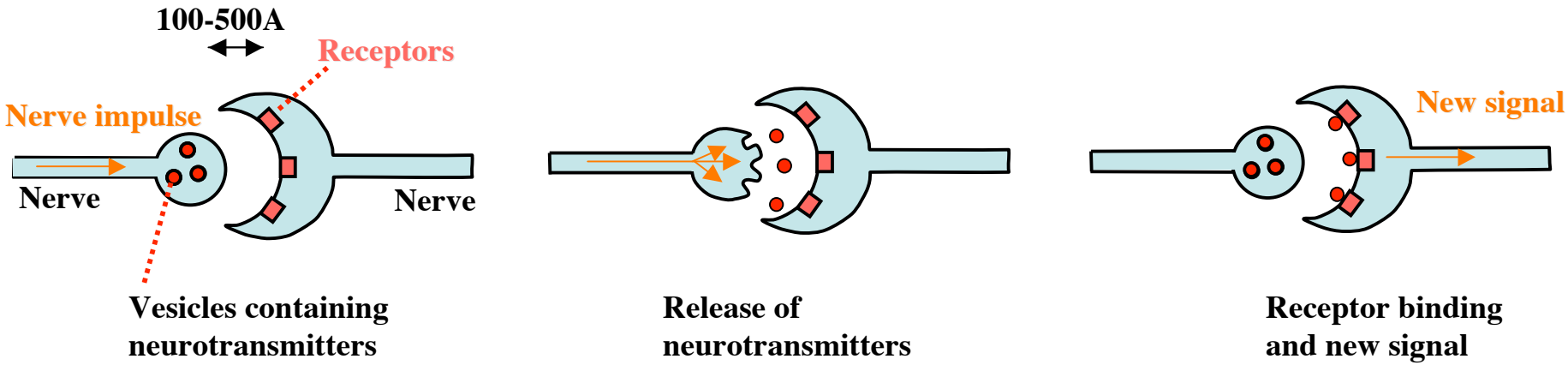
1. Nerve Transmission

Peripheral nervous system



1. Nerve Transmission

Synapses



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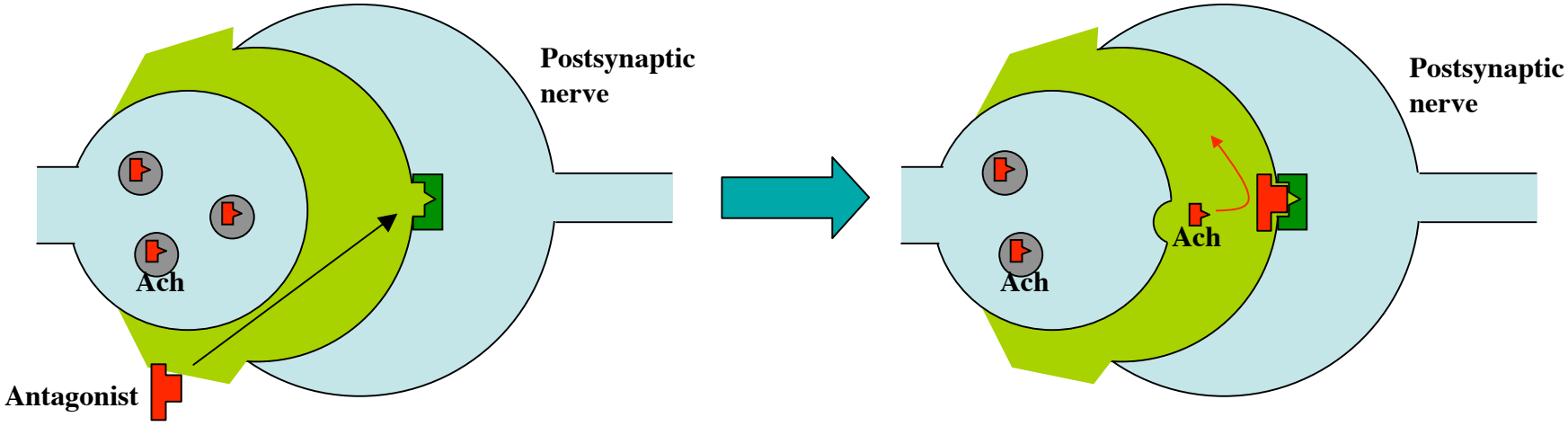
12. Cholinergic Antagonists (Muscarinic receptor)

- **Drugs which bind to cholinergic receptor but do not activate it**
- **Prevent acetylcholine from binding**
- **Opposite clinical effect to agonists - lower activity of acetylcholine**



12. Cholinergic Antagonists (Muscarinic receptor)

Clinical Effects

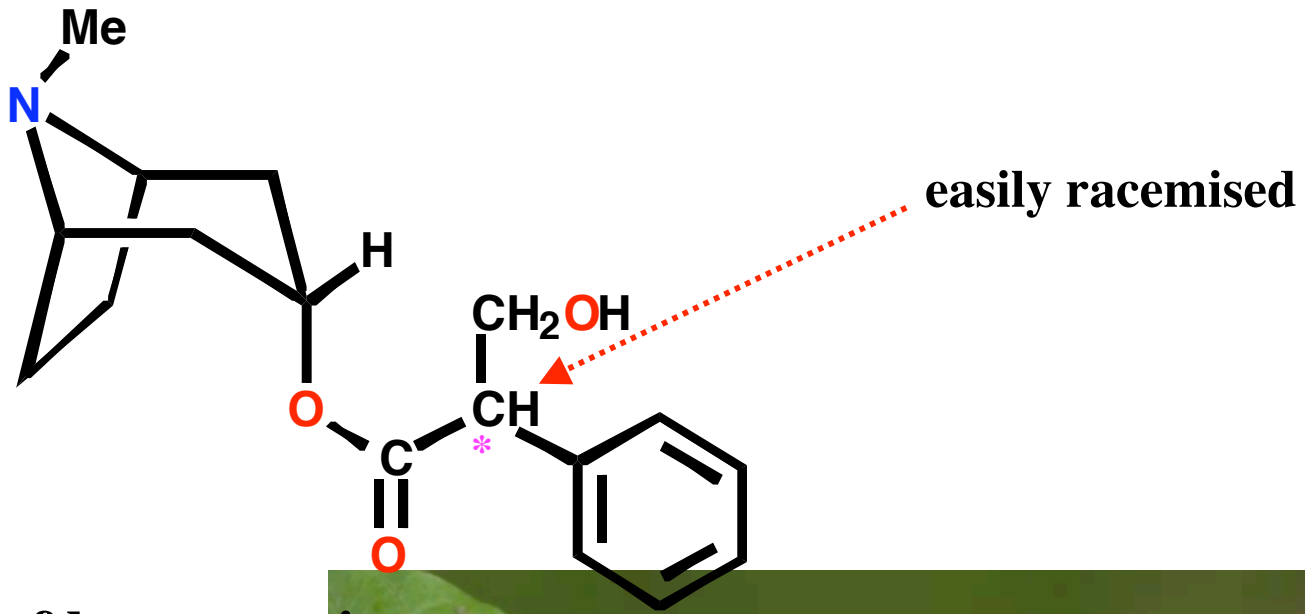
- Decrease of saliva and gastric secretions
- Relaxation of smooth muscle
- Decrease in motility of GIT and urinary tract
- Dilation of pupils

Uses

- Shutting down digestion for surgery
- Ophthalmic examinations
- Relief of peptic ulcers
- Treatment of Parkinson's Disease
- Anticholinesterase poisoning
- Motion sickness

12. Cholinergic Antagonists (Muscarinic receptor)

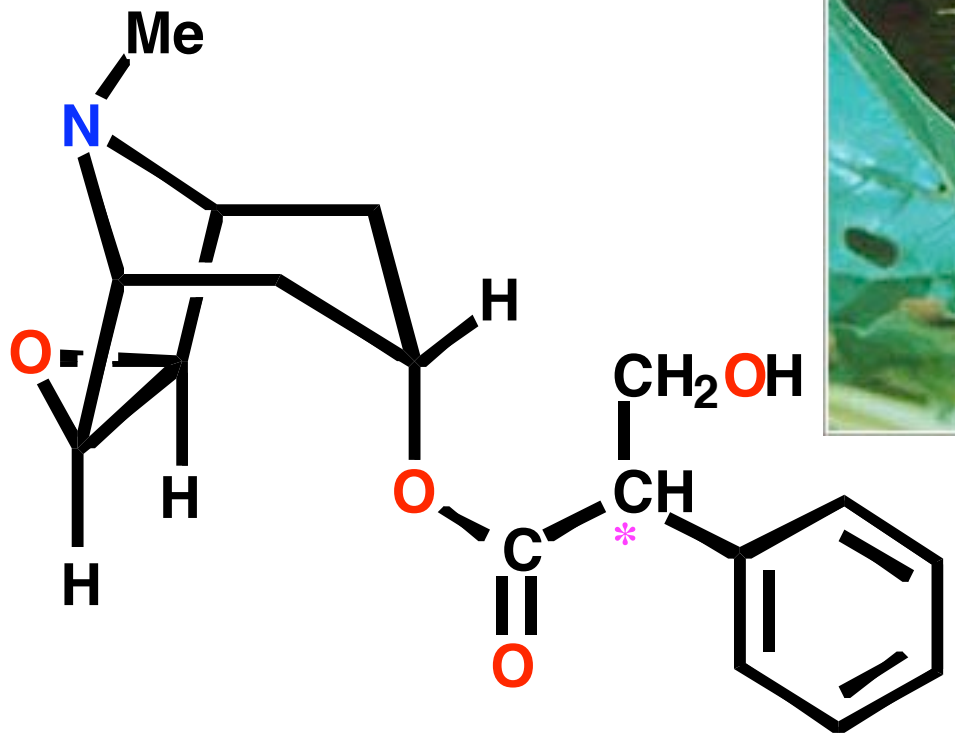
12.1 Atropine



- Racemic form of hyoscyamine
- Source - roots of belladonna (1831) (deadly nightshade)
- Used as a poison
- Used as a medicine
  - decreases GIT motility
  - antidote for anticholinesterase poisoning
  - dilation of eye pupils
- CNS side effects - hallucinations

12. Cholinergic Antagonists (Muscarinic receptor)

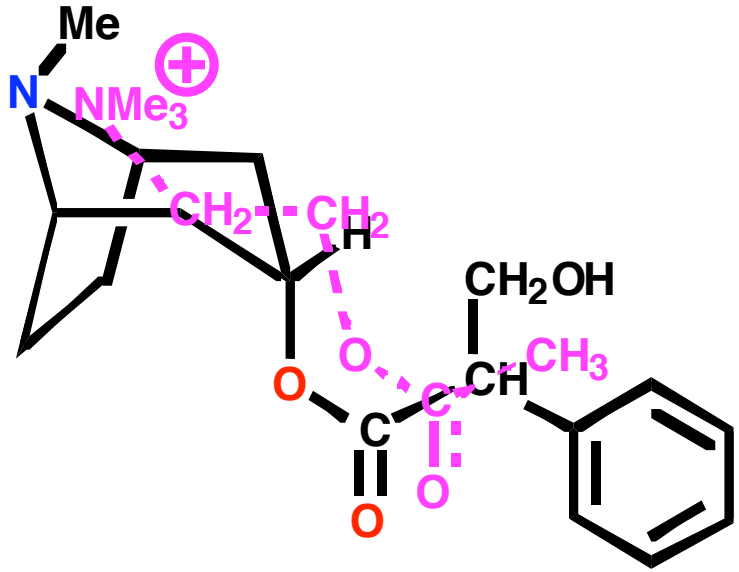
12.2 Hyoscine (scopolamine)



- Source - thorn apple-*Datura*-jimsonweed
- Medical use - treatment of motion sickness
- CNS effects, hallucinations

12. Cholinergic Antagonists (Muscarinic receptor)

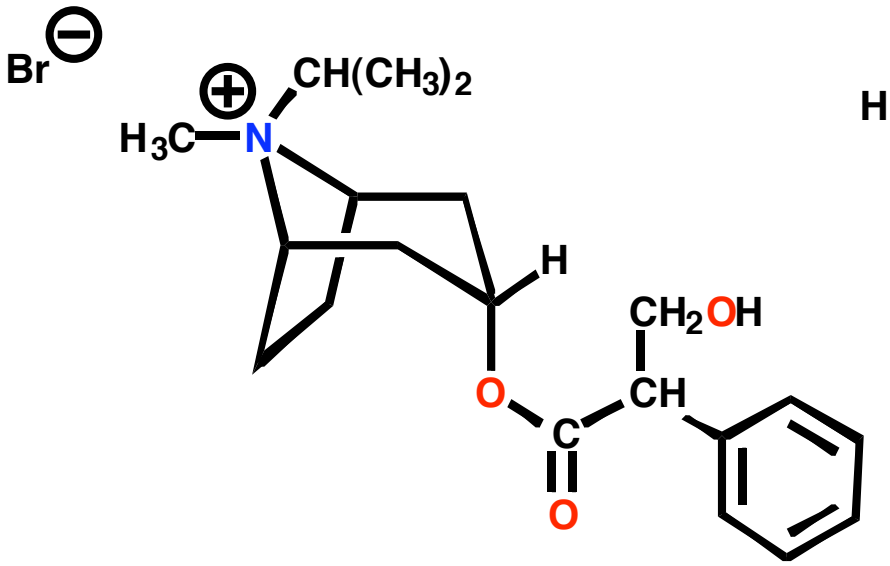
12.3 Comparison of atropine with acetylcholine



