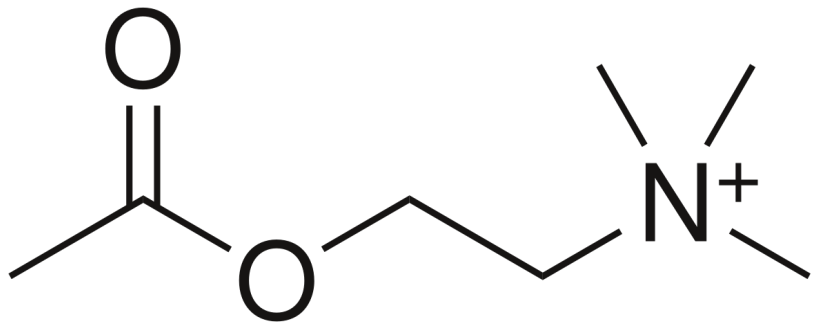
ACh

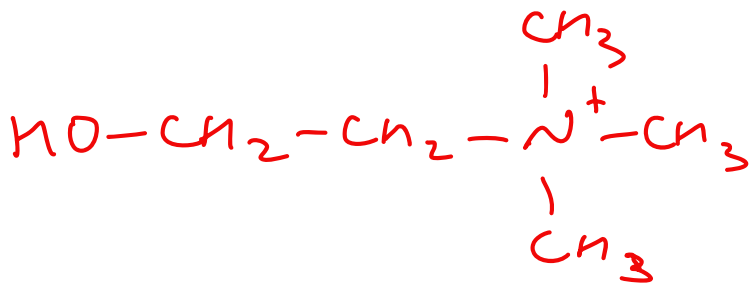
Acetylcholine Receptors

AChR



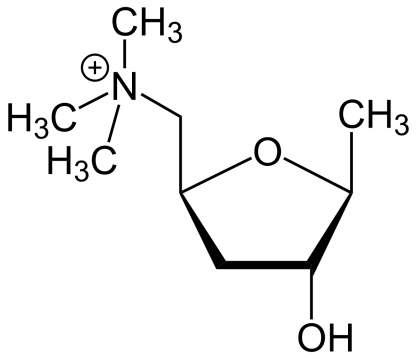
acetyl

Choline



- used by cholinergic system
- nicotinic + muscarinic receptors

low ACh levels associated with Alzheimer's

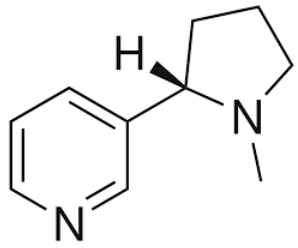


found in poisonous Amanita muscaria mushroom

muscarine

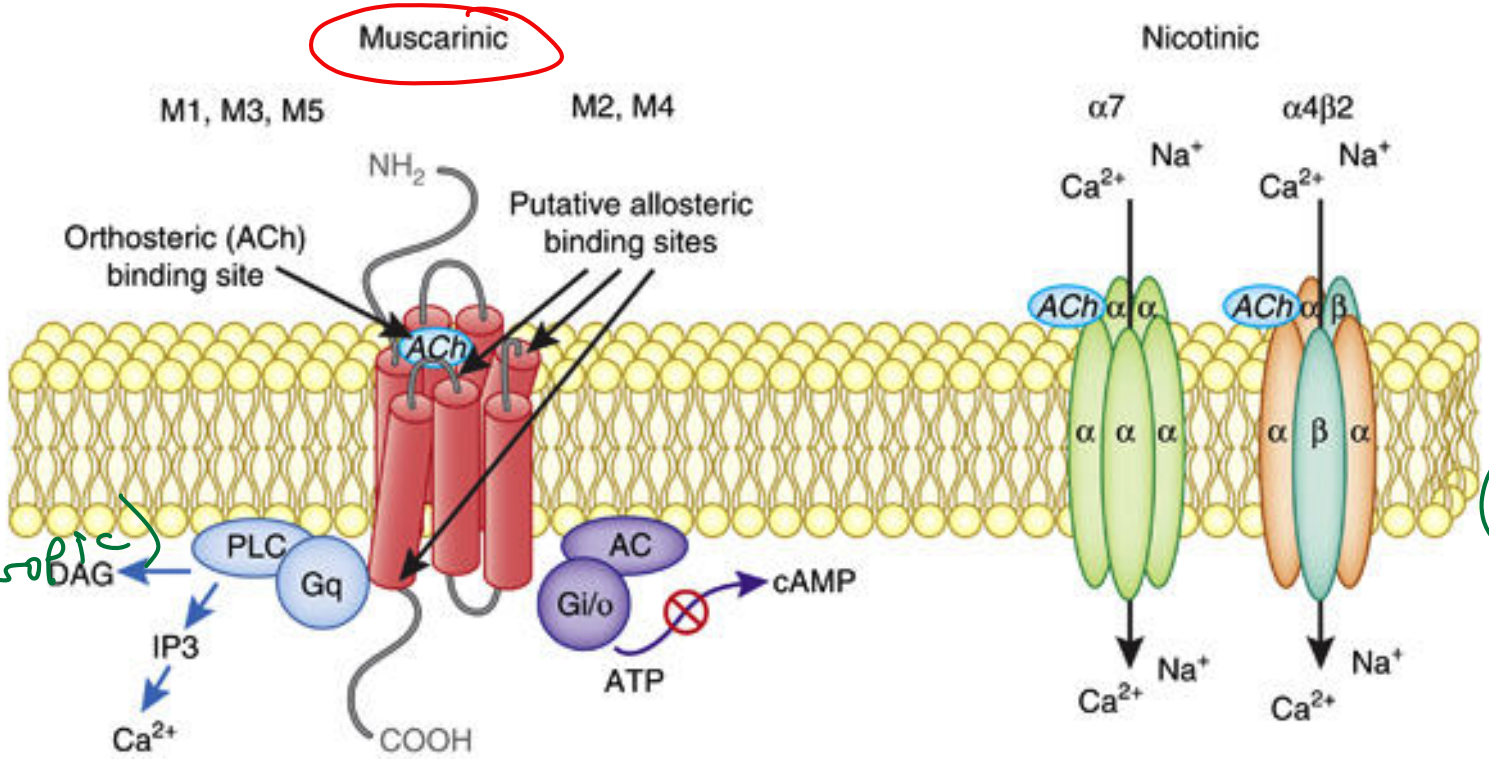
- smooth muscle involuntary
- cardiac muscle

nerve to



nicotine

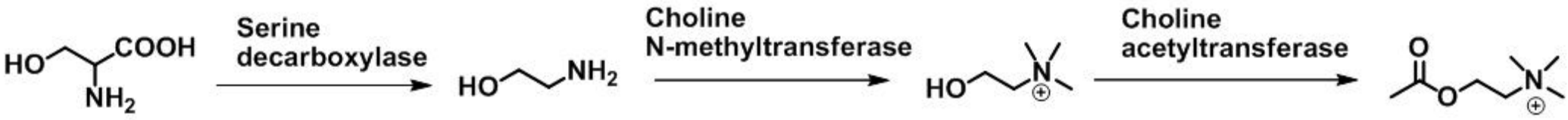
nerve to skeletal muscle



M type is GPCR (metabotropic)

