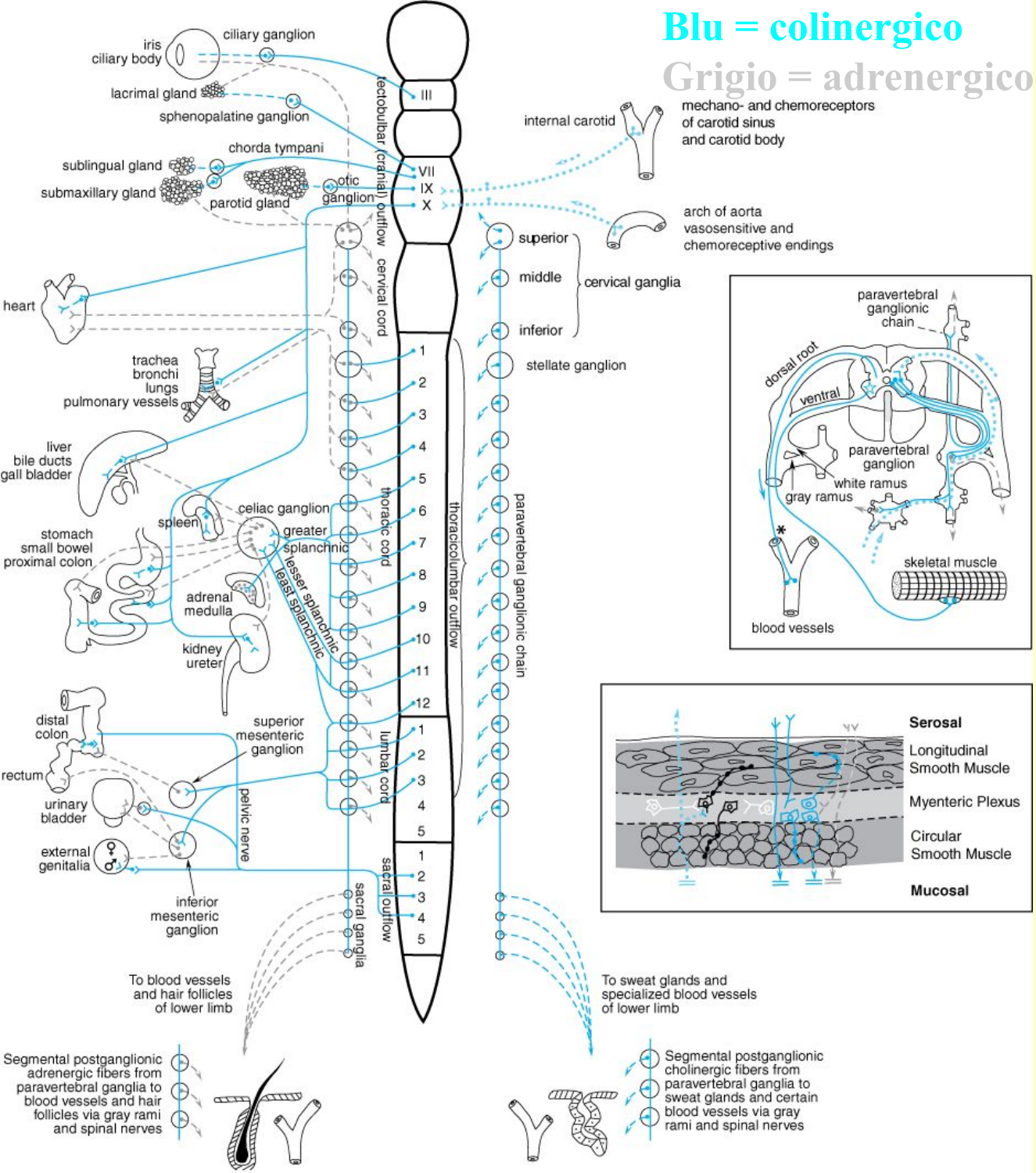


SISTEMA AUTONOMO

Il sistema nervoso autonomo (SNA), conosciuto anche come sistema nervoso vegetativo o viscerale, è quell'insieme di cellule e fibre che innervano gli organi interni e cosiddet quelle fu di fuori questo v **autonomo** Il sistema nervoso a nomo è soprattutto un sistema effettore, che controlla la muscolatura liscia, il muscolo cardiaco e le ghiandole esocrine. E' divisibile in tre sezioni:

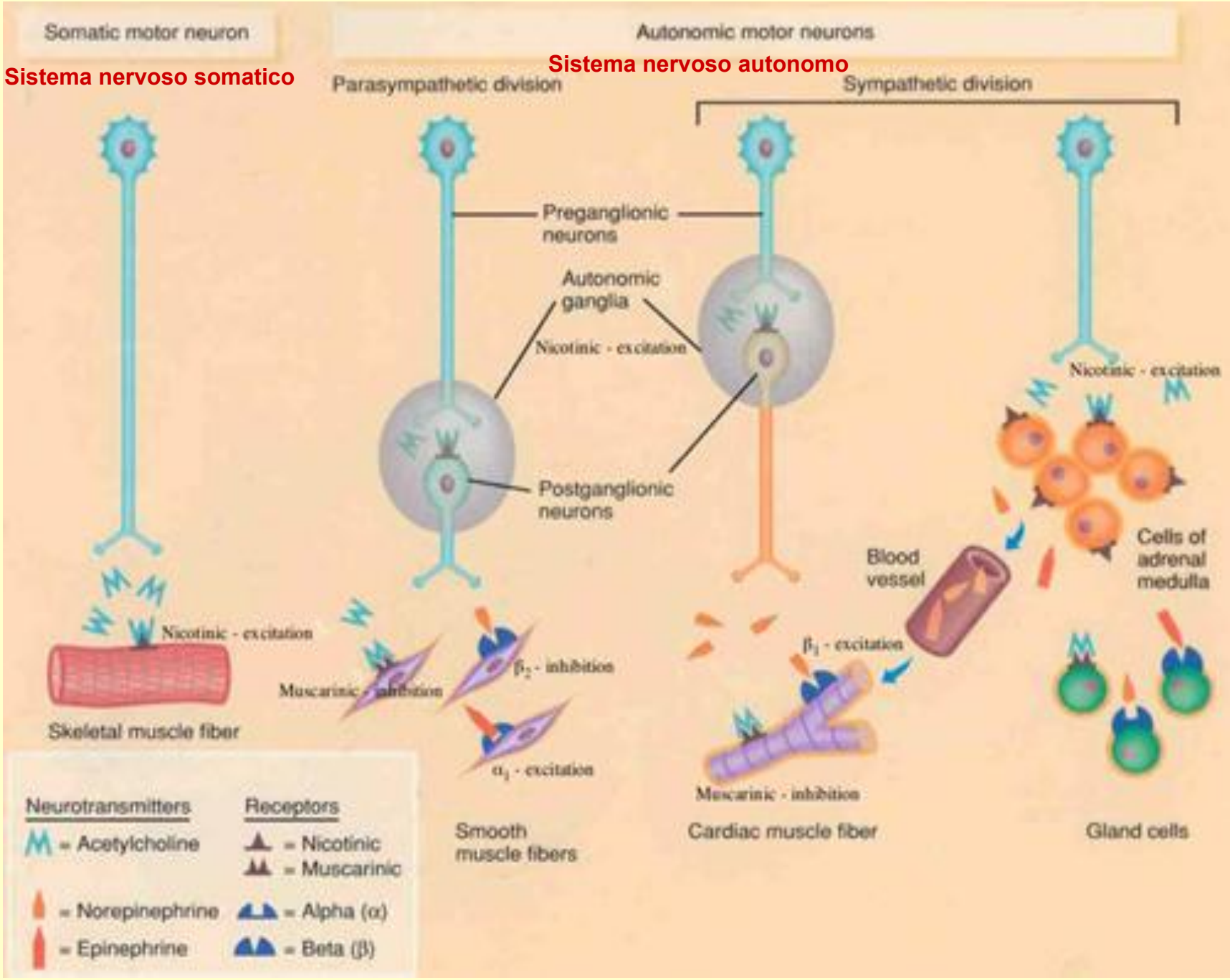
a) Toracolombare (sistema ortosimpatico o simpatico)

b) Craniosacrale (sistema parasimpatico)