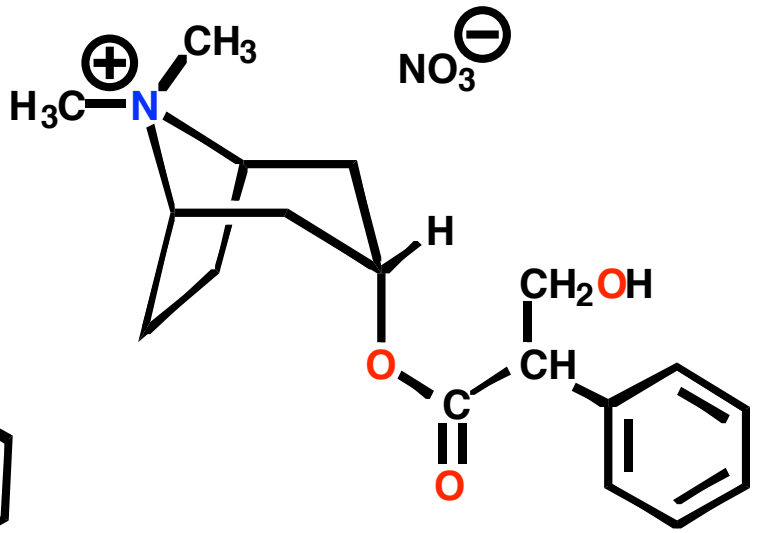
- **Relative positions of ester and nitrogen similar in both molecules**
- **Nitrogen in atropine is ionised**
- **Amine and ester are important binding groups (ionic + H-bonds)**
- **Aromatic ring of atropine is an extra binding group (vdW)**
- **Atropine binds with a different induced fit - no activation**
- **Atropine binds more strongly than acetylcholine**

12. Cholinergic Antagonists (Muscarinic receptor)

12.4 Analogues of atropine



Ipratropium
(bronchodilator & anti-asthmatic)



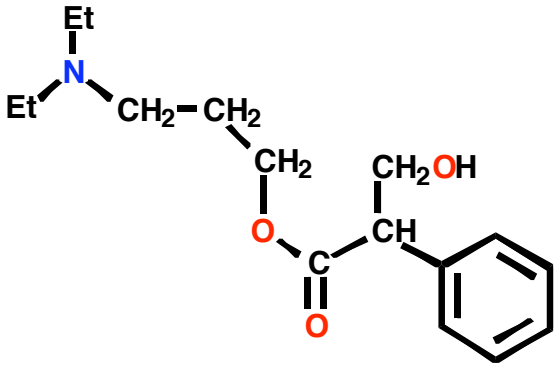
Atropine methonitrate
(lowers GIT motility)

- **Analogues are fully ionized**
- **Analogues unable to cross the blood brain barrier**
- **No CNS side effects**

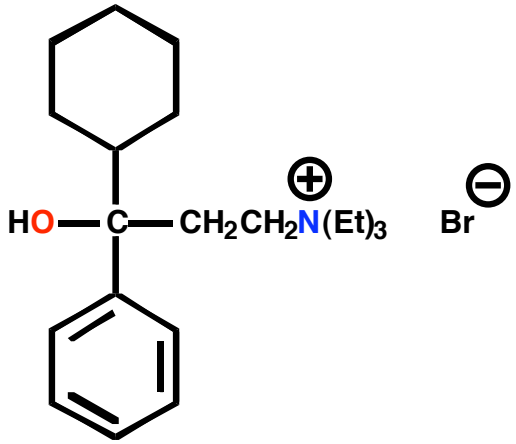
12. Cholinergic Antagonists (Muscarinic receptor)

12.5 Simplified Analogues

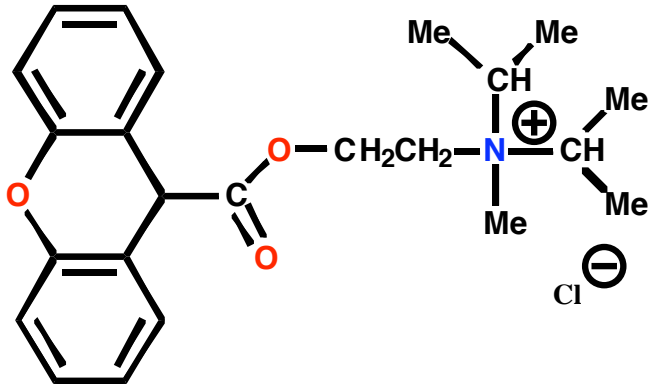
Pharmacophore = ester + basic amine + aromatic ring



Amprotropine



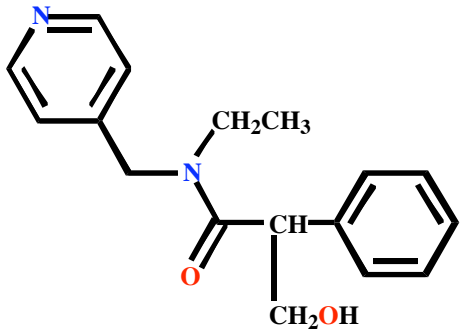
Tridihexethyl bromide



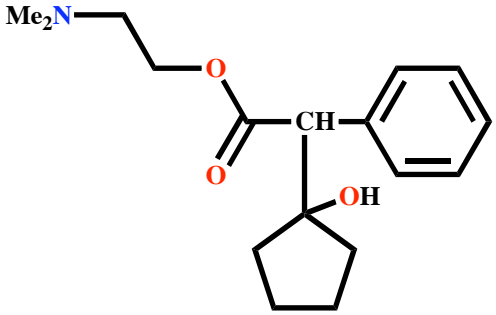
Propantheline chloride

12. Cholinergic Antagonists (Muscarinic receptor)

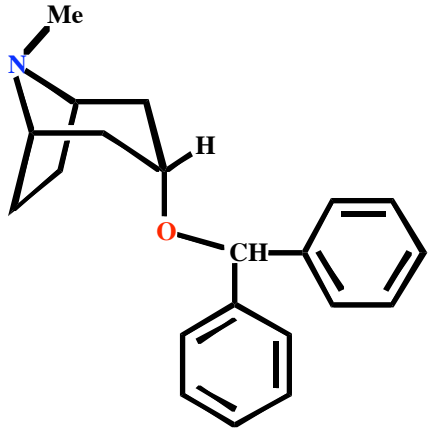
12.5 Simplified Analogues



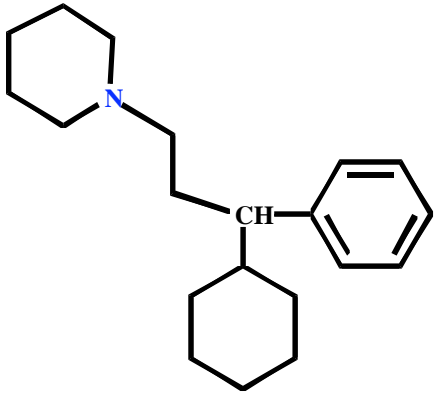
Tropicamide (opthalmics)



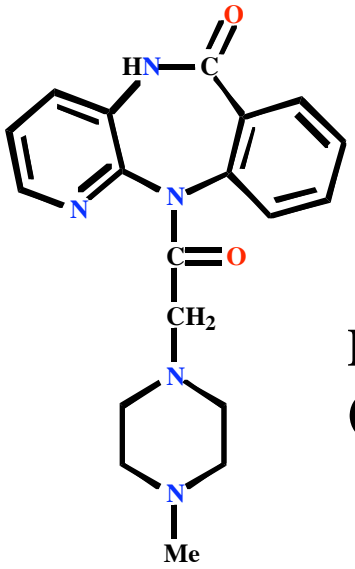
Cyclopentolate (opthalmics)



Benztropine (Parkinsons disease)



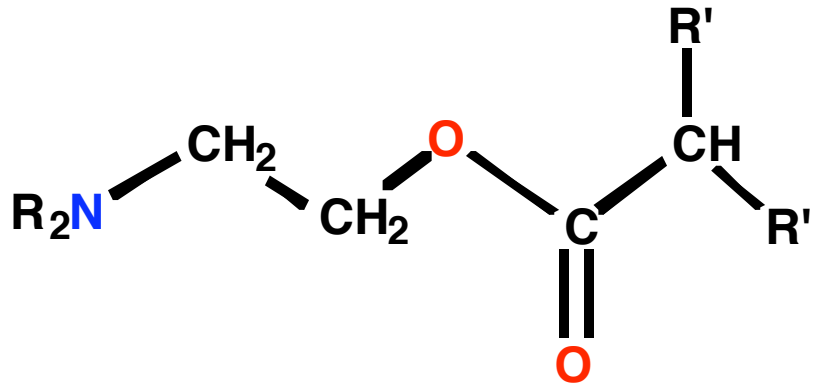
Benzhexol (Parkinsons disease)



Pirenzepine (anti-ulcer)

12. Cholinergic Antagonists (Muscarinic receptor)

12.6 SAR for Antagonists



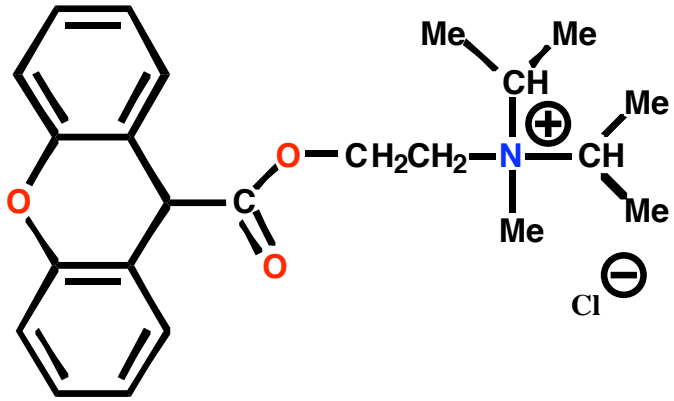
R' = Aromatic or Heteroaromatic

Important features

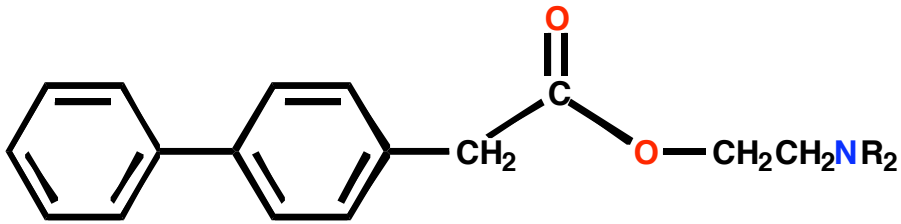
- Tertiary amine (ionised) or a quaternary nitrogen
- Aromatic ring
- Ester
- *N*-Alkyl groups (R) can be larger than methyl (unlike agonists)
- Large branched acyl group
- R' = aromatic or heteroaromatic ring
- Branching of aromatic/heteroaromatic rings is important

12. Cholinergic Antagonists (Muscarinic receptor)

12.6 SAR for Antagonists



Active



Inactive

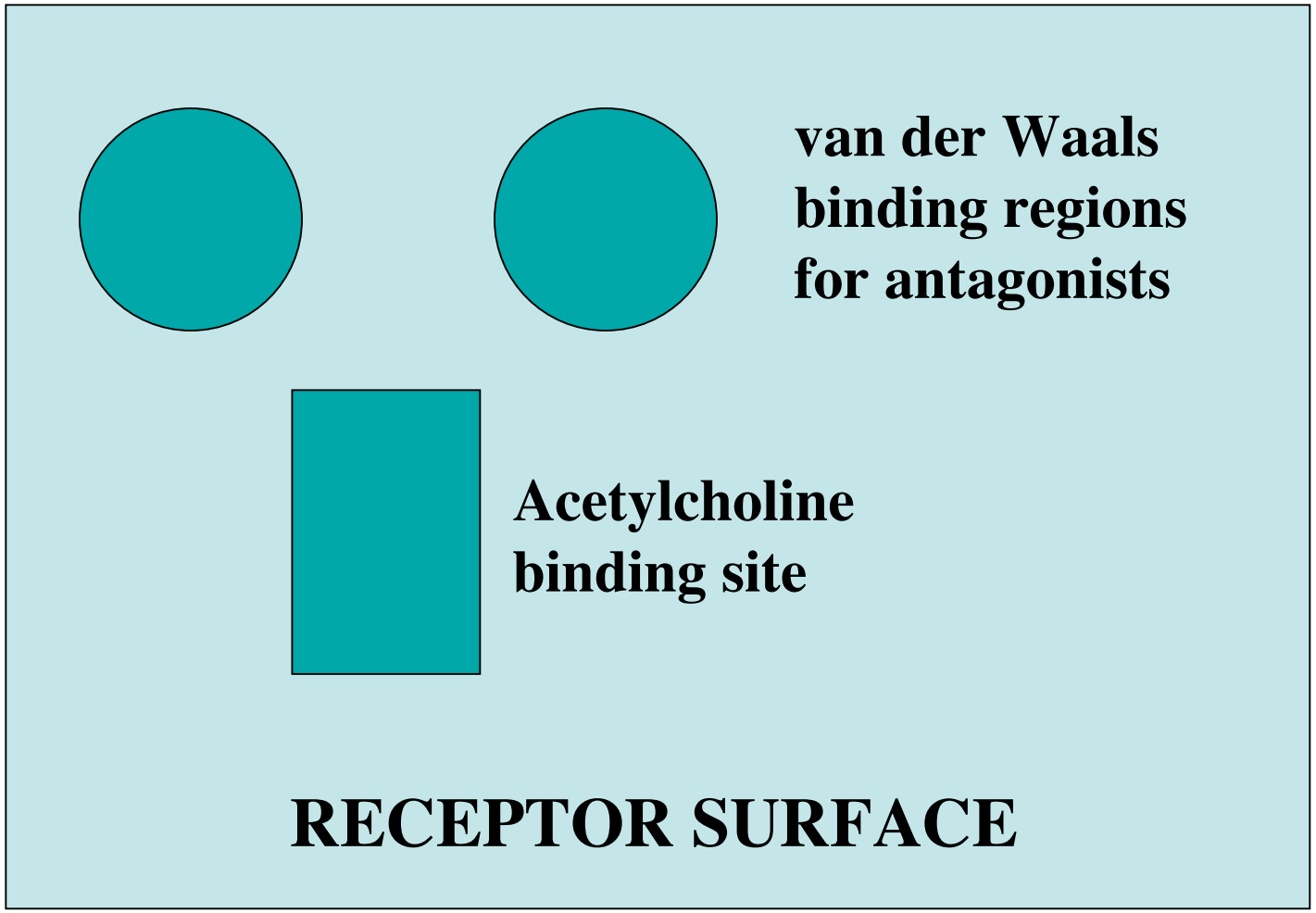
12. Cholinergic Antagonists (Muscarinic receptor)