N type ion channel (ionotropic)

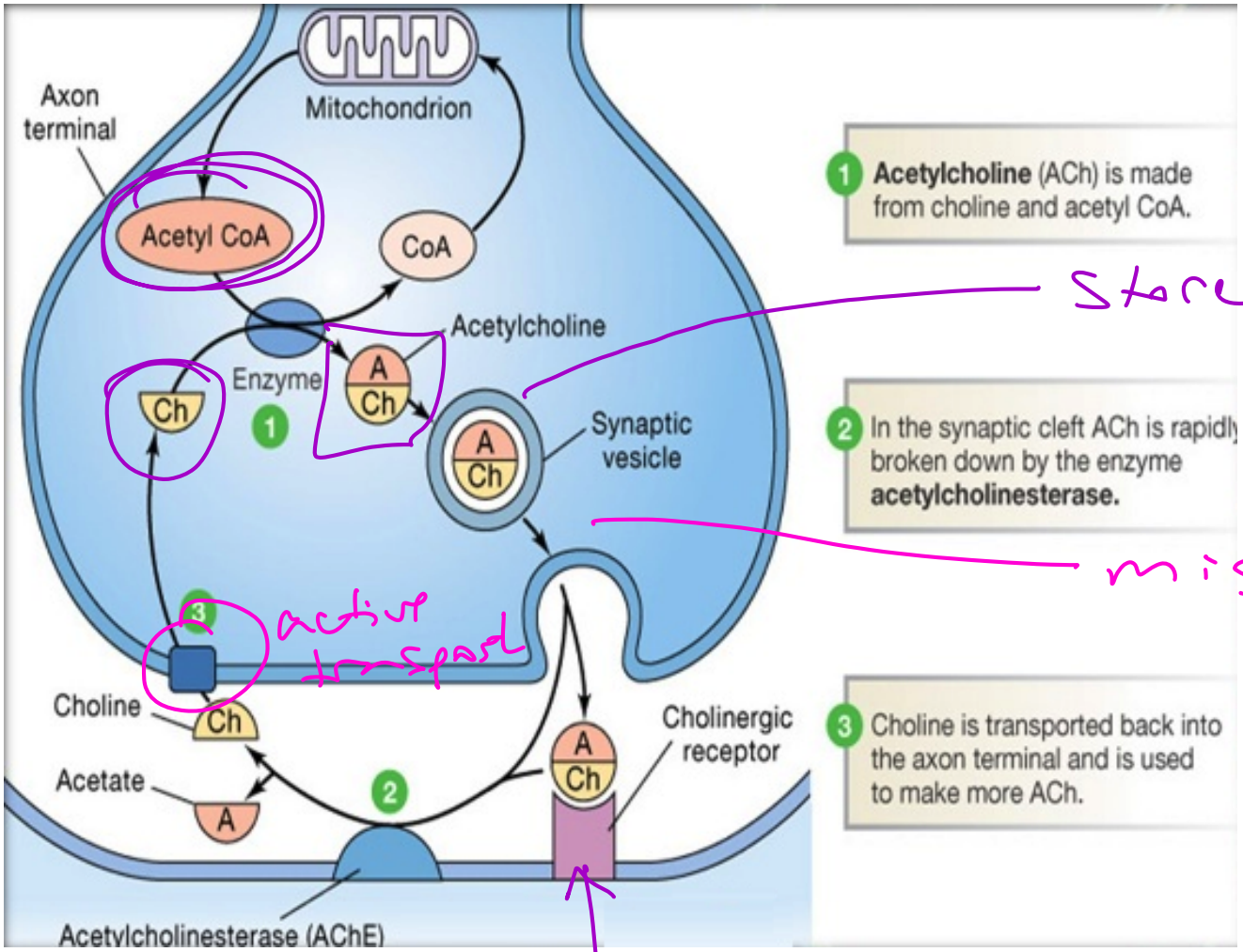
Biosynthesis Starts with Serine



ethanolamine

choline

Ach



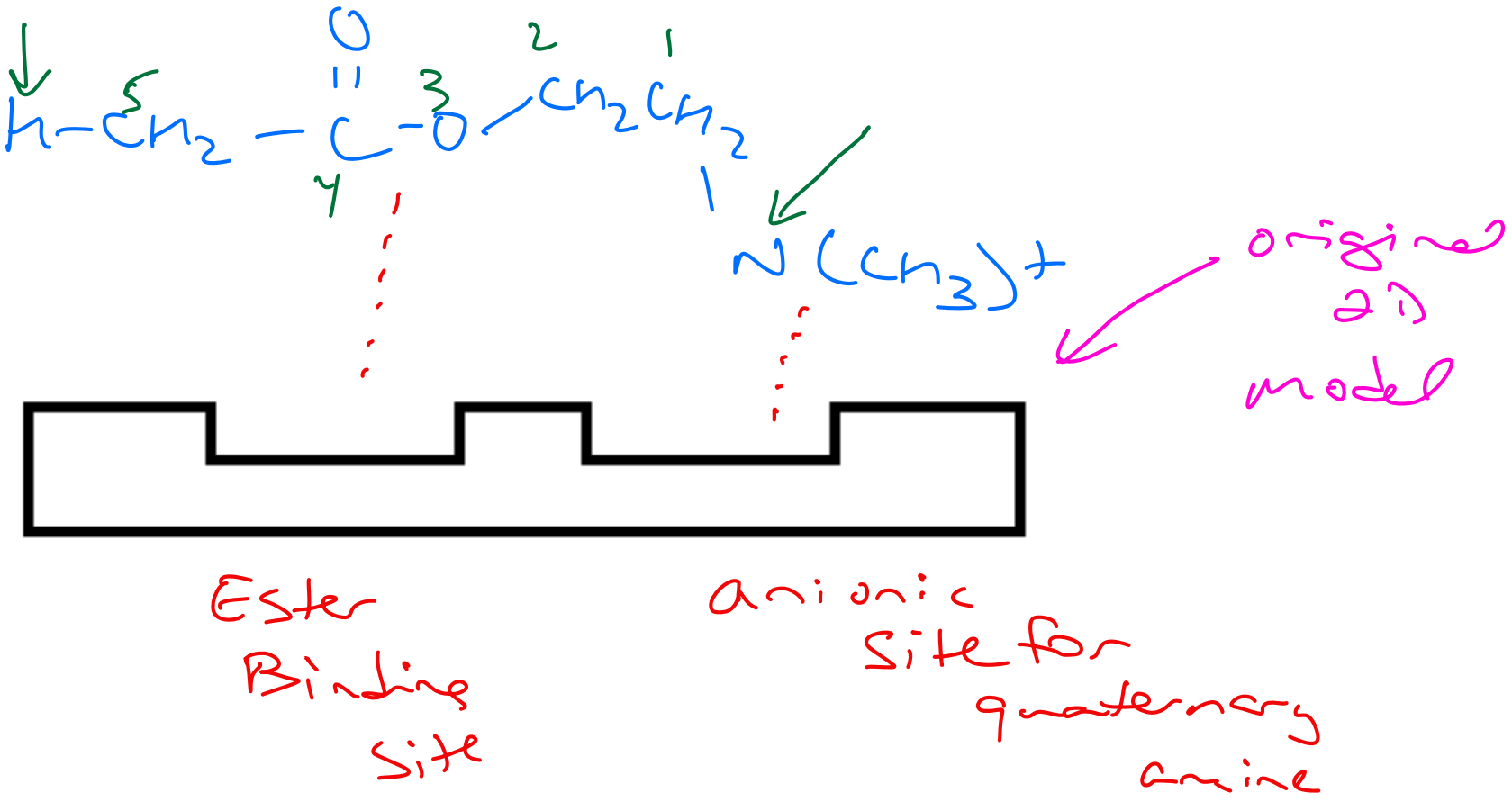
store in vesicle

migration of vesicle is triggered by Ca^{++} signal

active transport

can create signal here

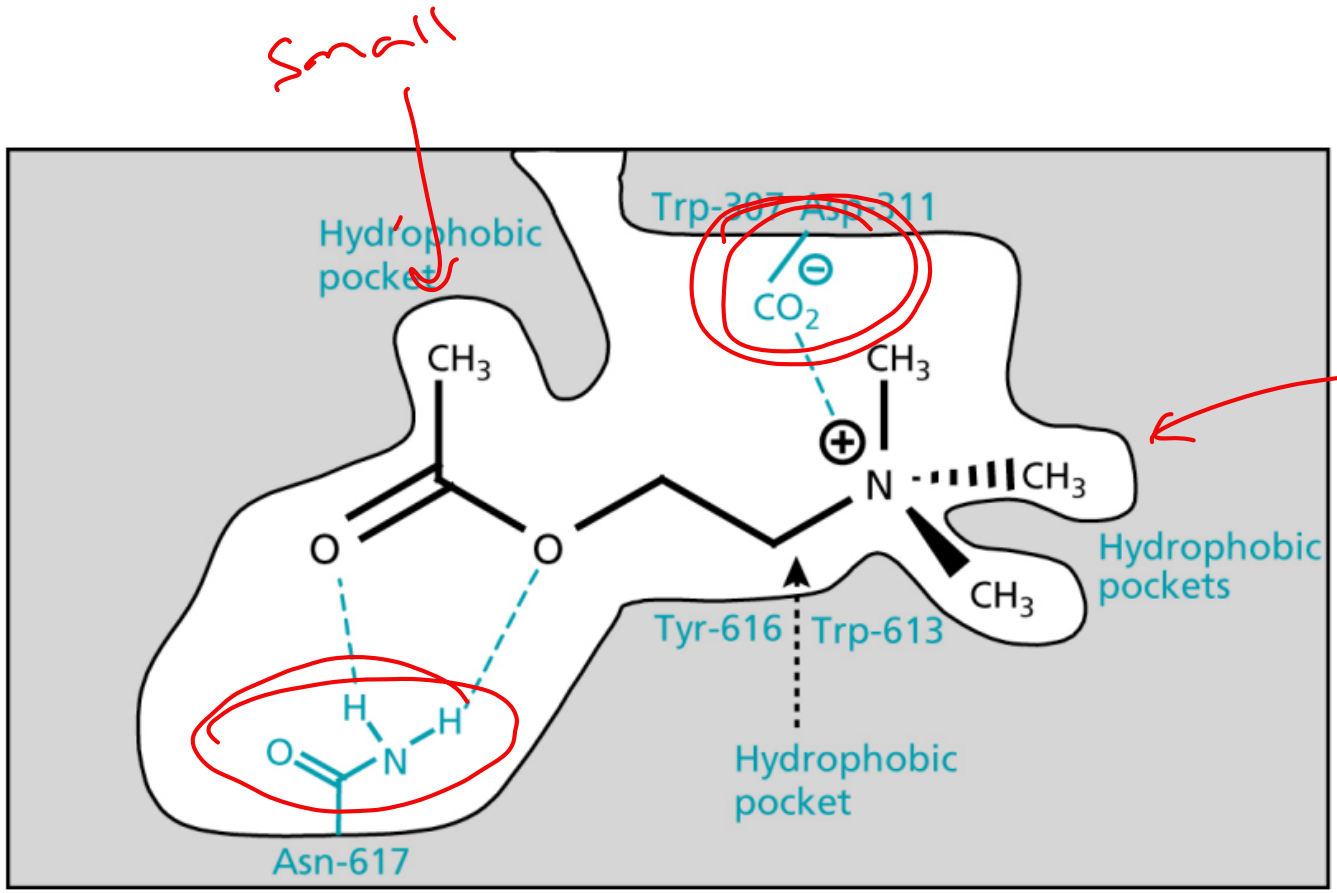
then broken down by AchE to stop signal



* 4° amine needs 2 methyl groups

* Stereochemistry matters

* Ing's Rule need 5 atoms between N + terminal H



Ach not very stable

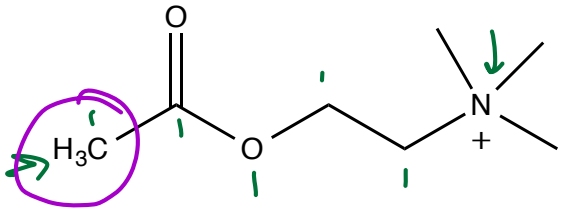
(1) ester hydrolyzes easily (H_2O hydrolysis)