c) Sistema enterico

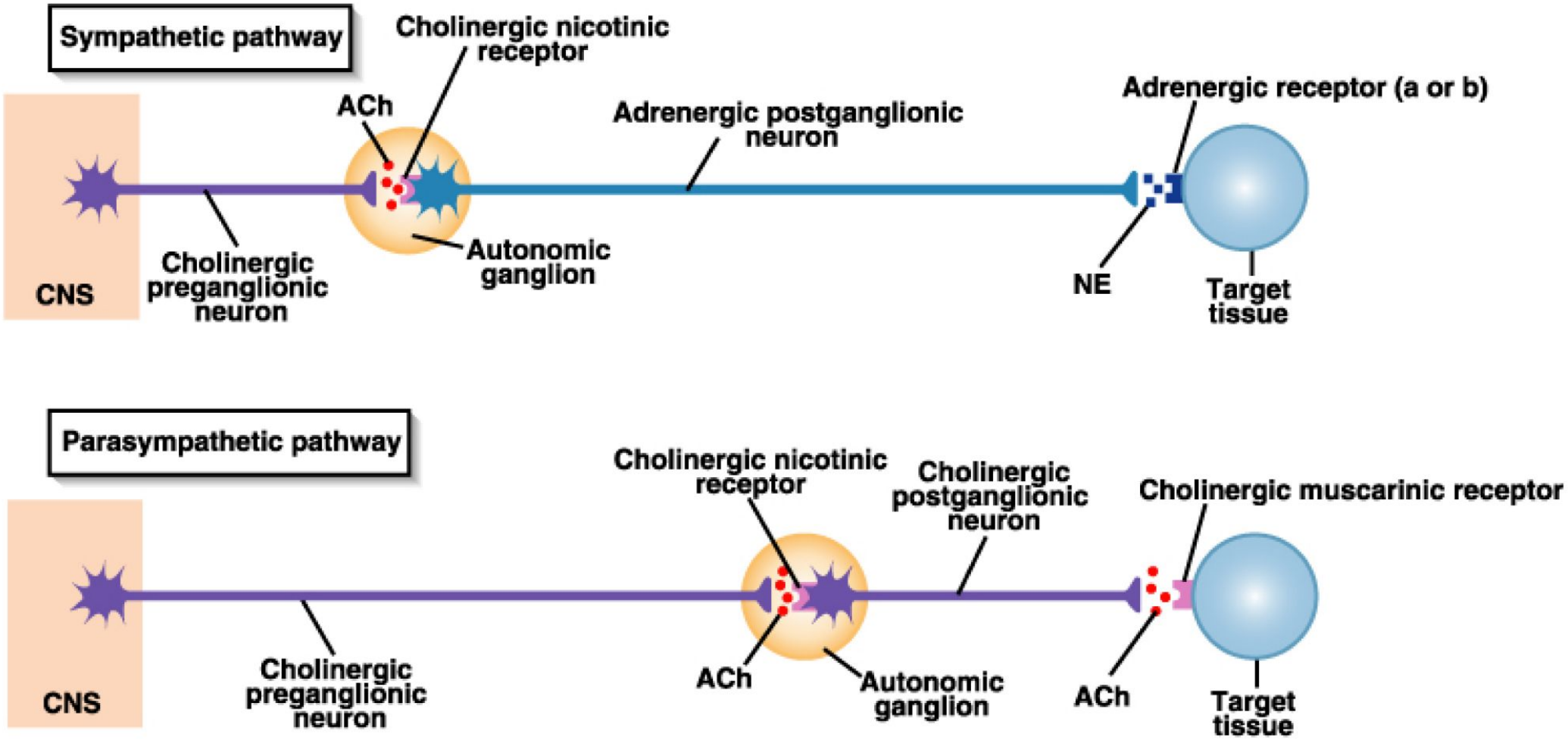
Terminazione di una fibra nervosa efferente, che ha il compito di trasmettere gli impulsi nervosi all'organo o al tessuto nel cui intimo è dislocata, determinandone l'attivazione

NEUROTRASMETTITORI



NEUROTRASMETTITORI

Anatomia funzionale del SNA: simpatico e parasimpatico



Anatomia funzionale del SNA: simpatico e parasimpatico

Simpatico

I neuroni pregangliari appartenenti al sistema simpatico hanno i loro corpi cellulari nelle corna laterali delle porzioni toracica e lombare del midollo spinale (T1-L3)

Dai gangli partono le fibre post-gangliari che innervano i vari organi effettori (cuore, vasi, occhio, bronchi, stomaco, rene intestino , vescica, ghiandole sudoripare etc..)

Attivazione del Simpatico determina:

Aumento della frequenza cardiaca, e della velocità di conduzione atrioventricolare, della forza di contrazione e un'alterazione del ritmo

Midriasi, broncodilatazione,

Aumento della pressione arteriosa (vasocostrizione), attivazione del metabolismo cellulare (gluconeogenesi e glicolisi)

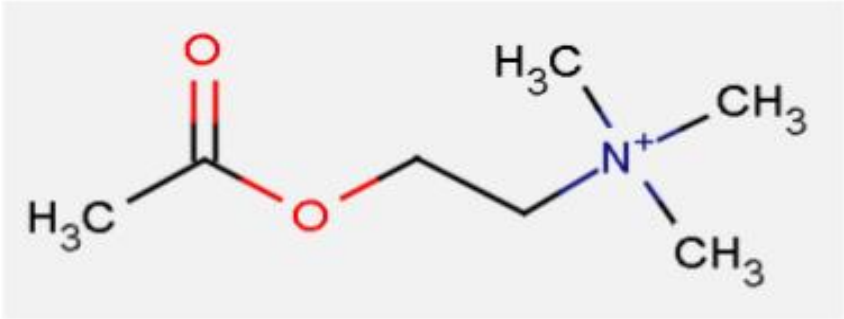
Ridotta motilità intestinale, rilasciamento vascica e contrazione degli sfinteri