12.6 SAR for Antagonists vs. Agonists

SAR for Antagonists	SAR for Agonists
Tertiary amine (ionized) or quaternary nitrogen Aromatic ring Ester *N*-Alkyl groups (R) can be larger than methyl R' = aromatic or heteroaromatic Branching of Ar rings important	Quaternary nitrogen Aromatic ring Ester *N*-Alkyl groups = methyl R' = H

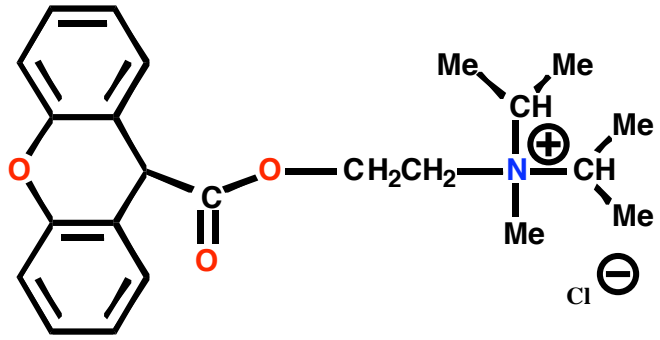
12. Cholinergic Antagonists (Muscarinic receptor)

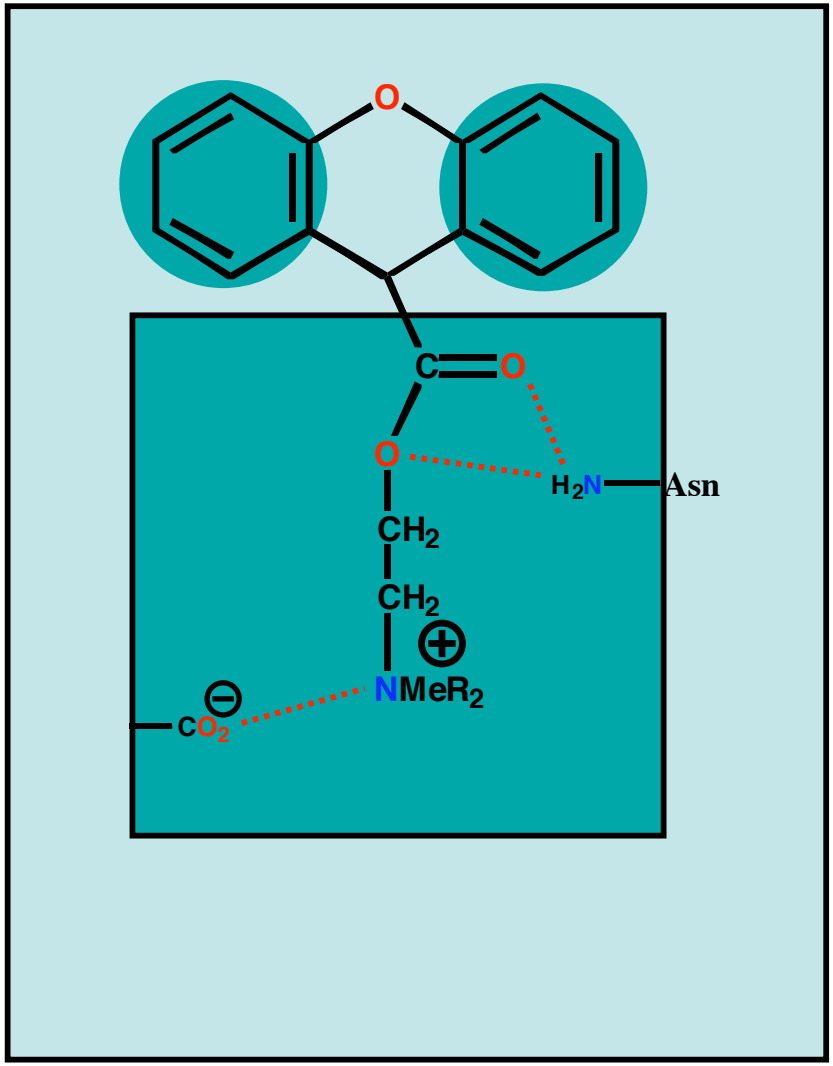
12.7 Binding Site for Antagonists



12. Cholinergic Antagonists (Muscarinic receptor)

12.7 Binding Site for Antagonists

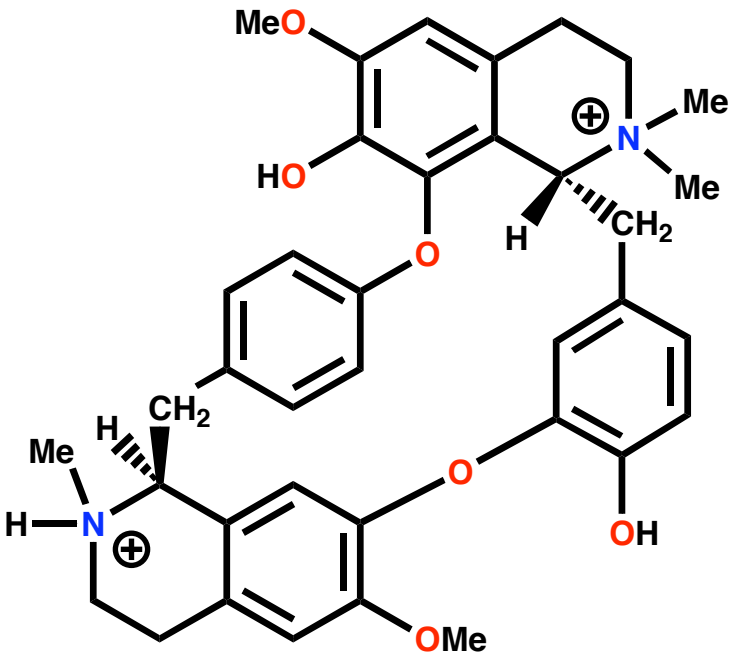




13. Cholinergic Antagonists (Nicotinic receptor)

13.1 Curare

- **Extract from curare plant-** *Strychnos toxifera*
- **Used for poison arrows**
- **Causes paralysis (blocks acetylcholine signals to muscles)**
- **Active principle = tubocurarine**



Tubocurarine

13. Cholinergic Antagonists (Nicotinic receptor)

Pharmacophore

- Two quaternary centres at specific separation (1.15nm)
- Different mechanism of action from atropine based antagonists
- Different binding interactions

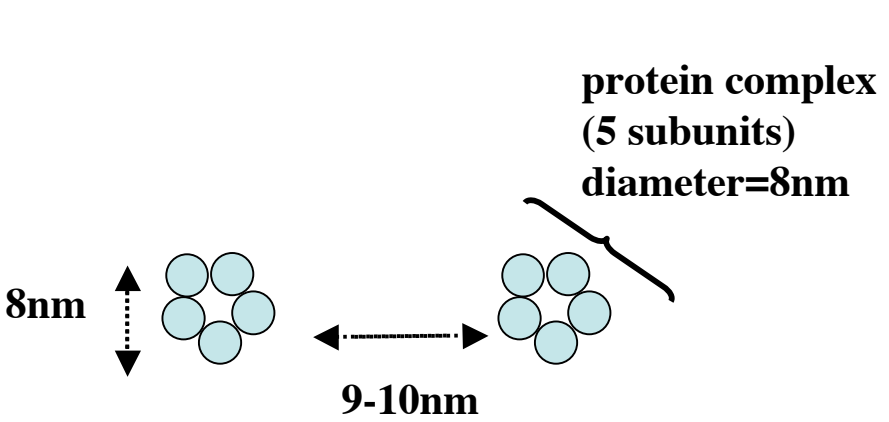
Clinical uses

- Neuromuscular blocker for surgical operations
- Permits lower and safer levels of general anaesthetic
- Tubocurarine used (previously) as neuromuscular blocker

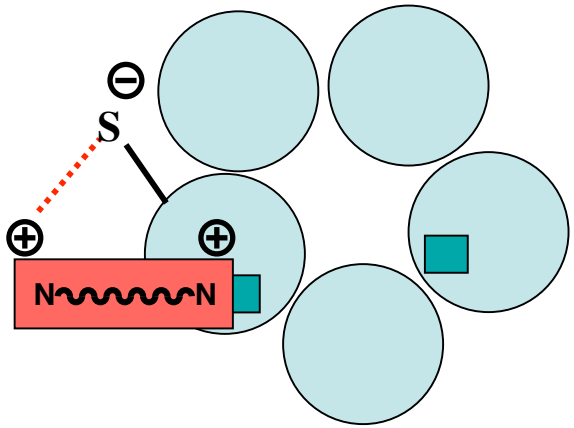
but side effects

13. Cholinergic Antagonists (Nicotinic receptor)

13.2 Binding

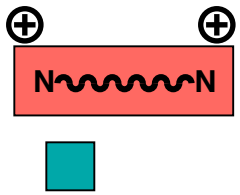


a) Receptor dimer



b) Interaction with tubocurarine

Probably not bridging Ach sites

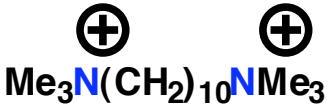


Tubocurarine

Acetylcholine binding site

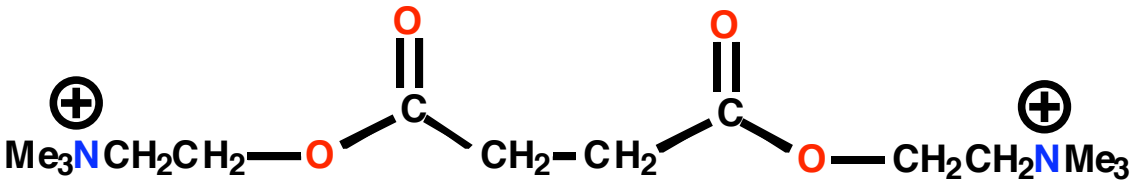
13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine



Decamethonium

- Long lasting
- Long recovery times
- Side effects on heart



Suxamethonium

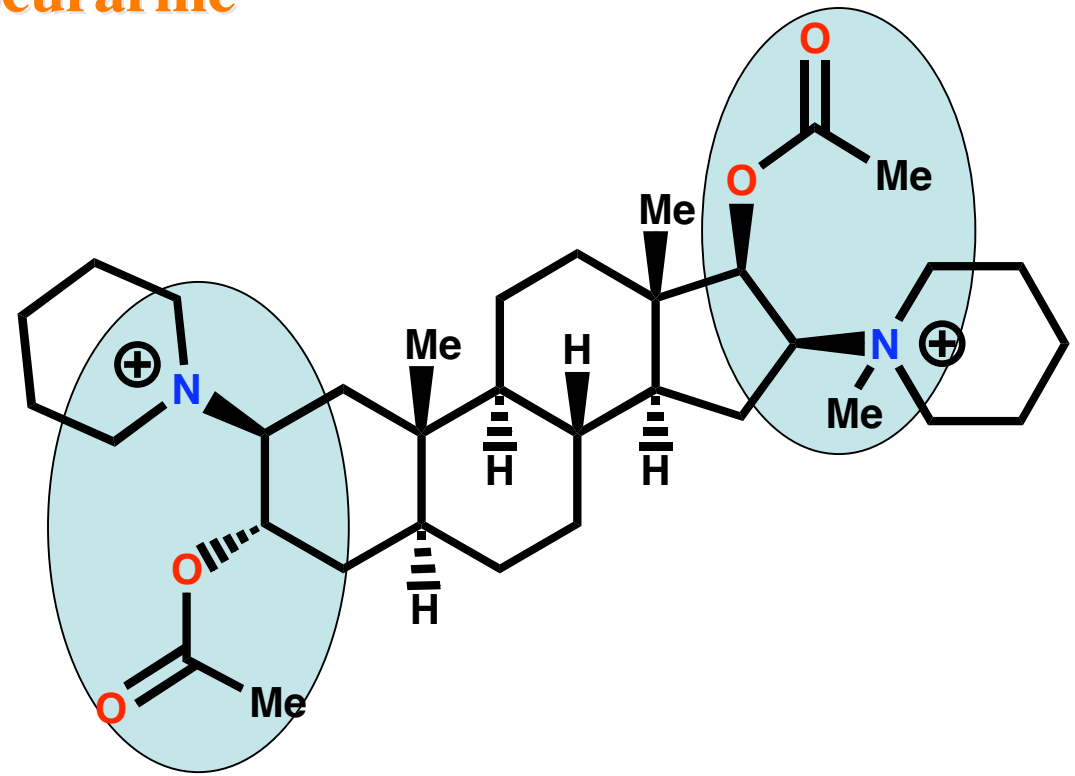
- Esters incorporated
- Shorter lifetime (5 min)
- Fast onset and short duration
- Side effects at autonomic ganglia

13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine

Pancuronium (R=Me)

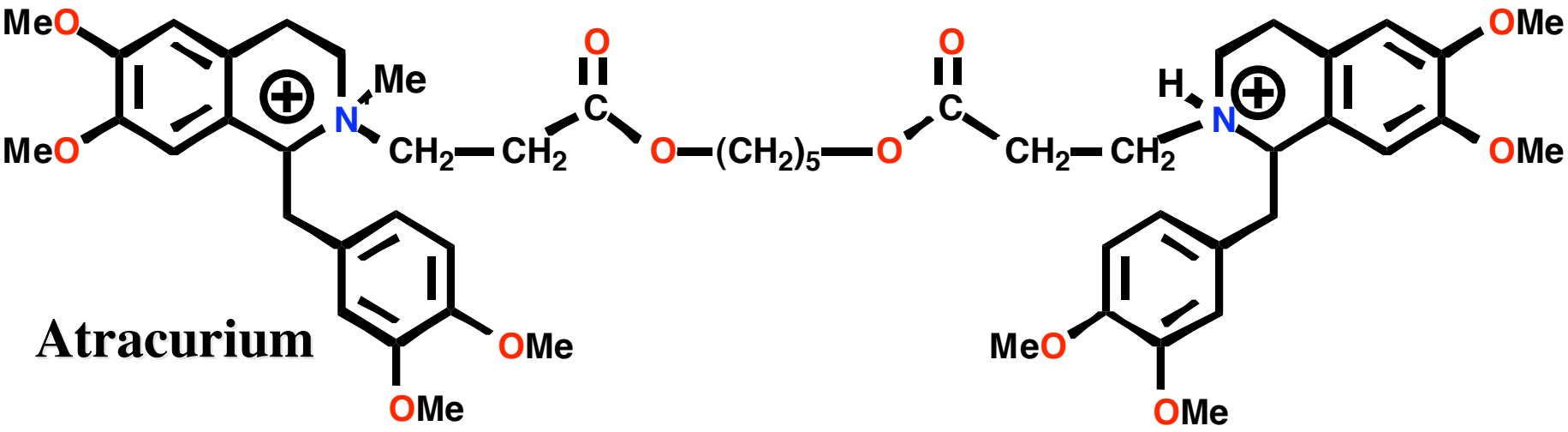
Vecuronium (R=H)