(2) esterases cleave it

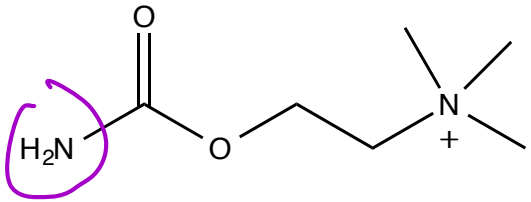
Direct Cholinergics

(1) make more stable to H^+ / OH^- H_2O hydrolysis

Ach



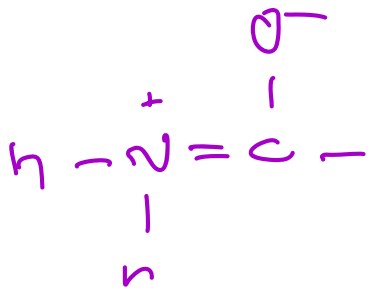
replace $-CH_3$ or / $-\ddot{N}H_2$



← Carbachol

miotic

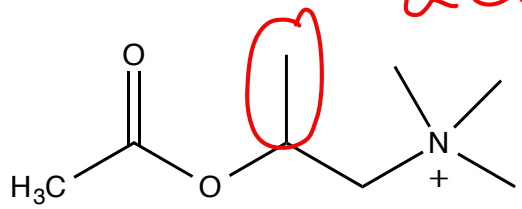
for ocular surgery



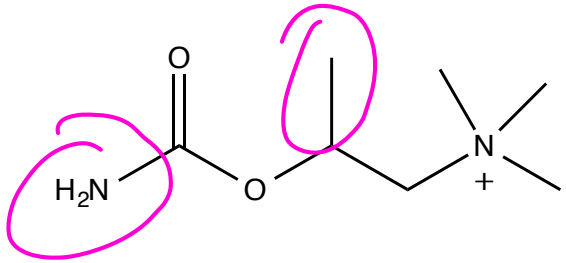
⟸ not as susceptible to nucleophilic attack

(2) make more stable to esterase

add a methyl to give steric hindrance



methacholine – used to diagnose asthma



Both = Bethanechol

orally effective

Empty bladder surgery?