Il sistema parasimpatico esercita azioni opposte a quelle del simpatico

EFFETTI ADRENERGICI E COLINERGICI

Table 6–1 Responses of Effector Organs to Autonomic Nerve Impulses

ORGAN SYSTEM	SYMPATHETIC EFFECT[a]	ADRENERGIC RECEPTOR TYPE[b]	PARASYMPATHETIC EFFECT[a]	CHOLINERGIC RECEPTOR TYPE[b]
Eye				
Radial muscle, iris	Contraction (mydriasis)++	α_1		
Sphincter muscle, iris			Contraction (miosis)+++	M_3, M_2
Ciliary muscle	Relaxation for far vision[+]	β_2	Contraction for near vision+++	M_3, M_2
Lacrimal glands	Secretion+	π	Secretion+++	M_3, M_2
Heart[c]				
Sinoatrial node	Increase in heart rate++	$\beta_1 > \beta_2$	Decrease in heart rate+++	$M_2 >> M_3$
Atria	Increase in contractility and conduction velocity++	$\beta_1 > \beta_2$	Decrease in contractility++ and shortened AP duration	$M_2 >> M_3$
Atrioventricular node	Increase in automaticity and conduction velocity++	$\beta_1 > \beta_2$	Decrease in conduction velocity; AV block+++	$M_2 >> M_3$
His–Purkinje system	Increase in automaticity and conduction velocity	$\beta_1 > \beta_2$	Little effect	$M_2 >> M_3$
Ventricle	Increase in contractility, conduction velocity, automaticity and rate of idioventricular pacemakers+++	$\beta_1 > \beta_2$	Slight decrease in contractility	$M_2 >> M_3$
Blood vessels				
(Arteries and arterioles)[d]				
Coronary	Constriction+; dilation[e]++	α_1, α_2; β_2	No innervation[h]	—
Skin and mucosa	Constriction+++	π_1, π_2	No innervation[h]	—
Skeletal muscle	Constriction; dilation[e,f]++	α_1; β_2	Dilation[g,h] (?)	—
Cerebral	Constriction (slight)	α_1	No innervation[h]	—
Pulmonary	Constriction+; dilation	α_1; β_2	No innervation[h]	—
Abdominal viscera	Constriction +++; dilation +	α_1; β_2	No innervation[h]	—
Salivary glands	Constriction+++	α_1, α_2	Dilation[h]++	M_3



ACETILCOLINA

mediatore della neurotrasmissione a livello di

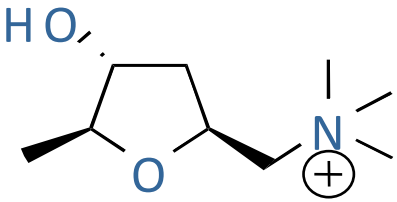
- gangli SNA
- terminazioni parasimpatiche
- giunzioni neuromuscolari
- alcuni neuroni del SNC