- **Steroid acts as a spacer for the quaternary centres (1.09nm)**
- **Acyl groups are added to introduce the Ach skeleton**
- **Faster onset then tubocurarine but slower than suxamethonium**
- **Longer duration of action than suxamethonium (45 min)**
- **No effect on blood pressure and fewer side effects**

13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine

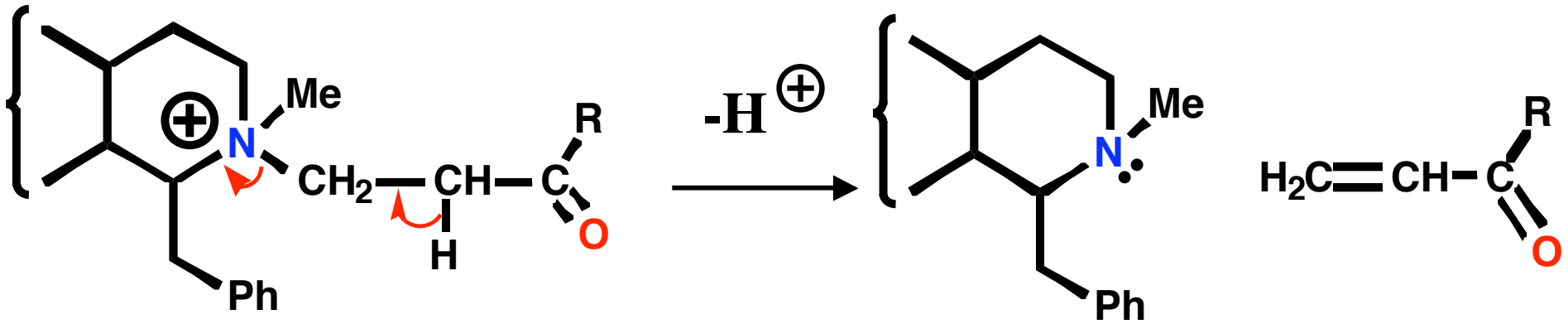


Atracurium

- Design based on tubocurarine and suxamethonium
- Lacks cardiac side effects
- Rapidly broken down in blood both chemically and metabolically
- Avoids patient variation in metabolic enzymes
- Lifetime is 30 minutes
- Administered as an i.v. drip
- Self destruct system limits lifetime

13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine



ACTIVE

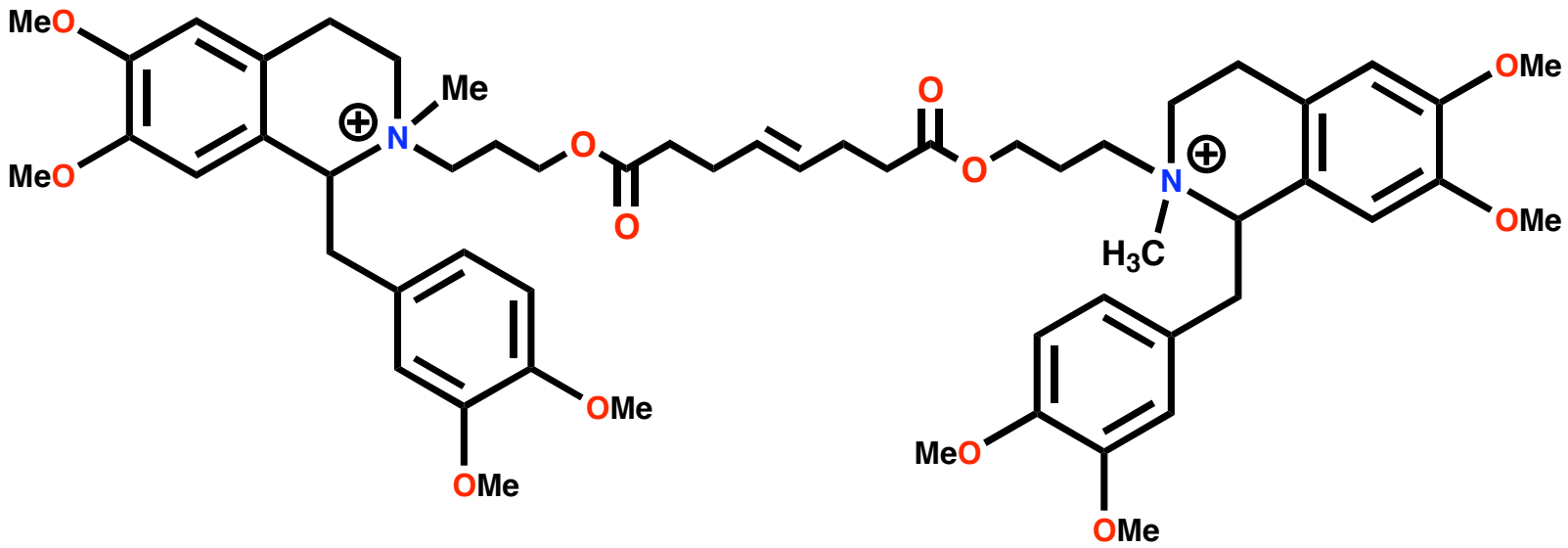
INACTIVE

Atracurium stable at acid pH
Hofmann elimination at blood pH (7.4)

13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine

Mivacurium



- **Faster onset (2 min)**
- **Shorter duration (15 min)**

Contents

Part 3: Cholinergics & anticholinesterases

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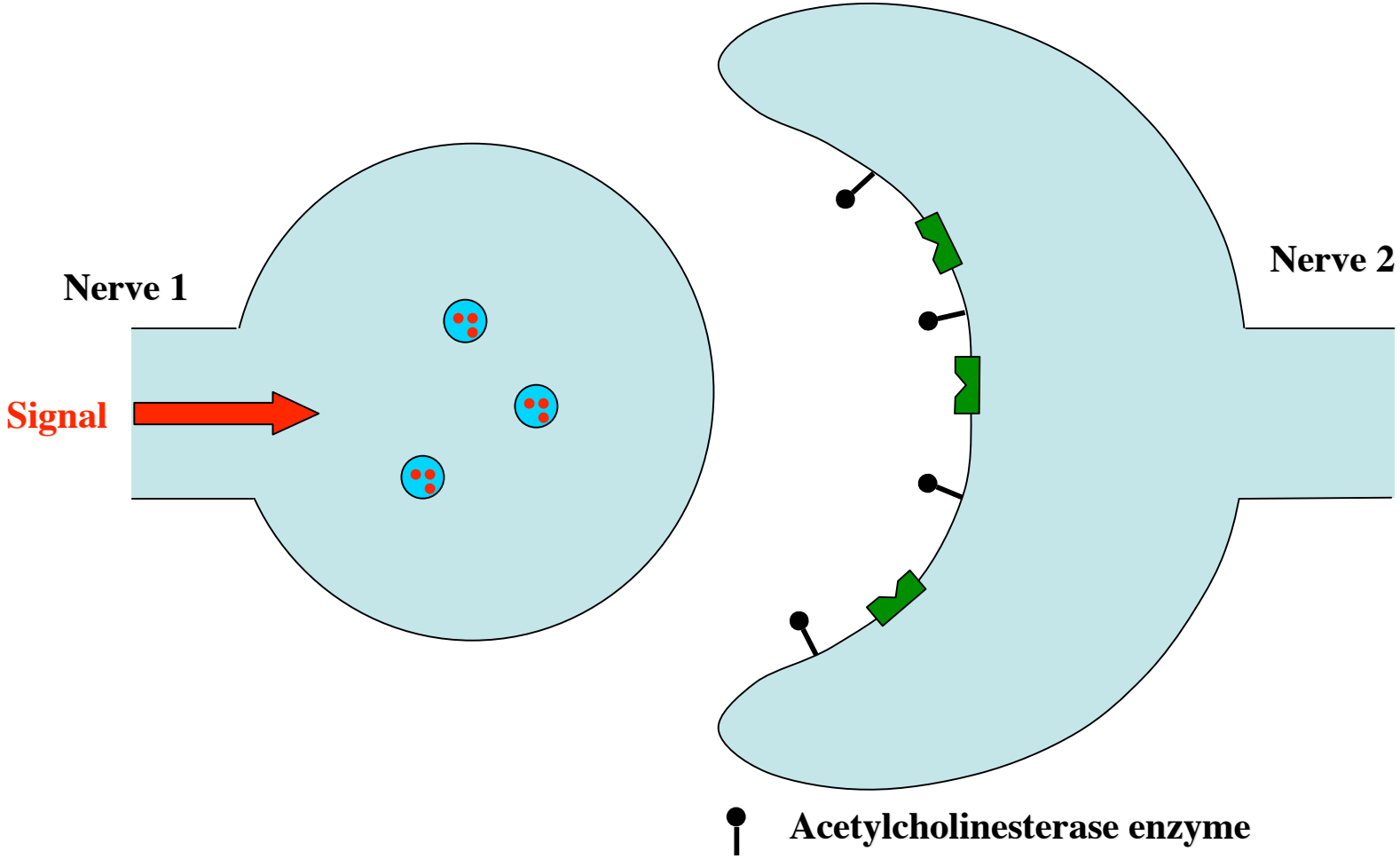
14. Acetylcholinesterase

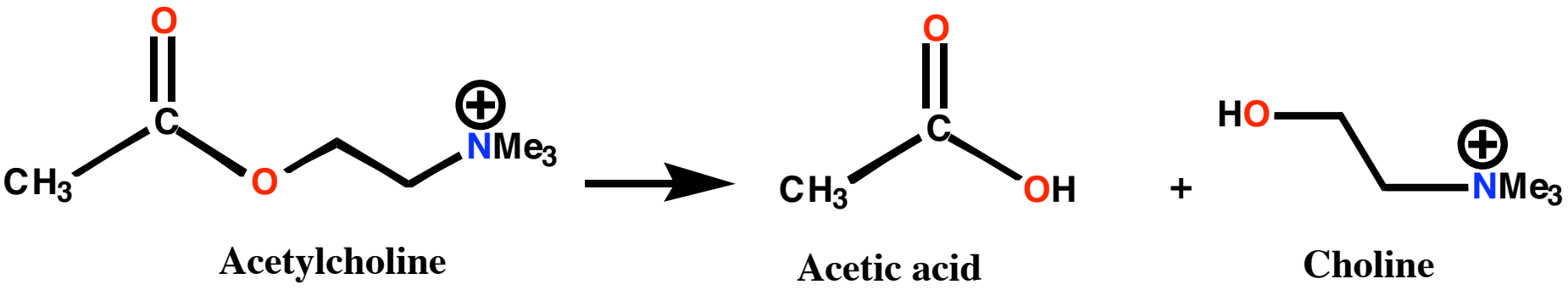
14.1 Role

- Hydrolysis and deactivation of acetylcholine
- Prevents acetylcholine reactivating receptor