Muscarinic Receptors

M_1 ganglia; gastric glands; CNS ← learning + motor fx

↑ acid secretion

M_2 cardiac muscle

↑ decreases contractility

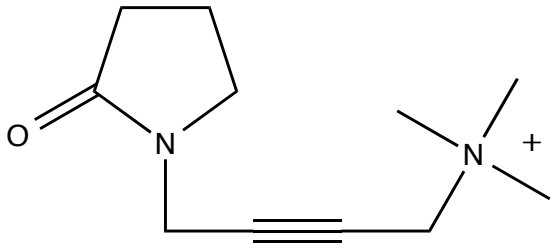
M_3 smooth muscle; endocrine glands

constriction of pupils, vasodilation

Agonists

Antagonists

M_1



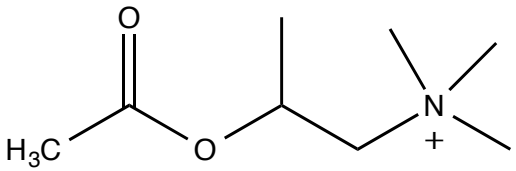
oxotremorine

Induces PD type symptoms

Pirenzepine

reduces gastric acid

M_2

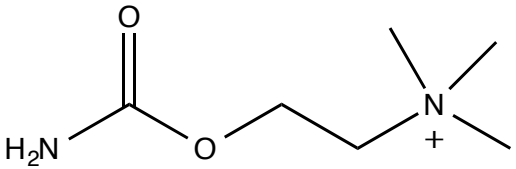


methacholine

gallamine

neuromuscular blocking agent

M_3



Bethanechol

darifenacin

incontinence + Overactive bladder

Nicotinic Receptors

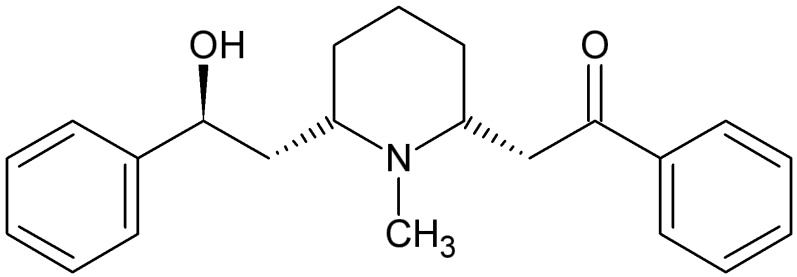
N_N Autonomic ganglia — release of epinephrine from adrenal medulla

neural

N_M Skeletal muscle — skeletal muscle contraction

muscle

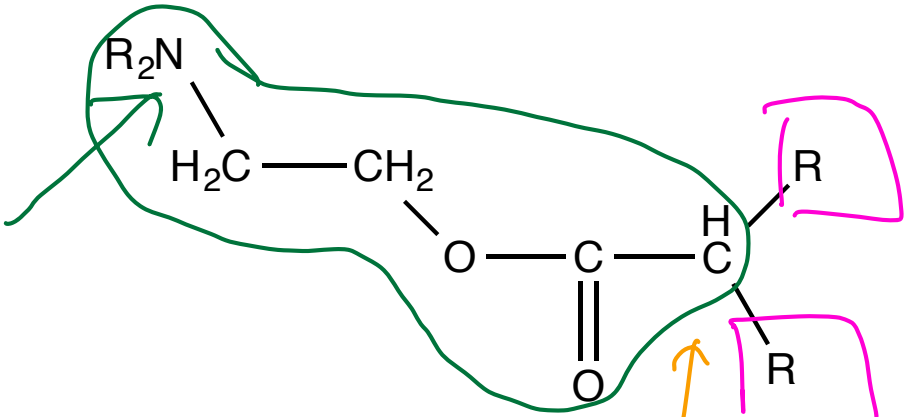
lobeline



lobelia

General AChR Antagonists

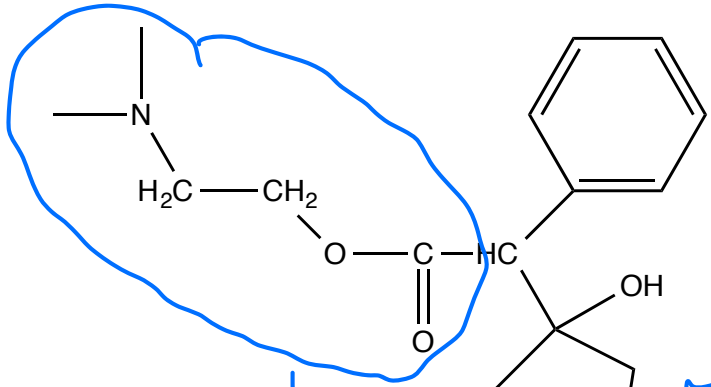
most are amino alcohol esters



aromatic or heteroaromatic

is $-CH_3$ in ACh

Cyclogyl



F

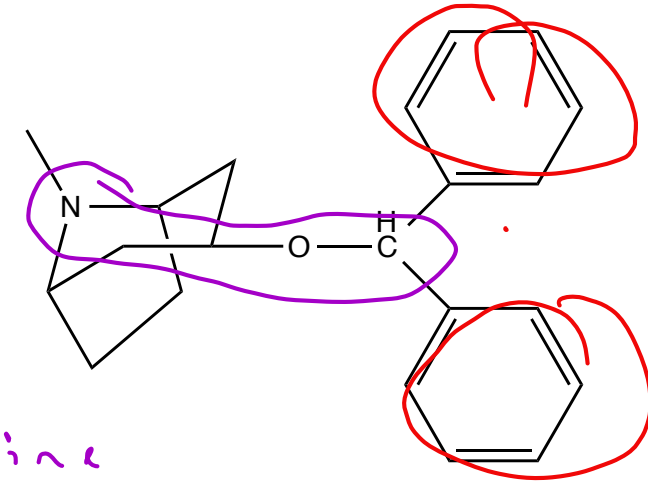
London Dispersion Interactions to extra sites