MUSCARINA E NICOTINA

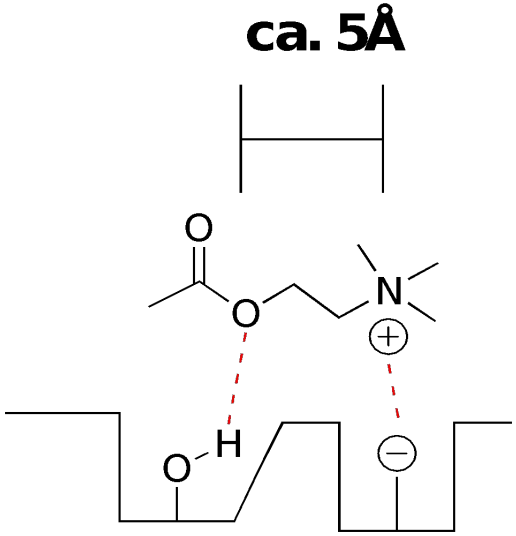
Amanita muscaria

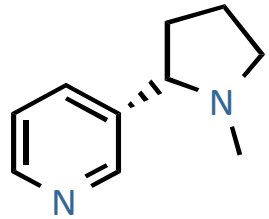
Nicotiana tabacum

Acetilcolina

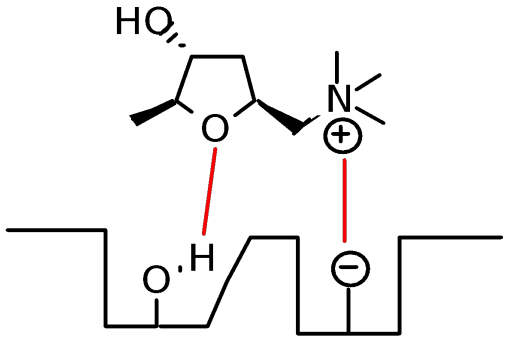


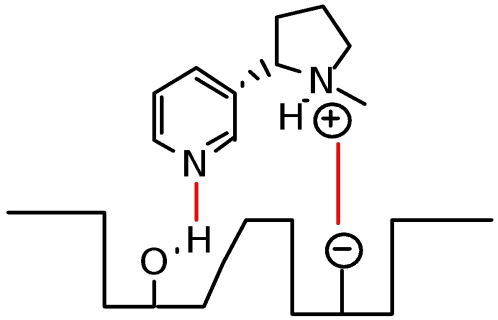
Muscarina



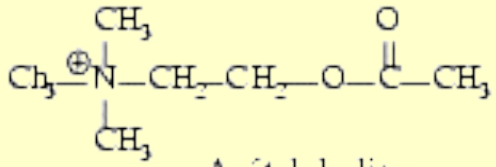


Nicotina

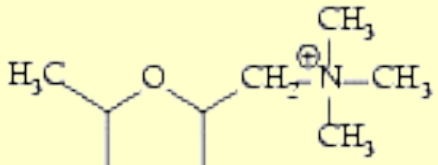