14. Acetylcholinesterase

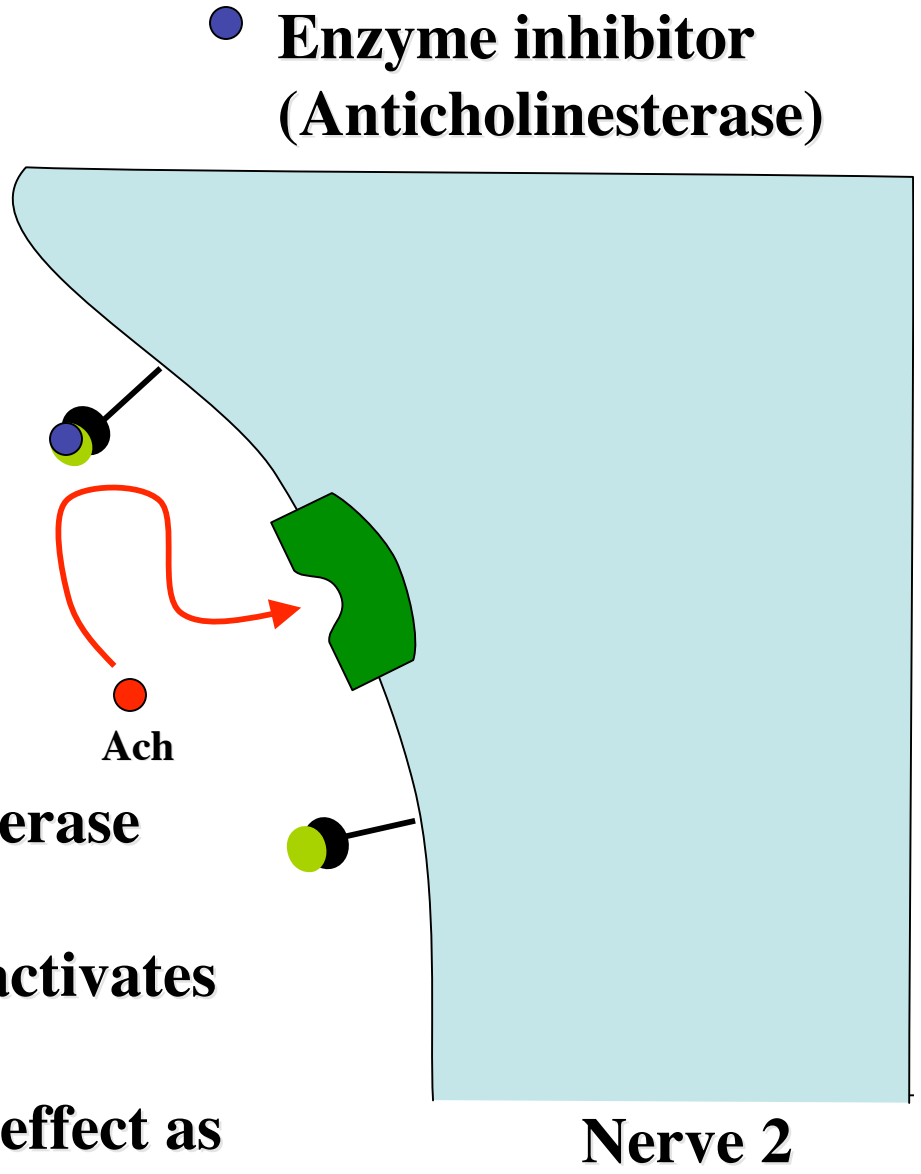
14.2 Hydrolysis reaction catalysed



active **inactive**

14. Acetylcholinesterase

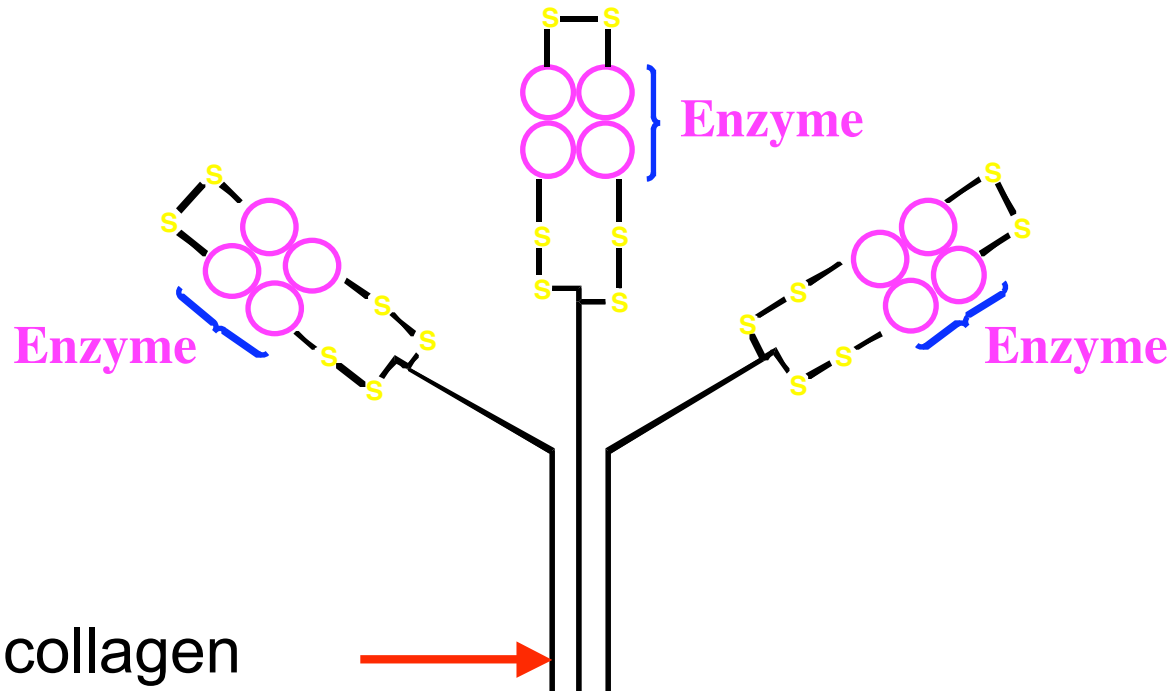
14.3 Effect of inhibition



- Inhibitor blocks acetylcholinesterase
- Ach is unable to bind
- Ach returns to receptor and reactivates it
- Enzyme inhibitor has the same effect as a cholinergic agonist

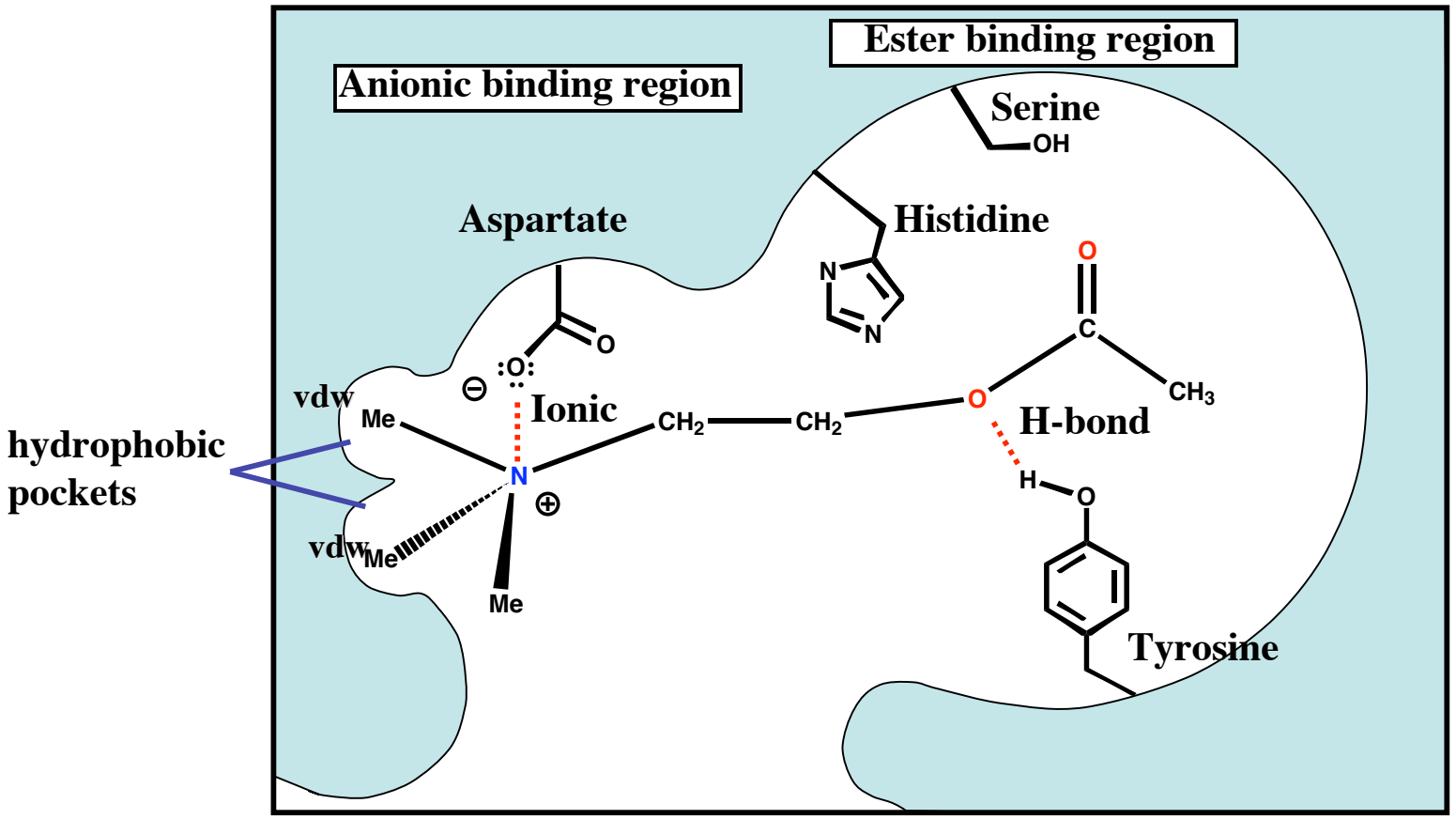
14. Acetylcholinesterase

14.4 Structure of enzyme complex



14. Acetylcholinesterase

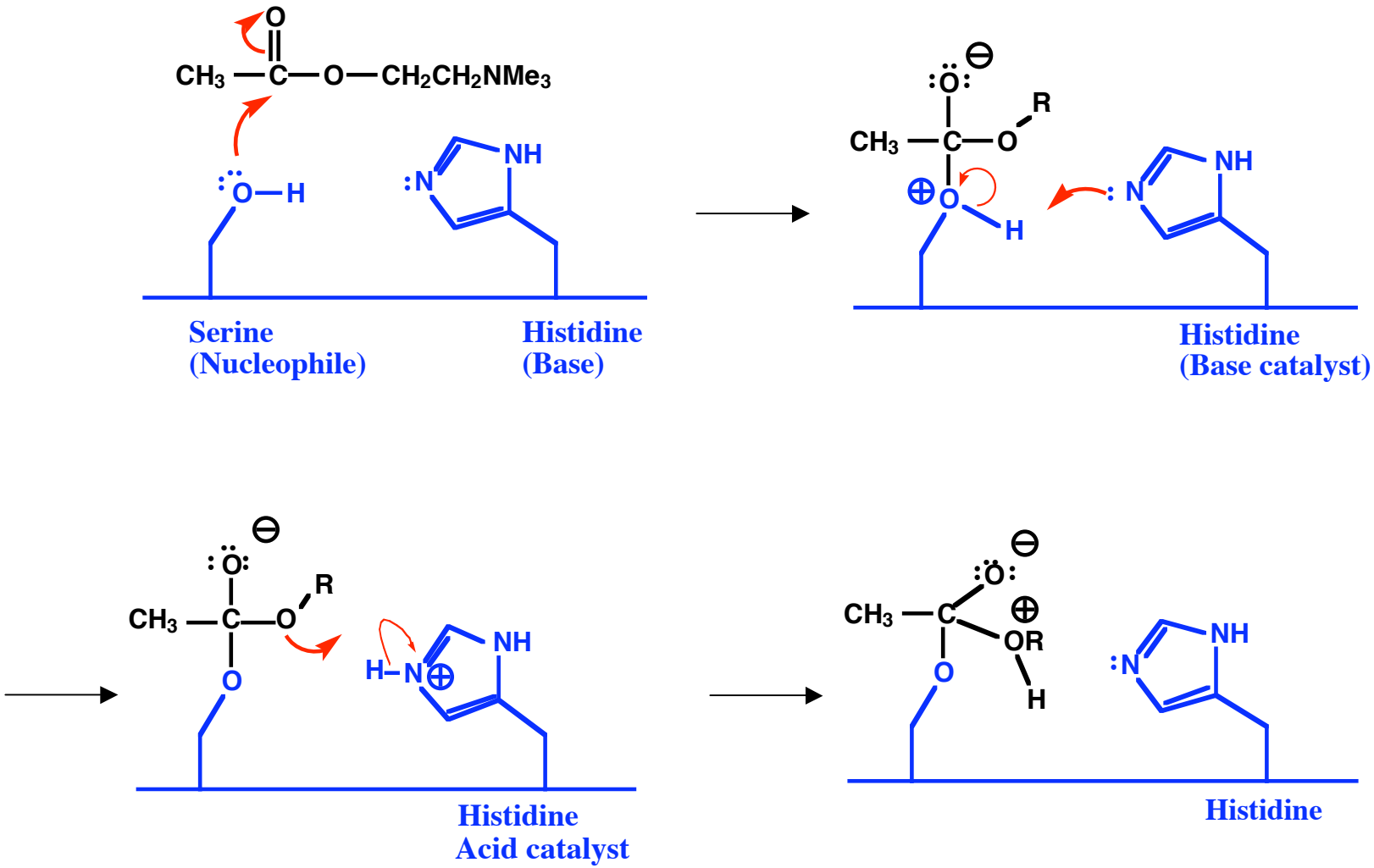
14.5 Active site - binding interactions



- Anionic binding region similar to cholinergic receptor site
- Binding and induced fit strains Ach and weakens bonds
- Molecule positioned for reaction with His and Ser