receptor

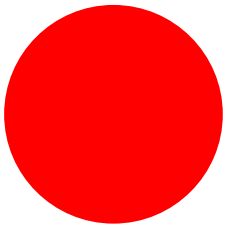
AChR Binding site

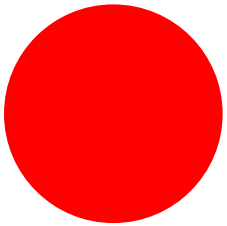
can use ethers instead of esters

Amino alcohol ethers



Benztropine
(cogentin)
used for PD

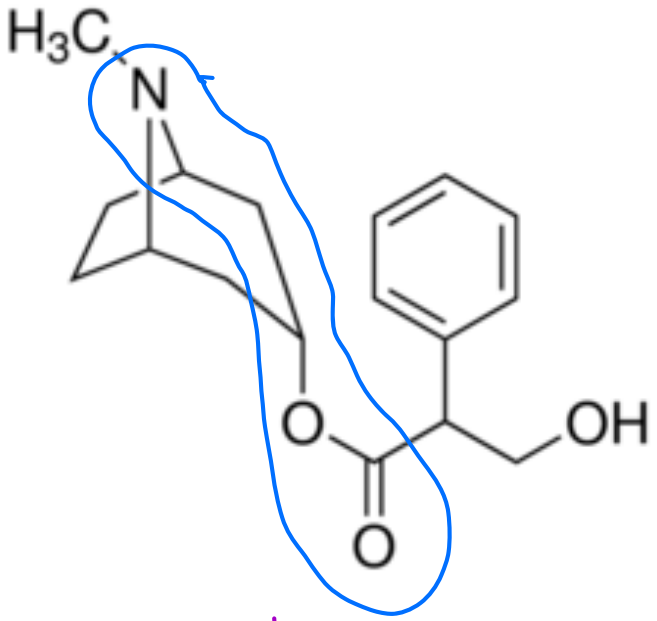




Similar
to atropine

AChR Antagonists

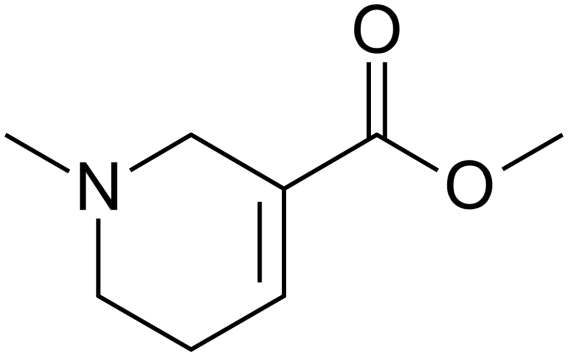
Atropine



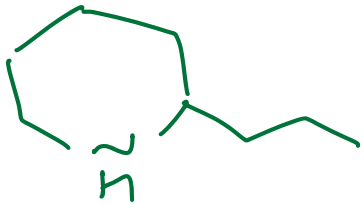
- antisecretory
- can be used for rhinitis
- dilates the eyes

Belladonna (deadly nightshade)