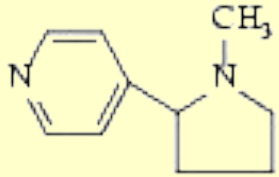
RECETTORI DELL'ACETILCOLINA



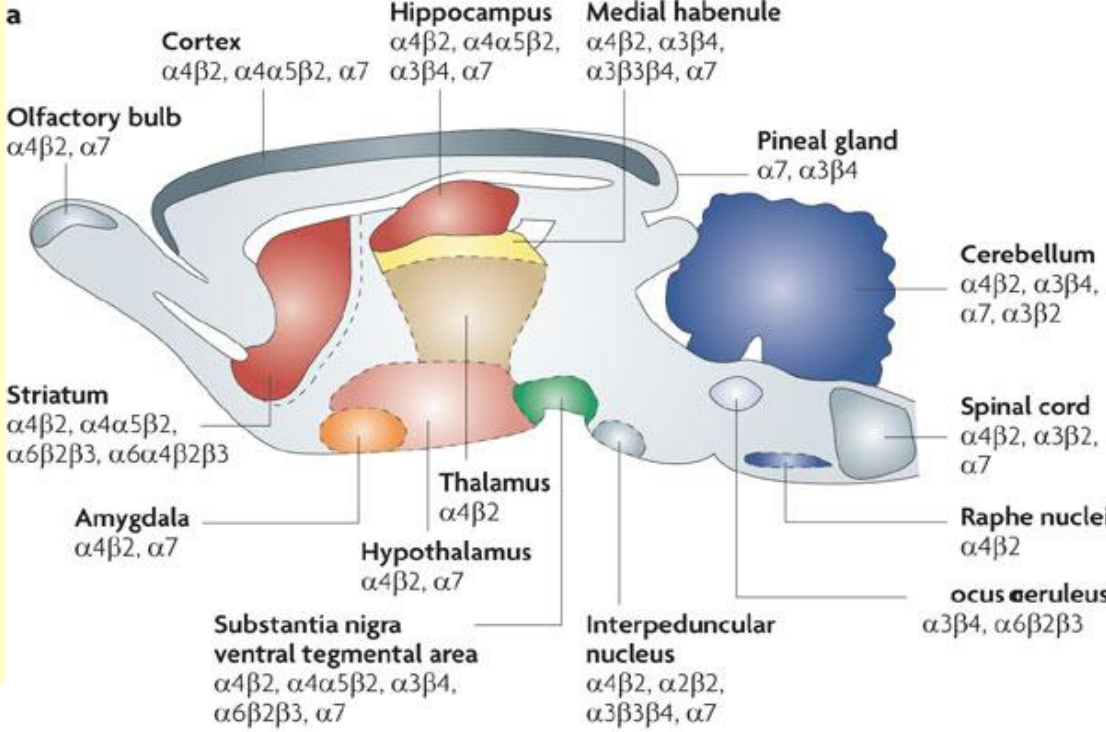
Acétylcholine

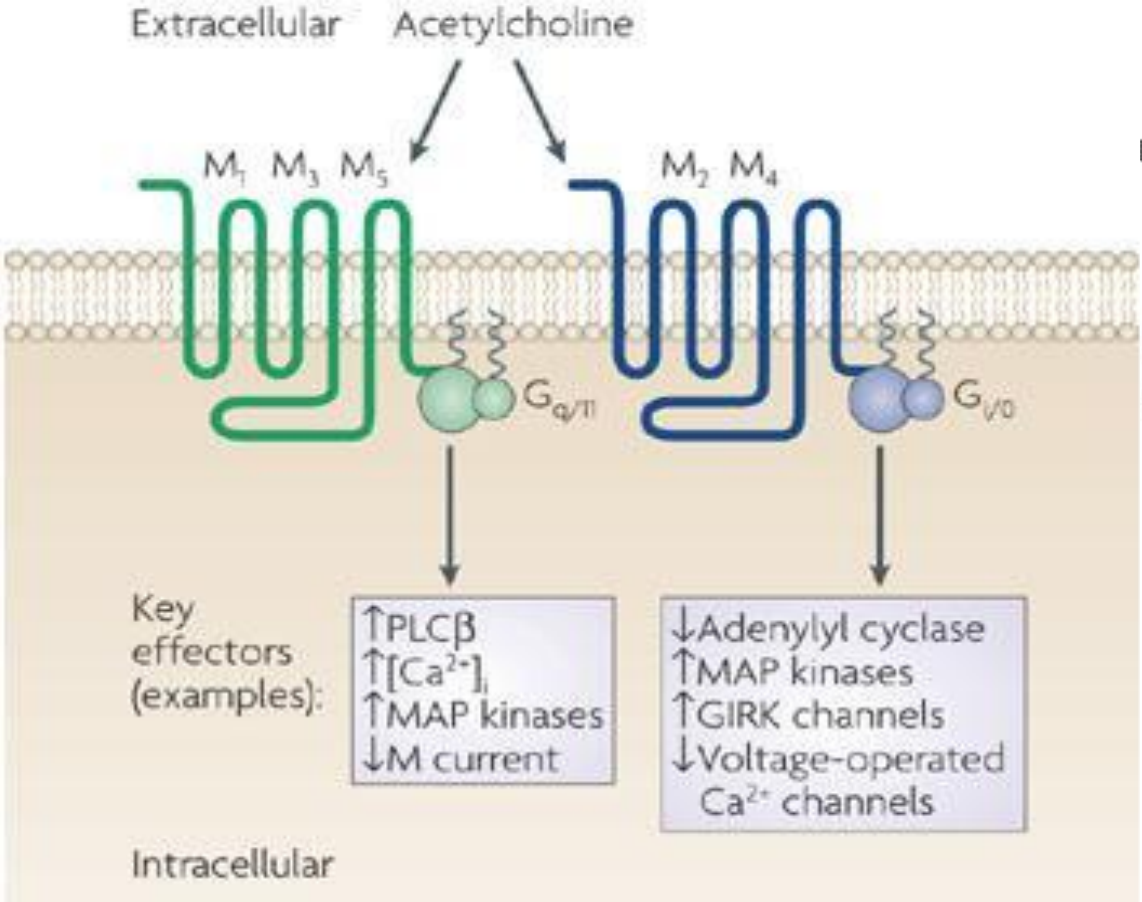


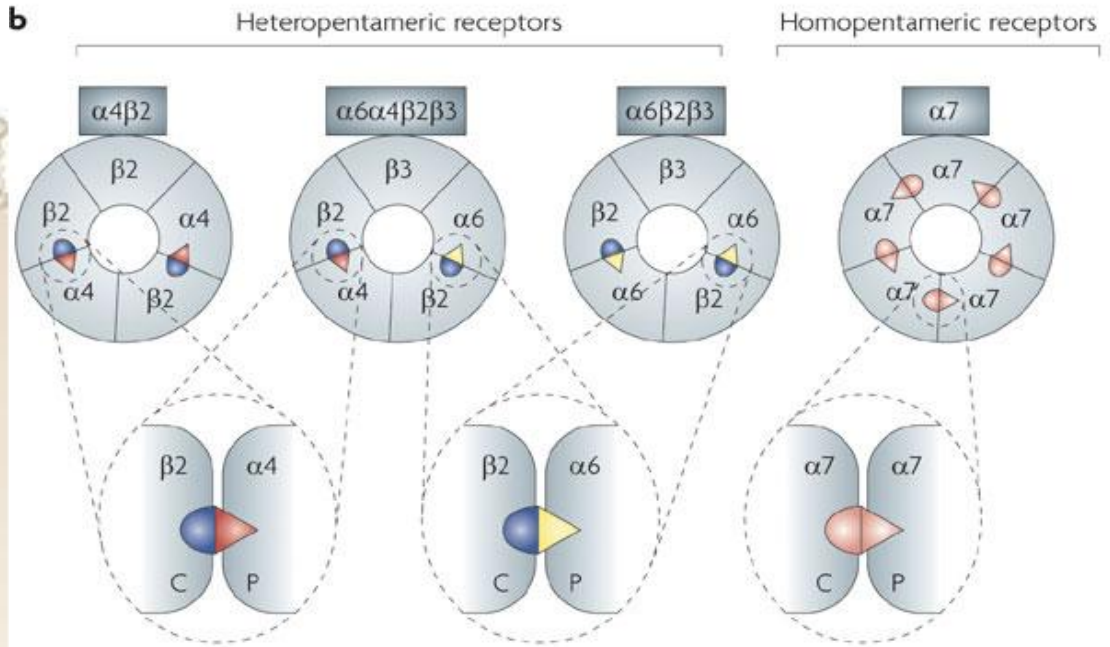
Muscarine



Nicotine







RECETTORI NICOTINICI

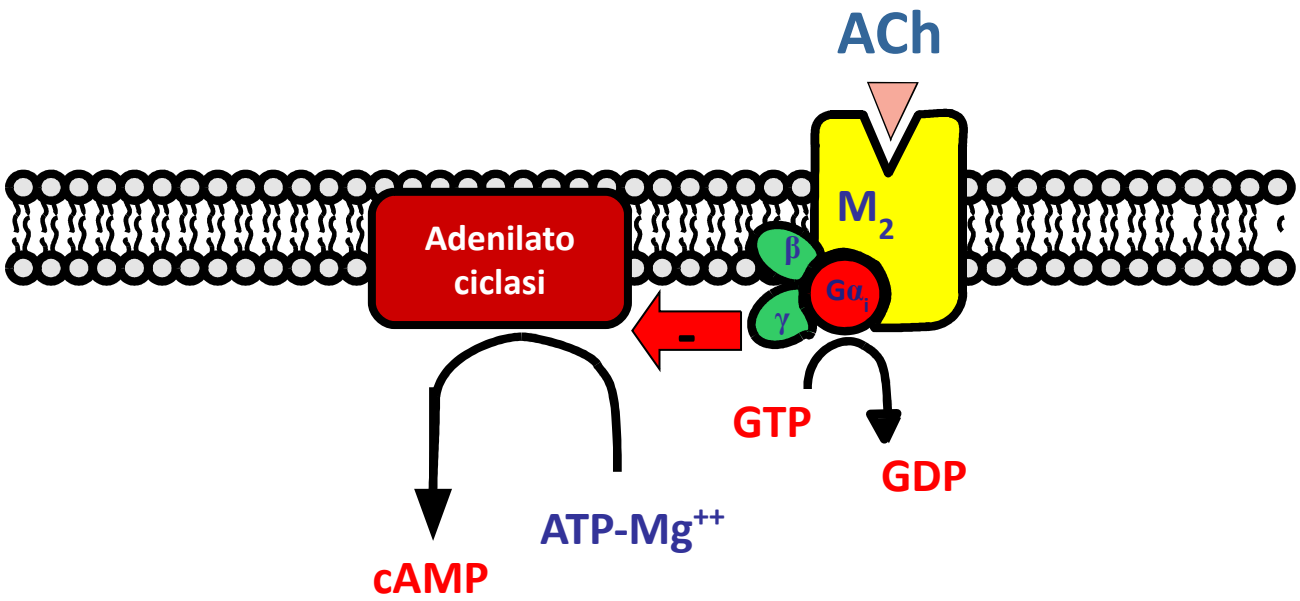
Table 6–2 Characteristics of Subtypes of Nicotinic Acetylcholine Receptors (nAChRs)