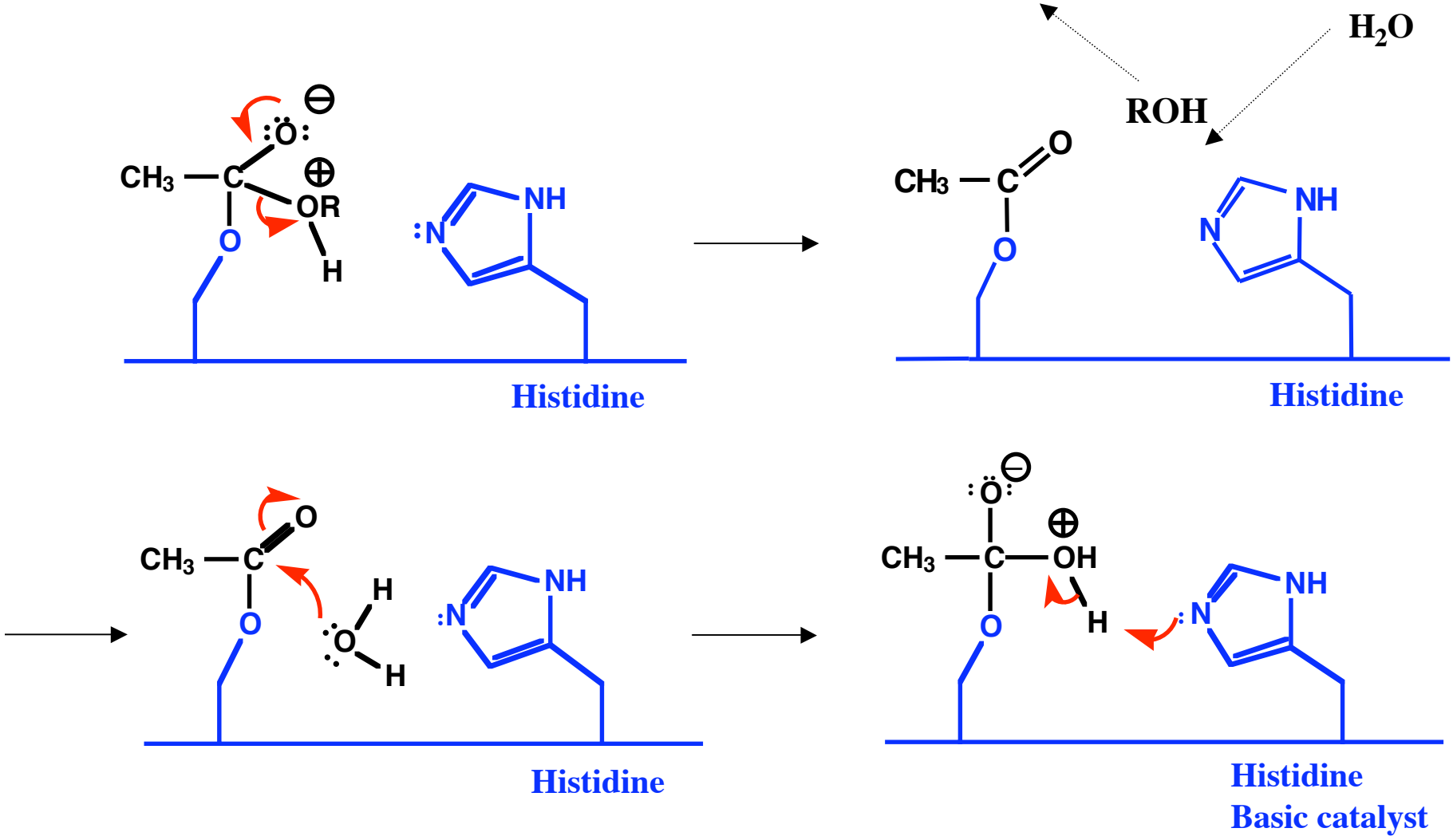
14. Acetylcholinesterase

14.6 Active site - Mechanism of catalysis



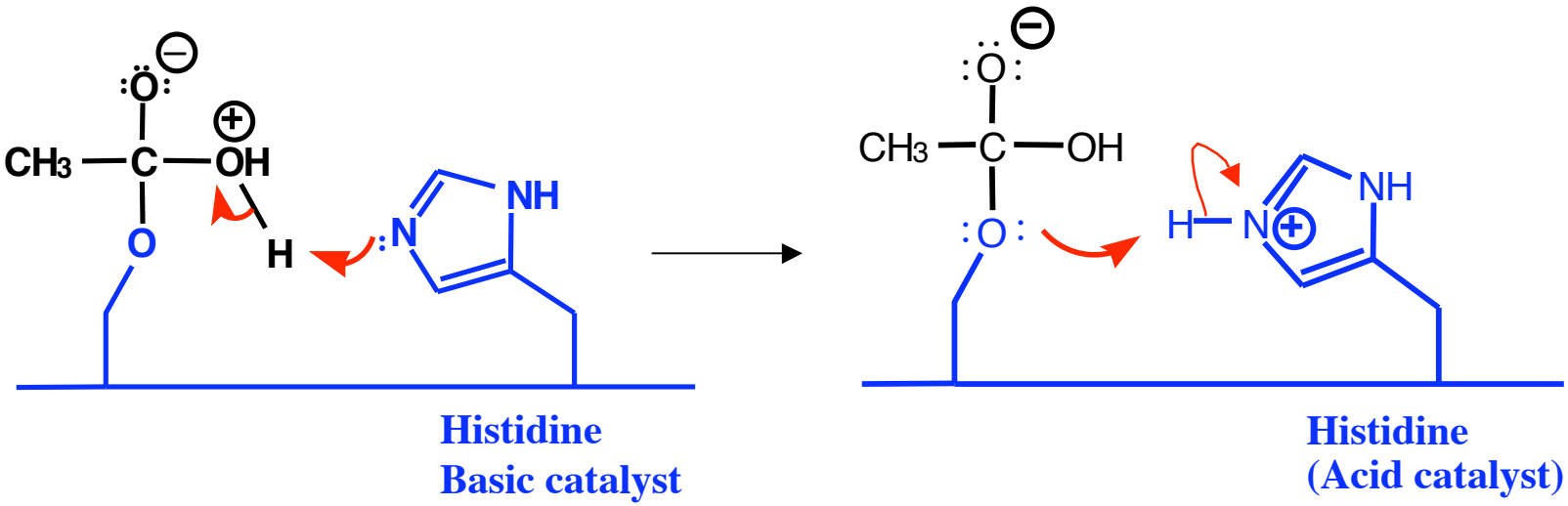
14. Acetylcholinesterase

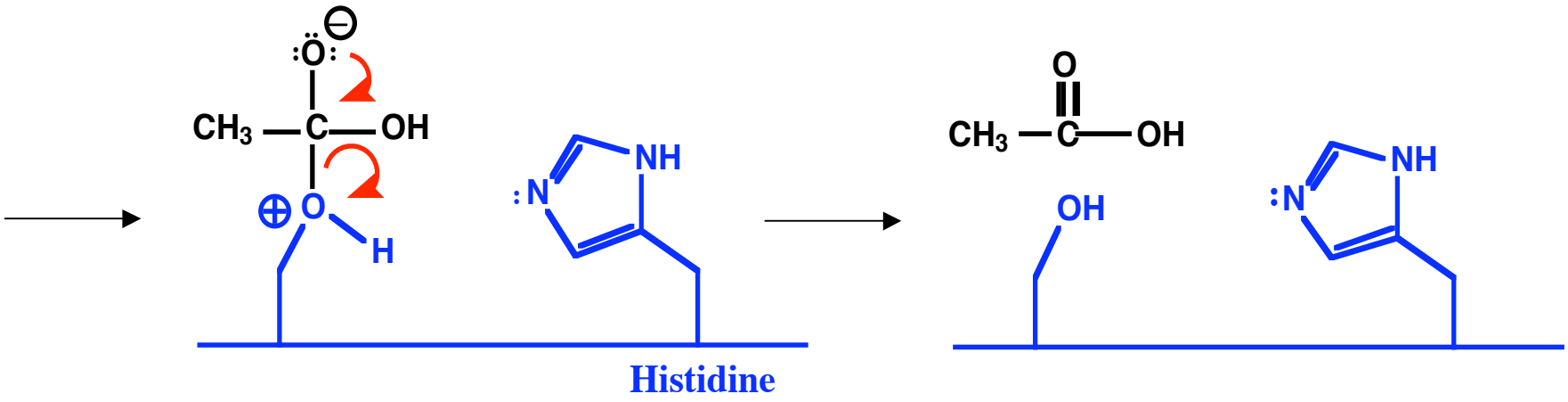
14.6 Active site - Mechanism of catalysis



14. Acetylcholinesterase

14.6 Active site - Mechanism of catalysis





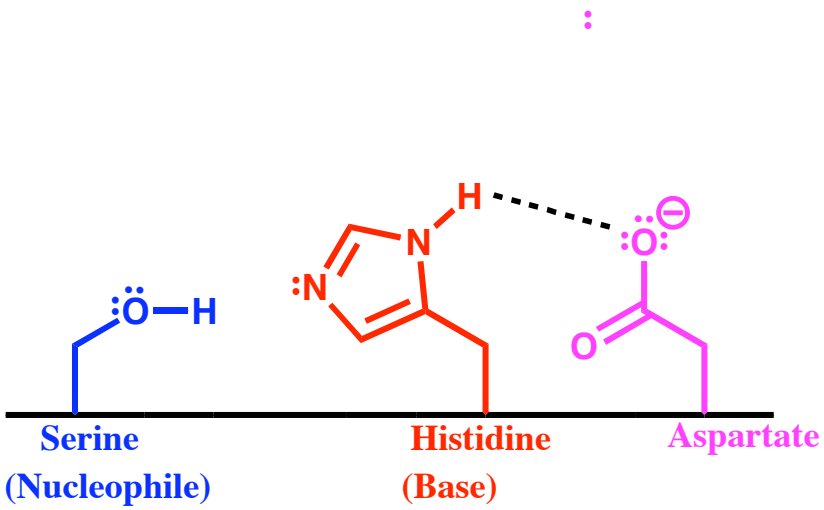
14. Acetylcholinesterase

- **Serine and water are poor nucleophiles**
- **Mechanism is aided by histidine acting as a basic catalyst**
- **Choline and serine are poor leaving groups**
- **Leaving groups are aided by histidine acting as an acid catalyst**
- **Very efficient - 100 x 10^6 faster than uncatalysed hydrolysis**
- **Acetylcholine hydrolysed within 100 μsecs of reaching active site**
- **An aspartate residue is also involved in the mechanism**

14. Acetylcholinesterase

The catalytic triad

- **An aspartate residue interacts with the imidazole ring of histidine to orient and activate it**

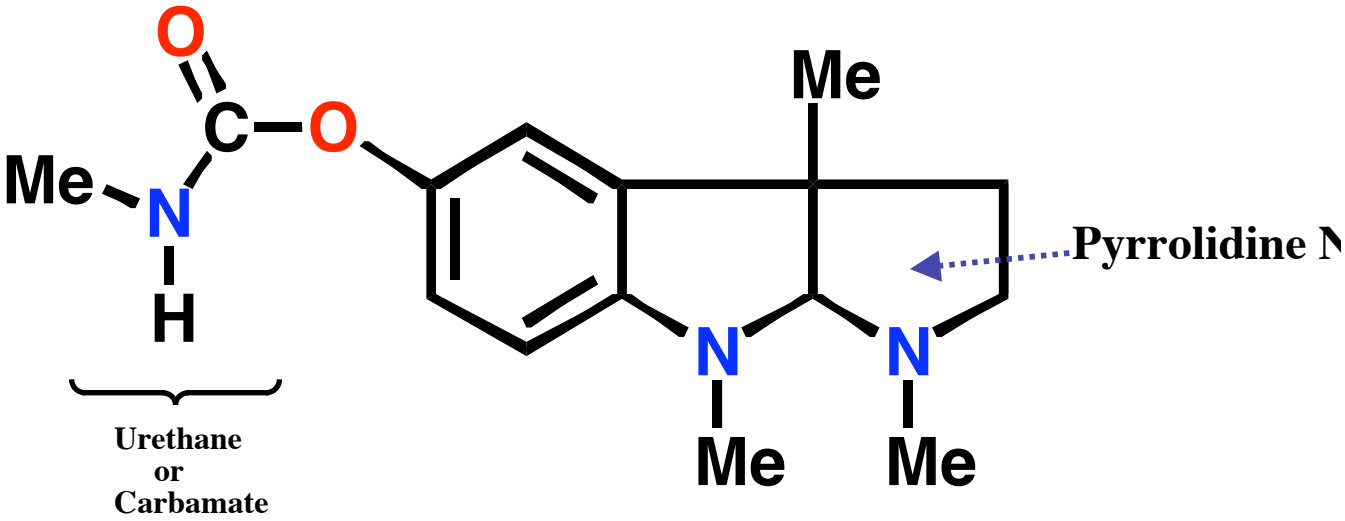


15. Anticholinesterases

- **Inhibitors of acetylcholinesterase enzyme**
- **Block hydrolysis of acetylcholine**
- **Acetylcholine is able to reactivate cholinergic receptor**
- **Same effect as a cholinergic agonist**