AChR Antagonists



Arecholine



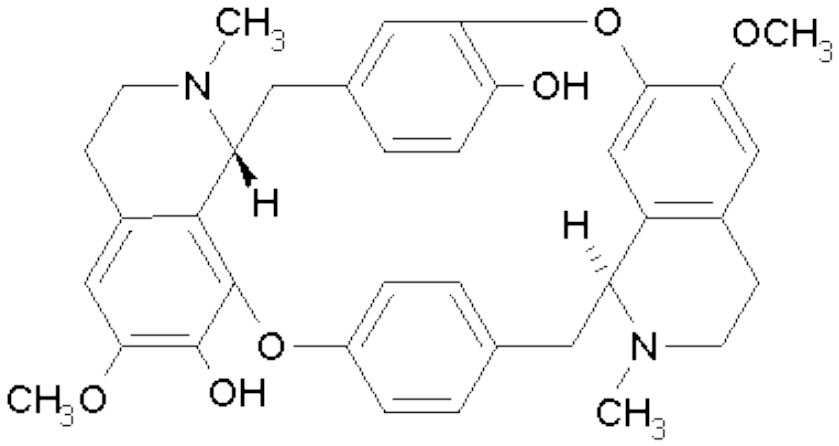
Coniine

Poison hemlock

Betelnut

Stimulant

AChR Antagonists



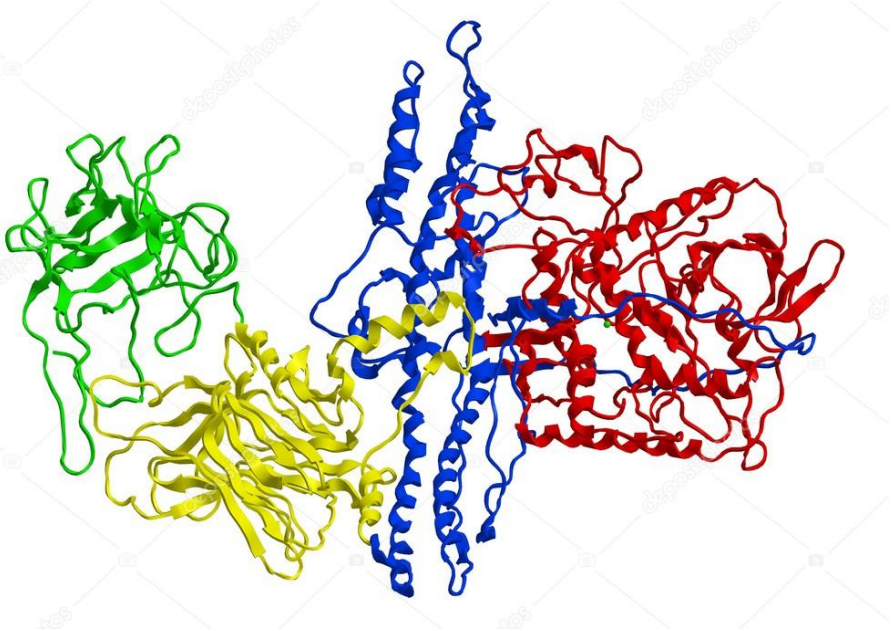
Curare

d-tubocurarine

used as poison
for tips of arrows

found in Amazon

AChR Antagonists



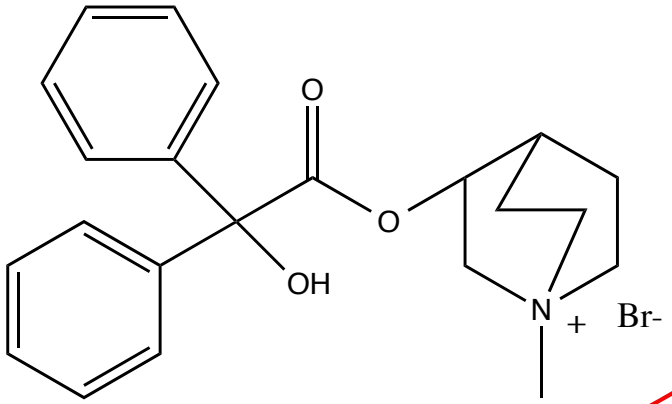
Botulinum toxin

~150 kDa

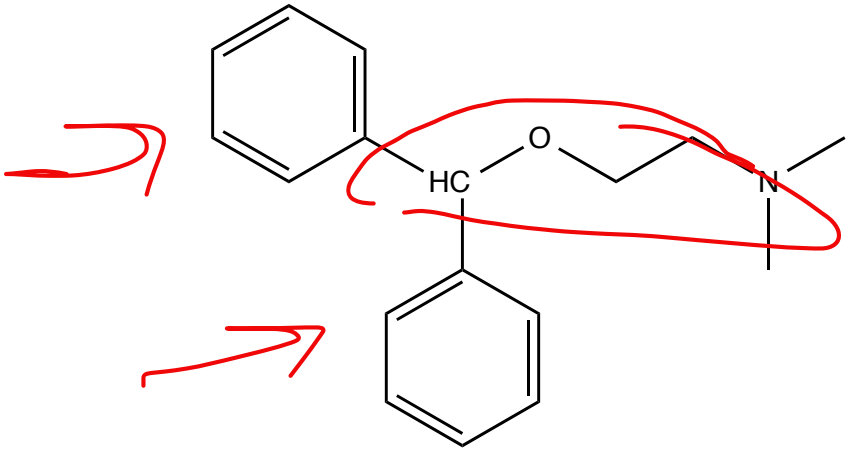
LD_{50} ~ 1ng/kg

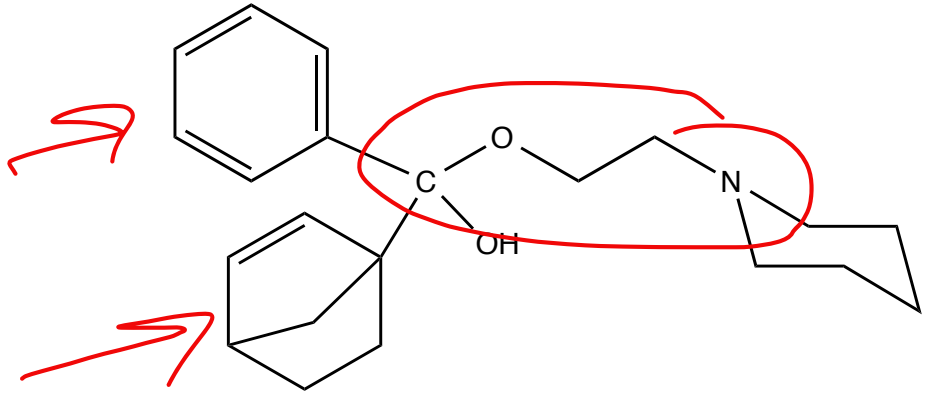
Clostridium botulinum

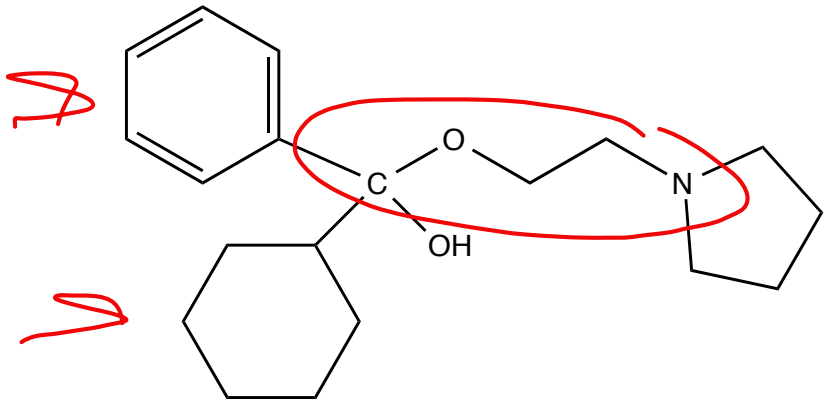
AChR Antagonists



AChR Antagonists







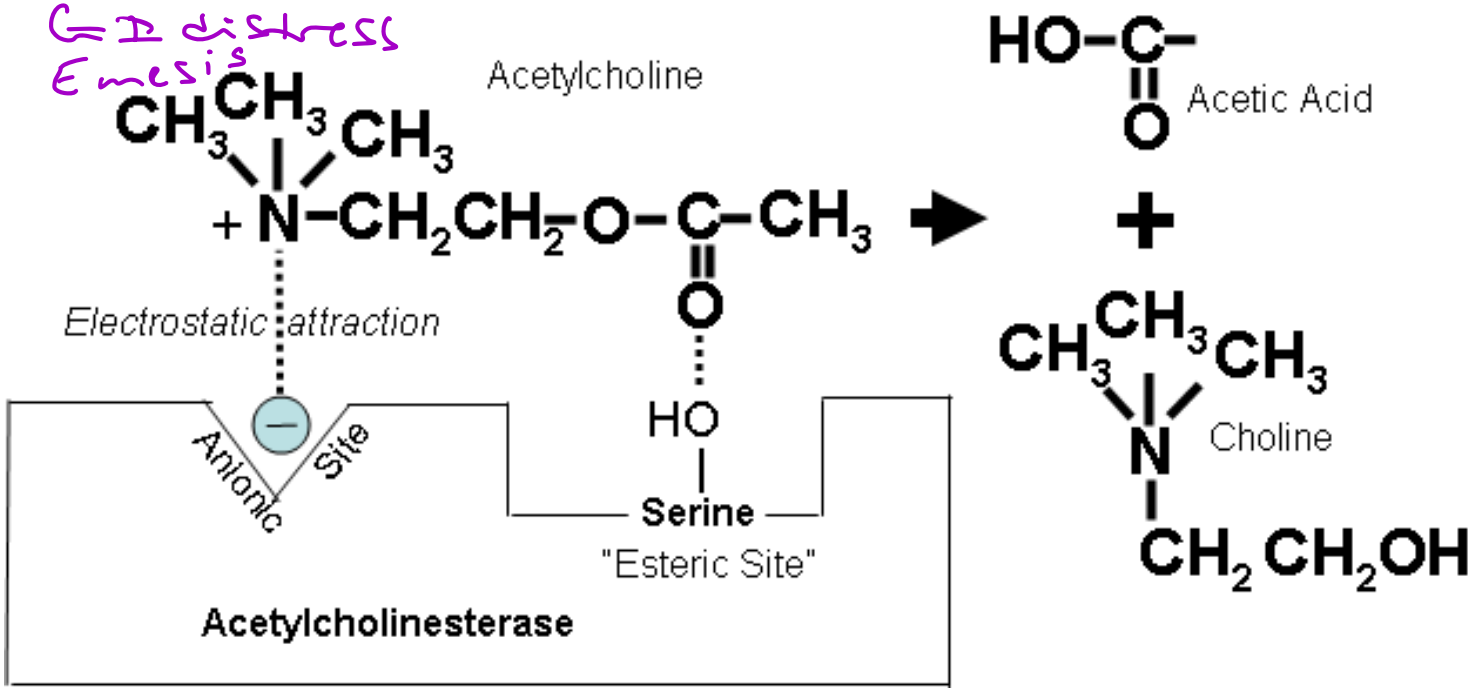
Indirect Cholinergics

→ mostly Ach esterase inhibitors

→ build up of Ach

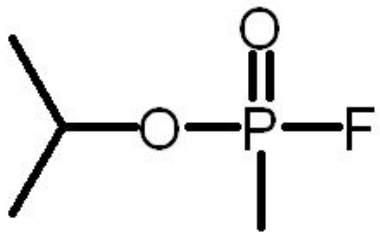
→ continous contraction of muscle → death