RECEPTOR (PRIMARY RECEPTOR SUBTYPE)*	MAIN SYNAPTIC LOCATION	MEMBRANE RESPONSE	MOLECULAR MECHANISM	AGONISTS	ANTAGONISTS
Skeletal muscle (N_M) $(\alpha 1)_2\beta_1\varepsilon\delta$ adult $(\alpha 1)_2\beta_1\gamma\delta$ fetal	Skeletal neuromuscular junction (postjunctional)	Excitatory; end-plate depolarization; skeletal muscle contraction	Increased cation permeability (Na^+; K^+)	ACh Nicotine Succinylcholine	Atracurium Vecuronium D-Tubocurarine Pancuronium ɑ-Conotoxin ɑ-Bungarotoxin
Peripheral neuronal (N_N) $(\alpha 3)_2(\beta 4)_3$	Autonomic ganglia; adrenal medulla	Excitatory; depolarization; firing of postganglion neuron; depolarization and secretion of catecholamines	Increased cation permeability (Na^+; K^+)	ACh Nicotine Epibatidine Dimethylphenylpiperazinium	Trimethaphan Mecamylamine
Central neuronal (CNS) $(\alpha 4)_2(\beta 4)_3$ (α-btox-insensitive)	CNS; pre- and postjunctional	Pre- and postsynaptic excitation Prejunctional control of transmitter release	Increased cation permeability (Na^+; K^+)	Cytisine, epibatidine Anatoxin A	Mecamylamine Dihydro-β-erythrodine Erysodine Lophotoxin
$(\alpha 7)_5$ (α-btox-sensitive)	CNS; Pre- and postsynaptic	Pre- and postsynaptic excitation Prejunctional control of transmitter release	Increased permeability (Ca^{2+})	Anatoxin A	Methyllycaconitine α-Bungarotoxin α-Conotoxin IMI

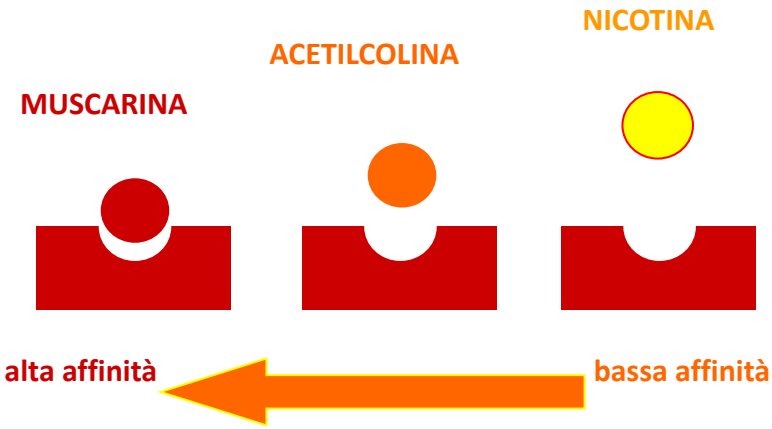
*Nine individual subunits have been identified and cloned in human brain, which combine in various conformations to form individual receptor subtypes. The structure of individual receptors and the subtype composition are incompletely understood. Only a finite number of naturally occurring functional nAChR constructs have been identified. ɑ-btox, ɑ-bungarotoxin.

IL RECETTORE MUSCARINICO

Appartiene alla famiglia dei recettori di membrana accoppiati alle Proteine G.