15. Anticholinesterases

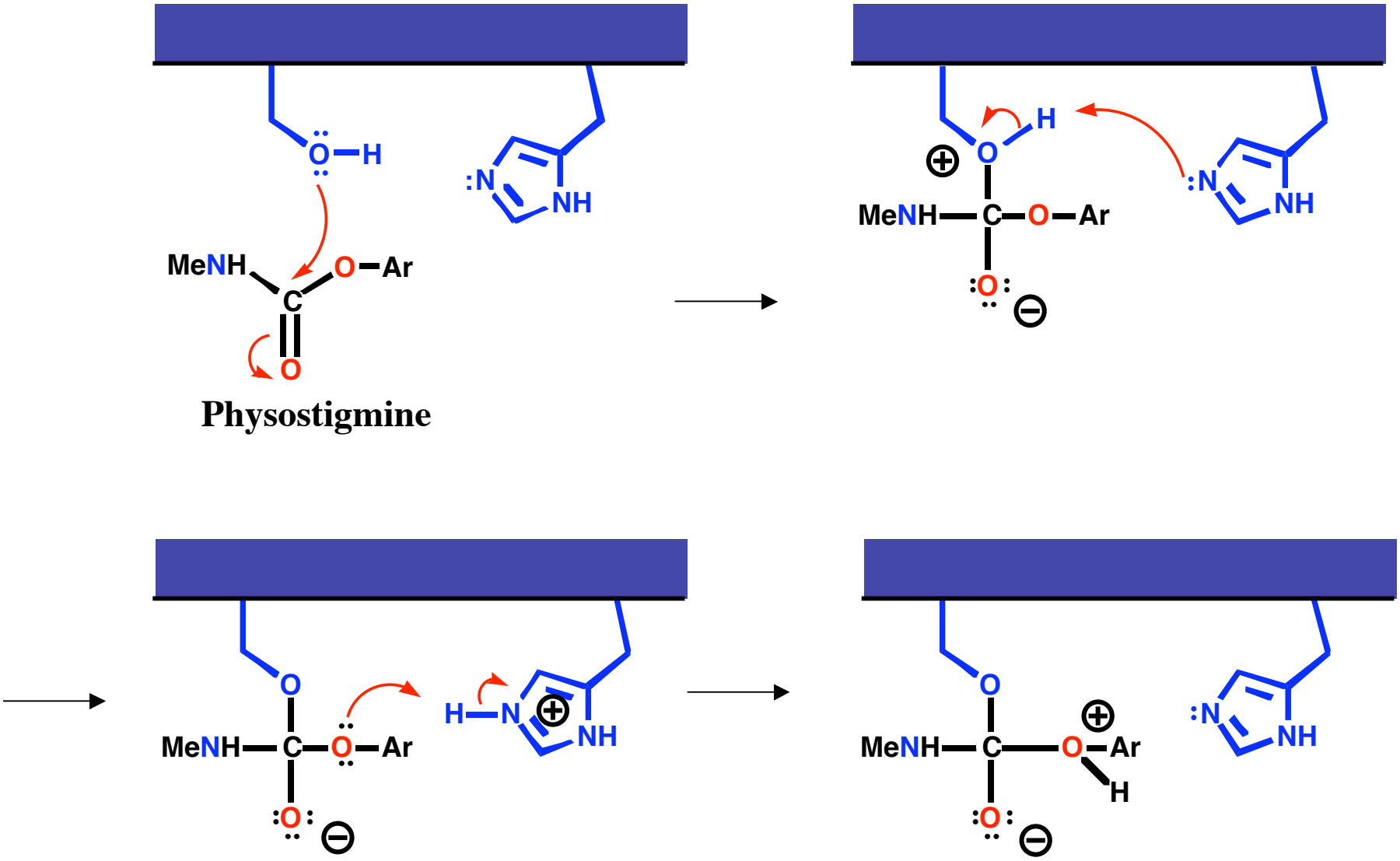
15.1 Physostigmine



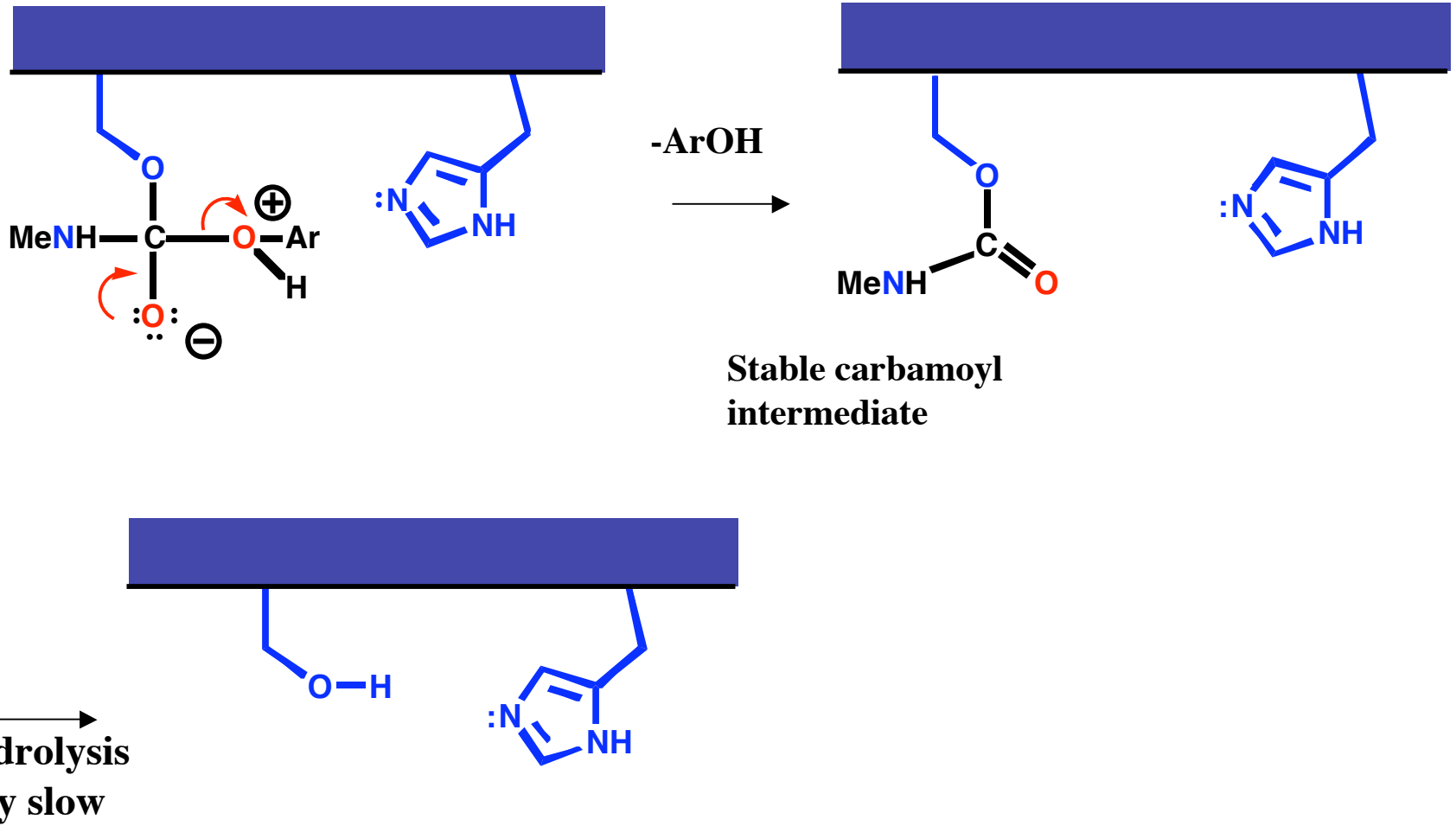
http://www.floradelaterre.com/index.php?id=19

- **Natural product from the African calabar (ordeal) bean-** ***Physostigma***
- **Carbamate is essential (equivalent to ester of Ach)**
- **Aromatic ring is important**
- **Pyrrolidine N is important (ionized at blood pH)**
- **Pyrrolidine N is equivalent to the quaternary nitrogen of Ach**

15.2 Mechanism of action

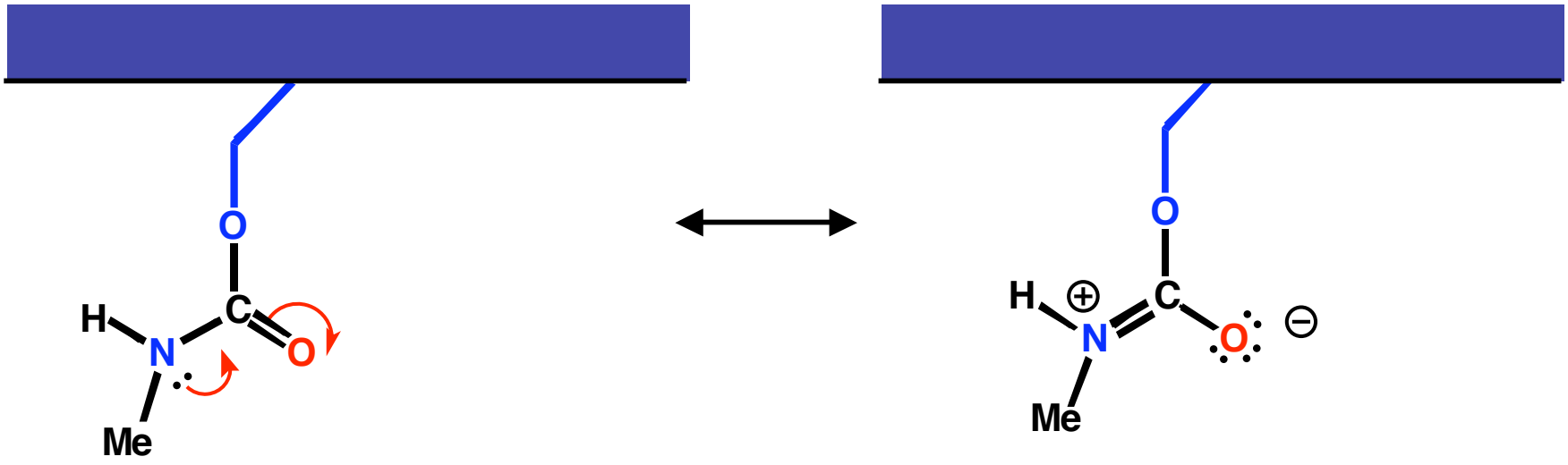


15.2 Mechanism of action



Rate of hydrolysis slower by 40 x 10^6

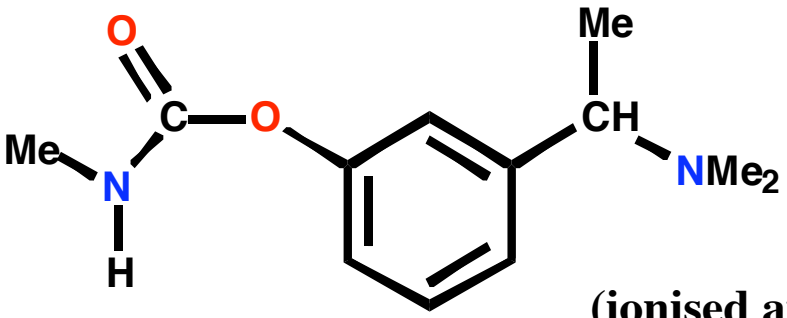
15.2 Mechanism of action



Stable carbamoyl intermediate

Carbonyl group 'deactivated'

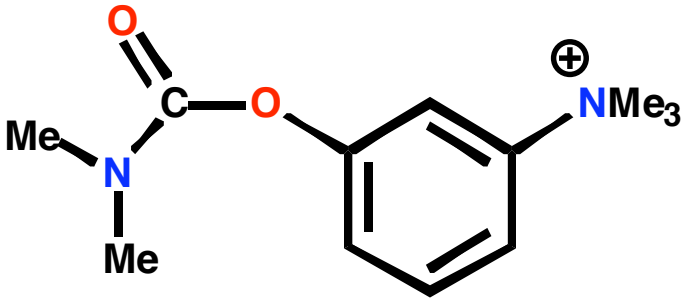
15.3 Physostigmine analogues



(ionised at blood pH)

Miotine

- Simplified analogue
- Susceptible to hydrolysis
- Crosses BBB as free base
- CNS side effects

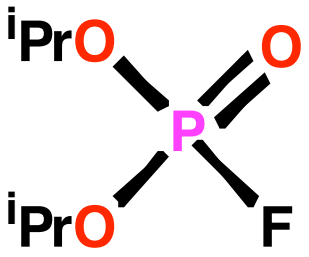


Neostigmine

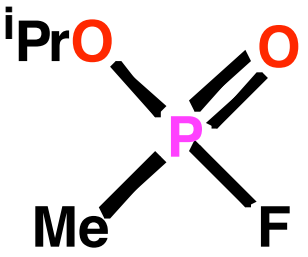
- Fully ionized
- Cannot cross BBB
- No CNS side effects
- More stable to hydrolysis
- Extra *N*-methyl group increases stability

15.4 Organophosphates

a) Nerve gases



Dyflos
(Diisopropyl fluorophosphonate)

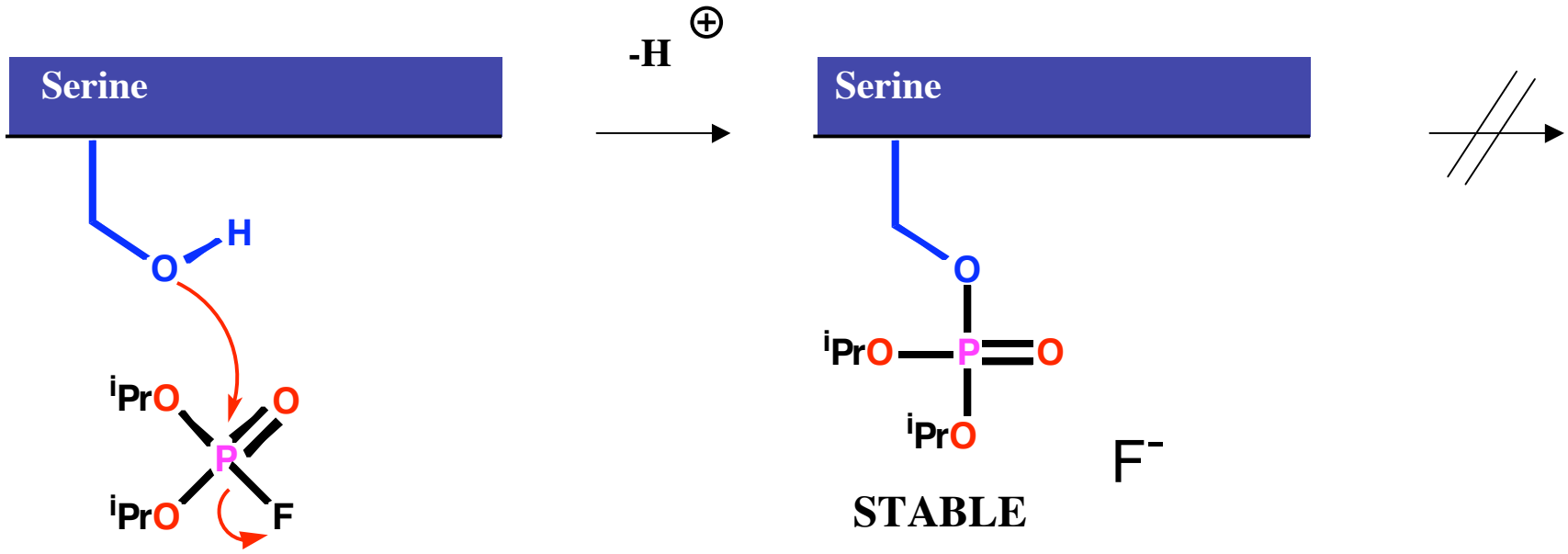


Sarin

- **Agents developed in World War 2**
- **Agents irreversibly inhibit acetylcholinesterase**
- **Permanent activation of cholinergic receptors by Ach**
- **Results in death**