Salivation
Lacrimation
Urination
Defecation
GI distress
Emesis

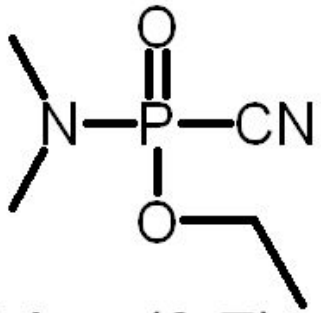


Irreversible AChE Is

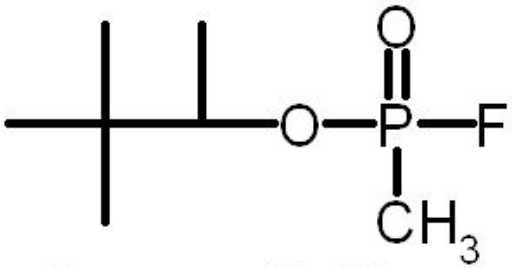
Nerve Gases (LD50,mg/kg) Insecticides



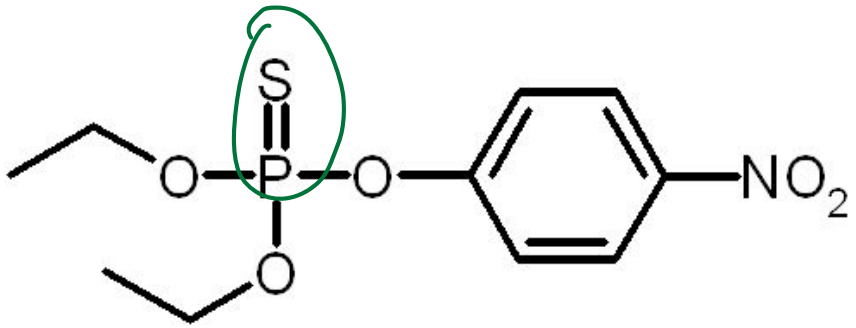
Sarin(0.55)



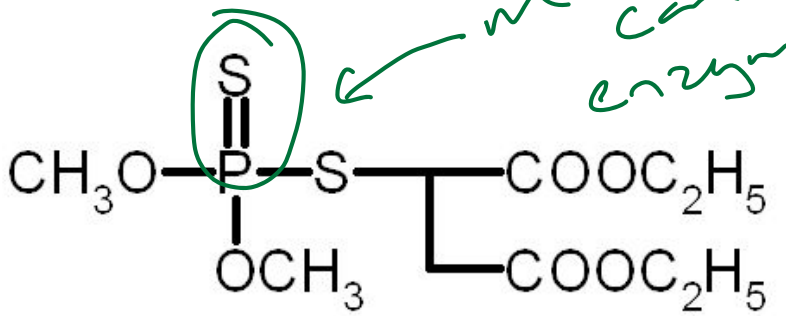
Tabun(3.7)



Soman(0.8)



Parathion(10)

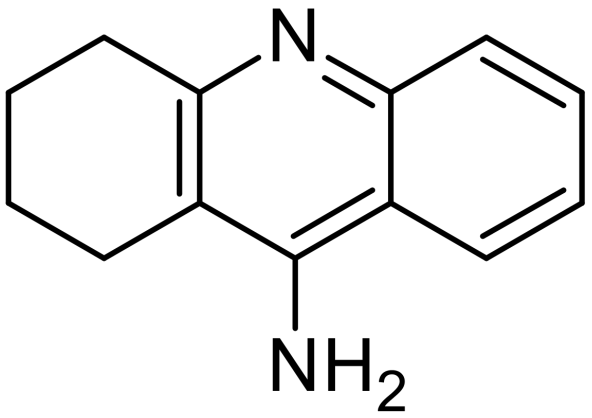


mammals can enzymatically cleave this

Malathion(1000)

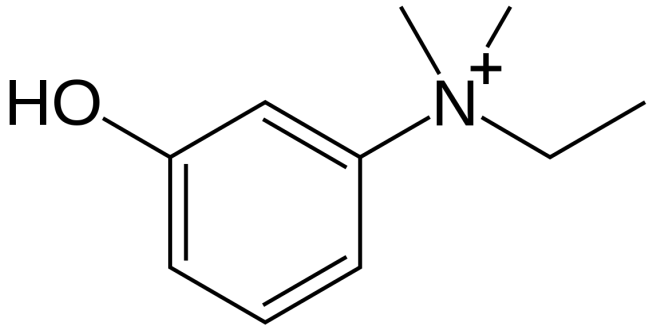
Reversible AchEI's

Tacrine



← used for Alzheimer's

Edrophonium



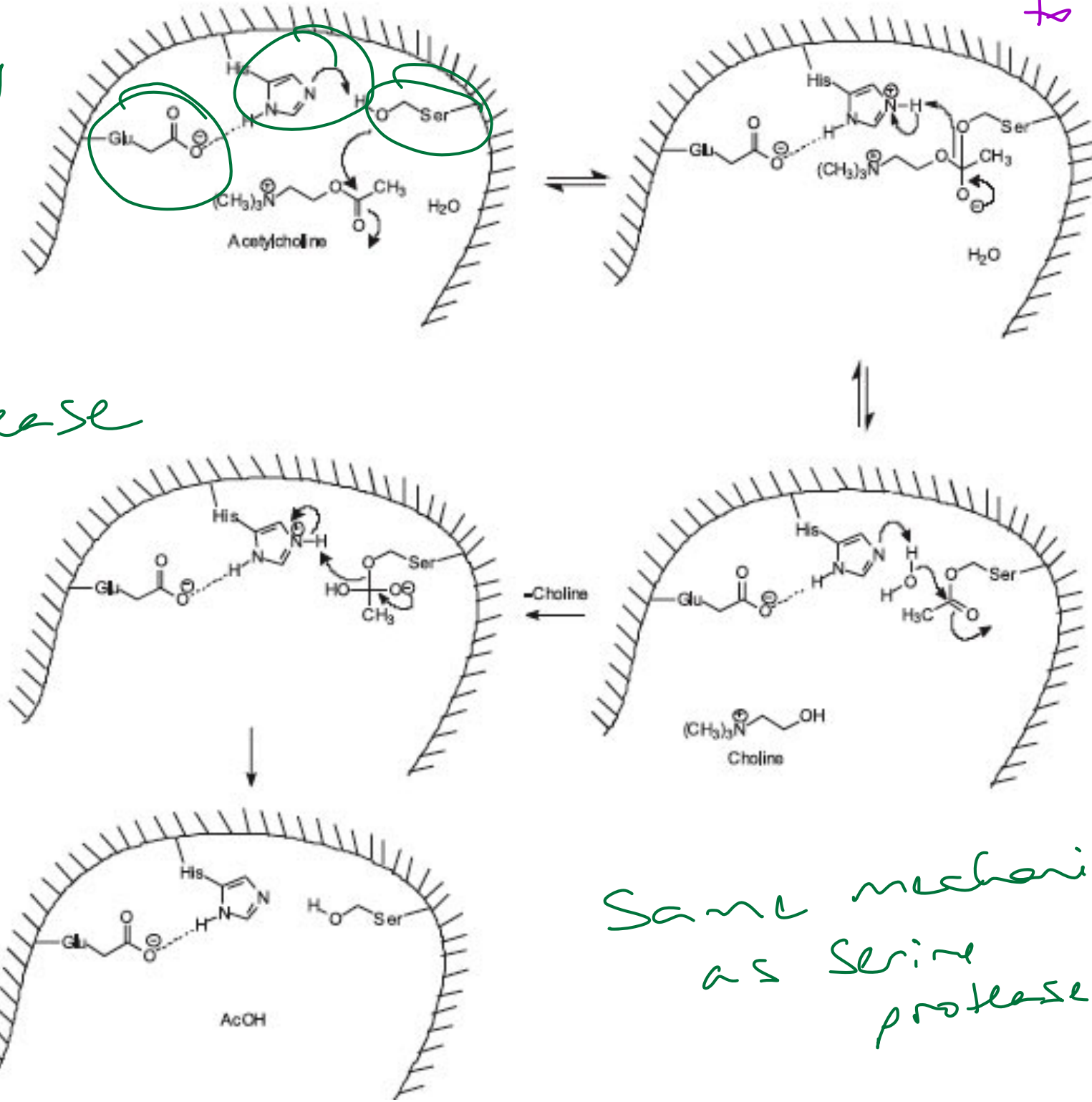
← used to treat poisonings by agonists like curare or atropine