15.4 Organophosphates

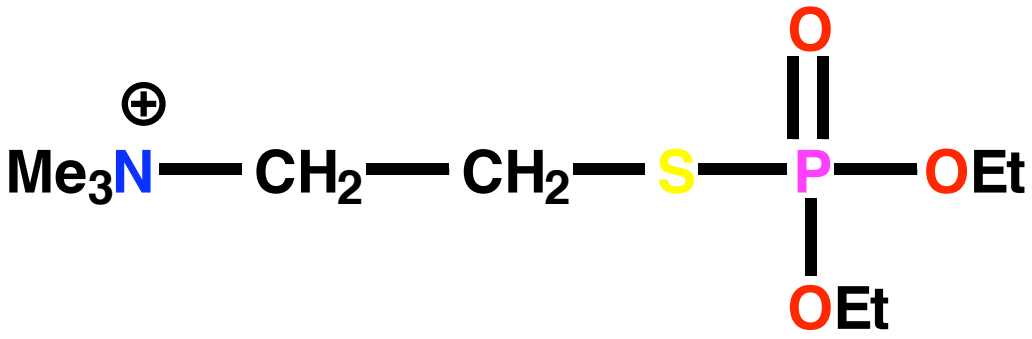
b) Mechanism of action



- **Irreversible phosphorylation**
- **P-O bond very stable**

15.4 Organophosphates

c) Medicinal organophosphate

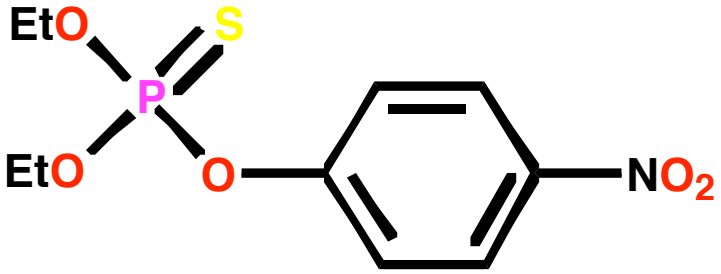


Ecothiopate

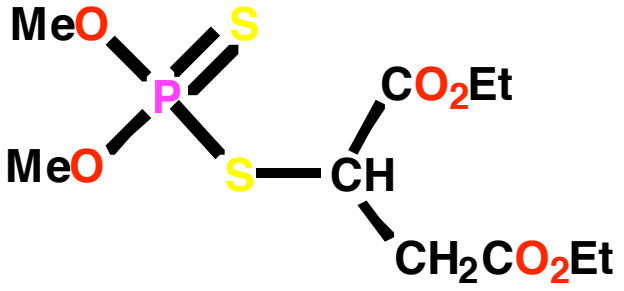
- Used to treat glaucoma
- Topical application
- Quaternary N is added to improve binding interactions
- Results in better selectivity and lower, safer doses

15.4 Organophosphates

d) Organophosphates as insecticides



Parathion



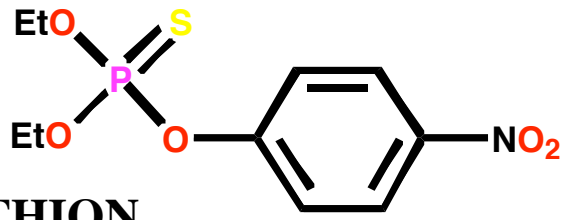
Malathion

- **Relatively harmless to mammals**
- **Agents act as prodrugs in insects**
- **Metabolised by insects to produce a toxic metabolite**

15.4 Organophosphates

d) Organophosphates as insecticides

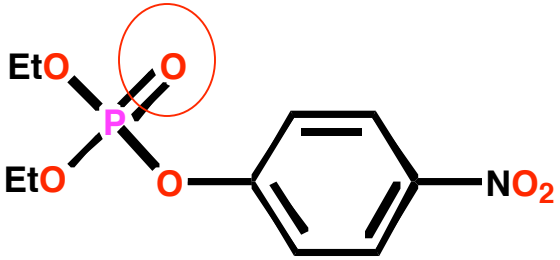
MAMMALS



PARATHION
(Inactive Prodrug)

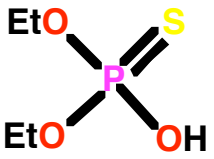
Insect
Oxidative
desulphurisation

INSECTS



Active drug

Mammalian
Metabolism



INACTIVE
& excreted

Phosphorylates enzyme

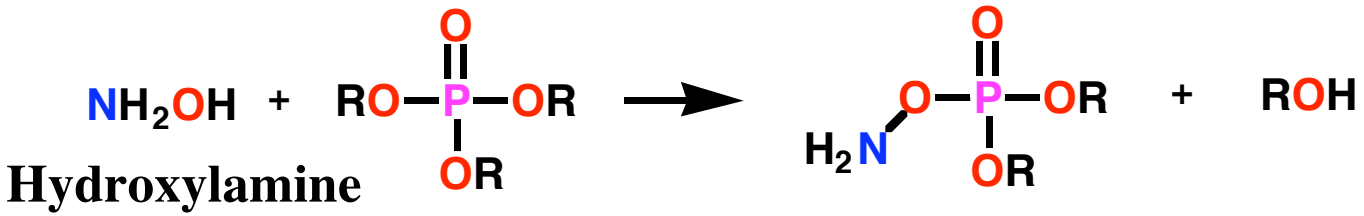
DEATH

15.4 Organophosphates

e) Design of Organophosphate Antidotes

Strategy

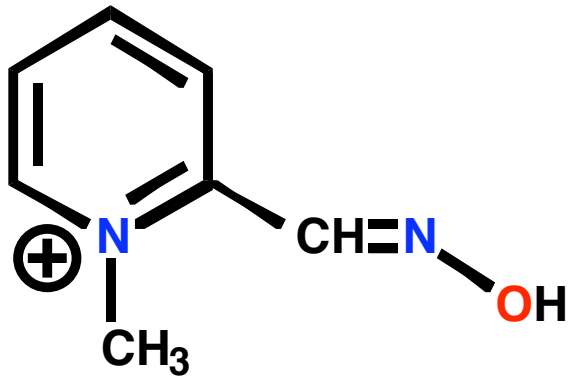
- **Strong nucleophile required to cleave strong P-O bond**
- **Find suitable nucleophile capable of cleaving phosphate esters**
- **Water is too weak as a nucleophile**
- **Hydoxylamine is a stronger nucleophile**



- **Hydroxylamine is too toxic for clinical use**
- **Increase selectivity by increasing binding interactions with active site**

15.4 Organophosphates

e) Design of Organophosphate Antidotes

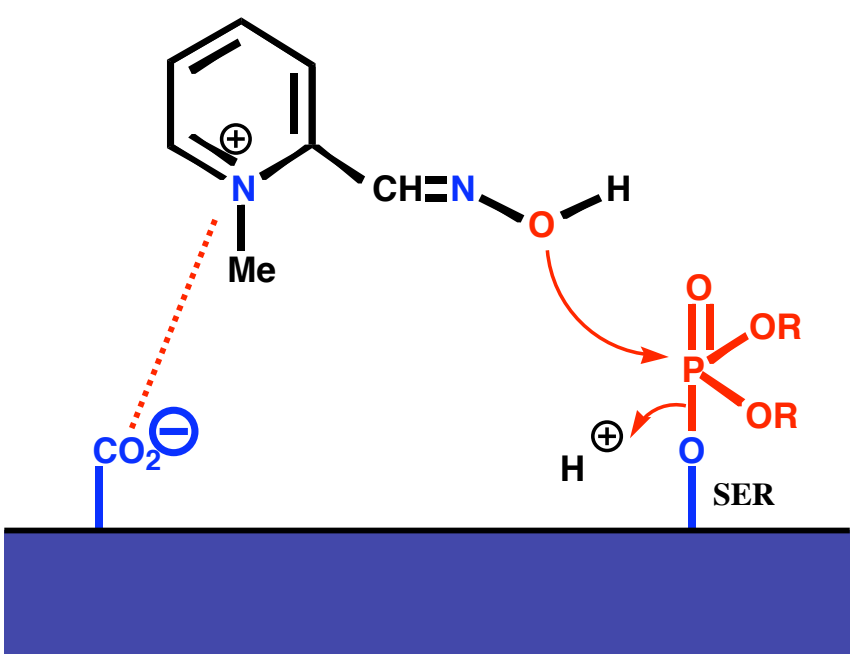


Pralidoxime

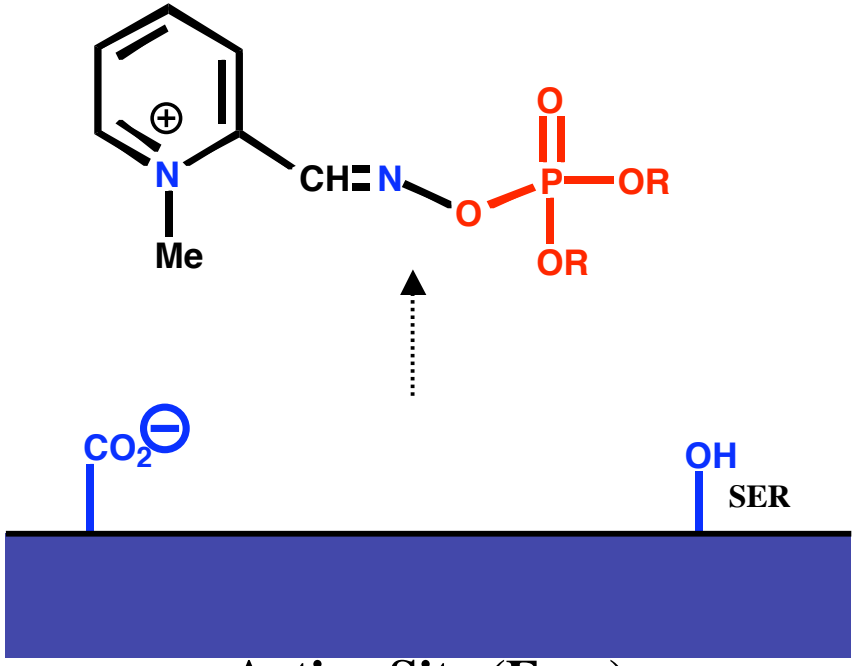
- **Quaternary N is added to bind to the anionic region**
- **Side chain is designed to place the hydroxylamine moiety in the correct position relative to phosphorylated serine**
- **Pralidoxime 1 million times more effective than hydroxylamine**
- **Cannot act in CNS due to charge - cannot cross bbb**

15.4 Organophosphates

e) Design of Organophosphate Antidotes



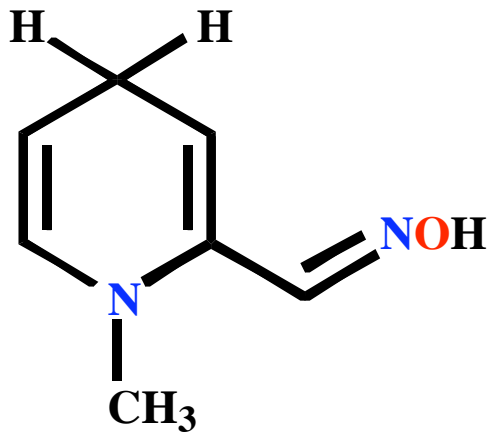
Active Site (Blocked)



Active Site (Free)

15.4 Organophosphates

e) Design of Organophosphate Antidotes



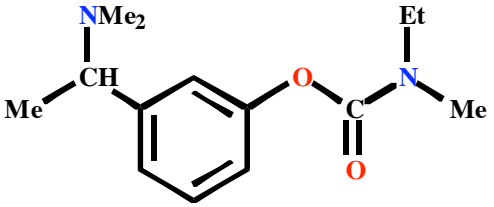
ProPAM

- **Prodrug for pralidoxime**
- **Passes through BBB as free base**
- **Oxidised in CNS to pralidoxime**

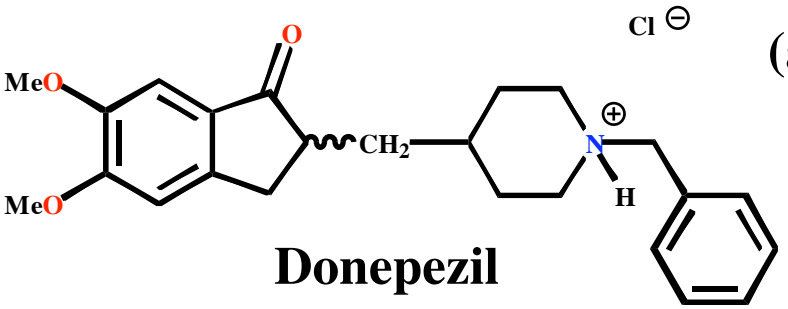
15.5 Anticholinesterases as 'Smart Drugs'

- **Act in CNS**
- **Must cross blood brain barrier**
- **Used to treat memory loss in Alzheimers disease**
- **Alzheimers causes deterioration of cholinergic receptors in brain**
- **Smart drugs inhibit Ach hydrolysis to increase activity at remaining receptors**

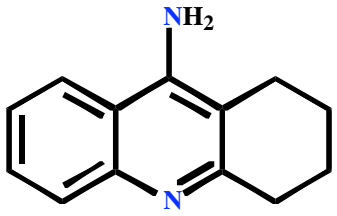
15.5 Anticholinesterases as 'Smart Drugs'



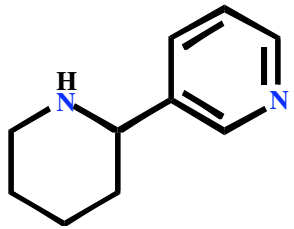
Rivastigmine (Exelon)
(analogue of physostigmine)



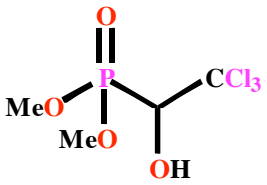
Donepezil



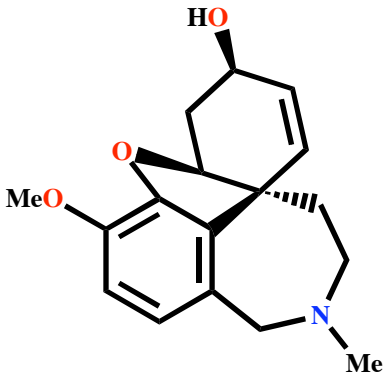
Tacrine (Cognex)
Toxic side effects



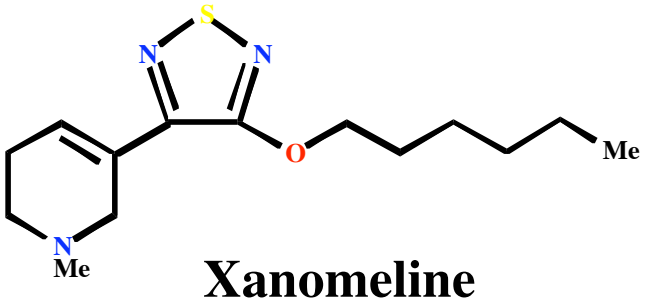
Anabaseine
(ants and marine worms)



Metrifonate
(organophosphate)



Galanthamine
(daffodil and snowdrop bulbs



Xanomeline