also to treat myasthenia gravis

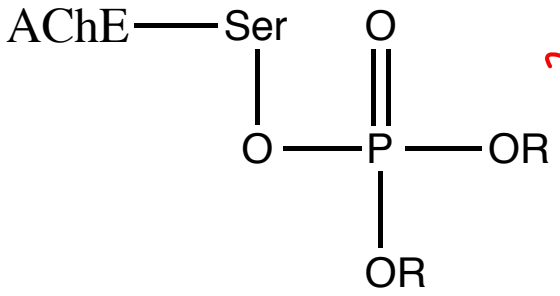
→ auto immune disease where body makes antibodies

to AchR's

Active site like Serine protease

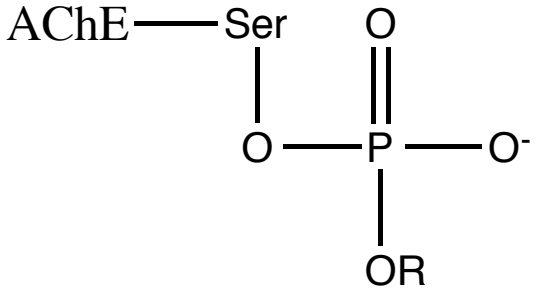


Same mechanism as Serine protease



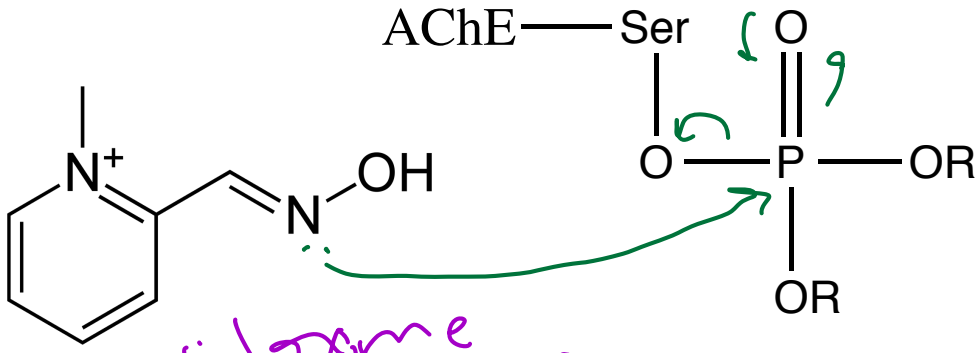
pretty stable

aging

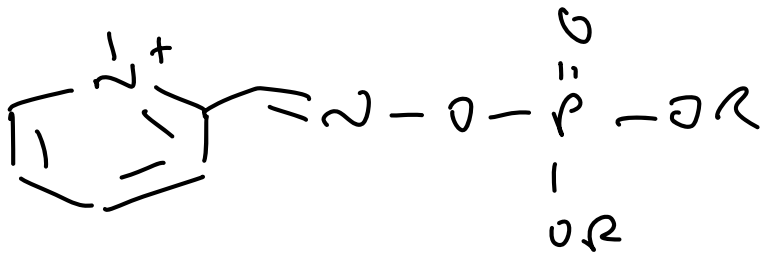


really stable

once here very stable to hydolysis



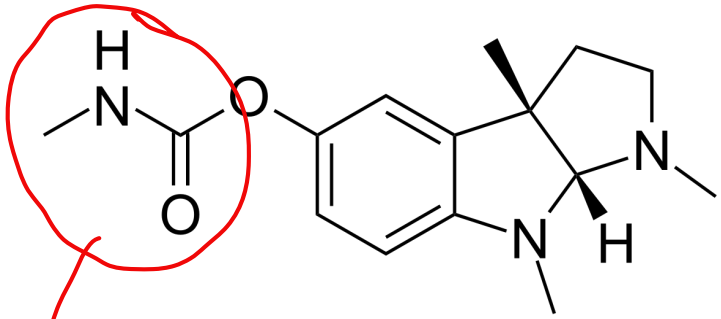
Pralidoxime can be used as antidote w/in 24-36 hrs (before aging)



Ser-O-

Other treatment is atropine to decrease symptoms

Reversible AChEI

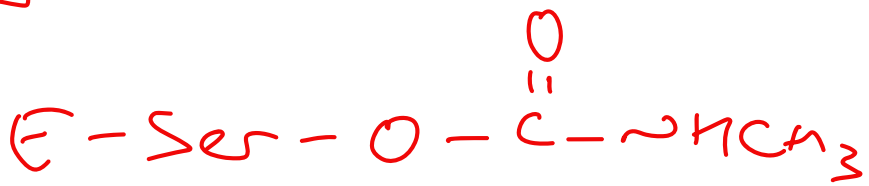


Physostigmine

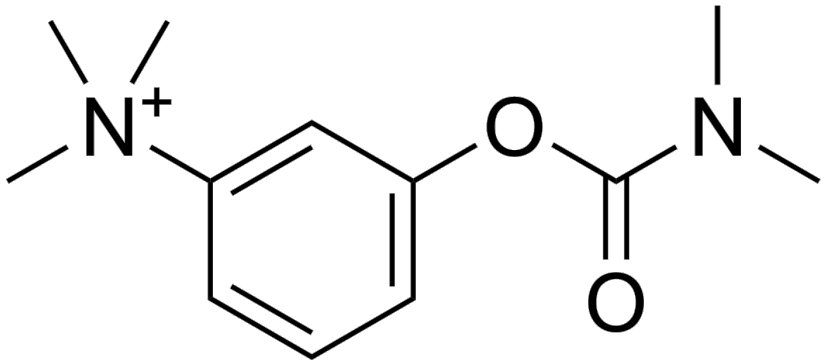
used for atropine poisoning

Calabar beans

Carbamoylates Ser



Will gradually hydrolyze



neostigmine

Similar with fewer side effects

Myasthenia Gravis