REC MUSCARINICI



M_1, M_2, M_3, M_4, M_5

- M_1 stomaco, SNC
- M_2 cuore e muscoli lisci
- M_3 ghiandole esocrine e muscoli lisci
- M_4 polmone e utero e SNC
- M_5 SNC

attivazione di Gαq

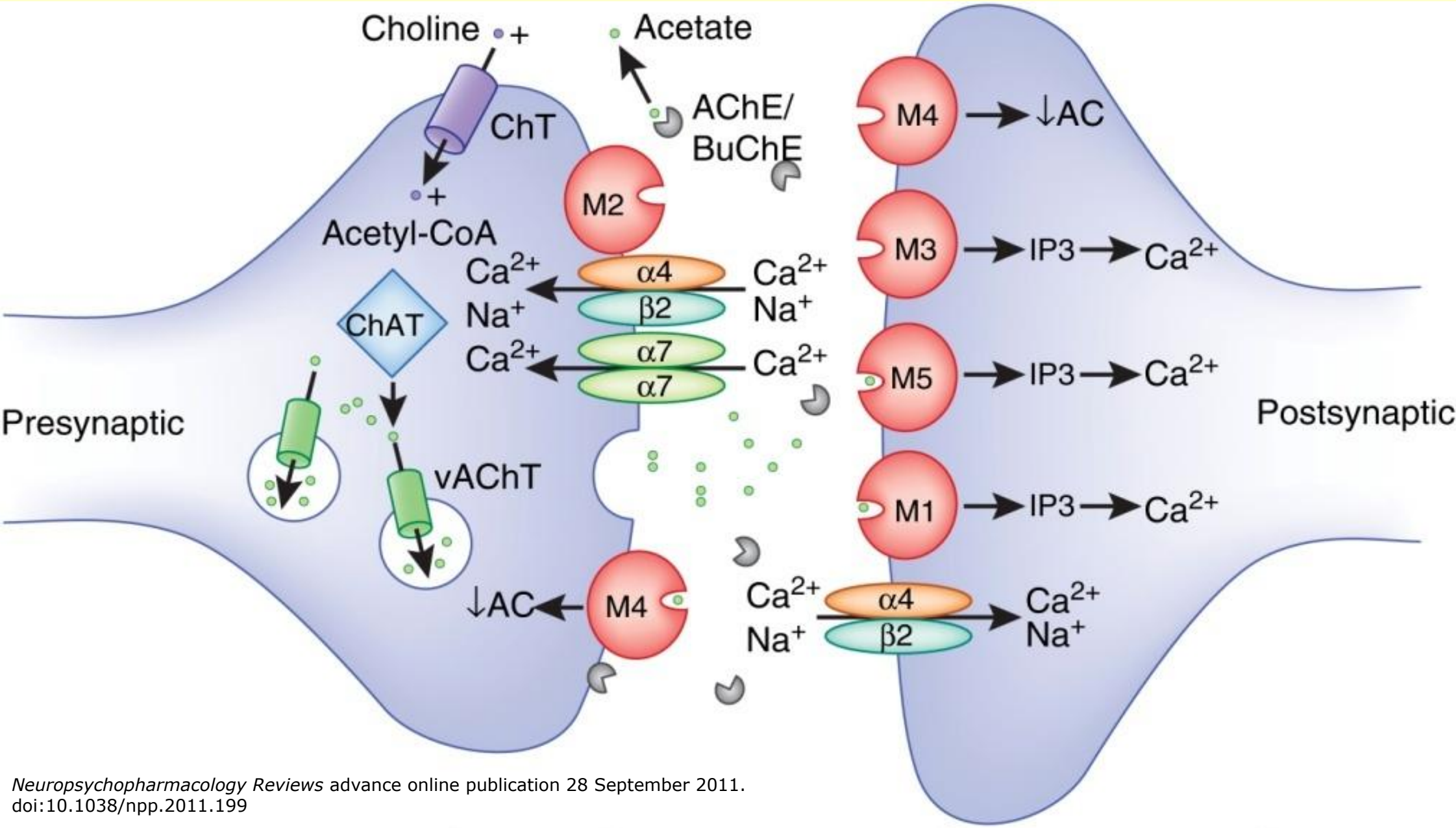
attivazione di Gαi/0

RECETTORI MUSCARINICI

Table 6–3 Characteristics of Muscarinic Acetylcholine Receptor Subtypes (mAChRs)

RECEPTOR	SIZE; CHROMOSOME LOCATION	CELLULAR AND TISSUE LOCATION*	CELLULAR RESPONSE†	FUNCTIONAL RESPONSE‡
M_1	460 aa	CNS; Most abundant in cerebral cortex, hippocampus and striatum	Activation of PLC; ↑ IP_3 and ↑DAG ⇒ ↑Ca^{2+} and PKC	Increased cognitive function (learning and memory)
	11q 12-13	Autonomic ganglia	Depolarization and excitation (↑ sEPSP)	Increased seizure activity
		Glands (gastric and salivary)	Activation of PLD_2, PLA_2; ↑ AA	Decrease in dopamine release and locomotion
		Enteric nerves	Couples *via* $G_{q/11}$	Increase in depolarization of autonomic ganglia Increase in secretions
M_2	466 aa	Widely expressed in CNS, heart, smooth muscle, autonomic nerve terminals	Inhibition of adenylyl cyclase, ↓cAMP	*Heart:*
	7 q 35-36		Activation of inwardly rectifying K^+ channels	SA node: slowed spontaneous depolarization; hyperpolarization, ↓HR
			Inhibition of voltage-gated Ca^{2+} channels	AV node: decrease in conduction velocity
			Hyperpolarization and inhibition	Atrium: ↓ refractory period, ↓ contraction
			Couples *via* G_i/G_o (PTX-sensitive)	Ventricle: slight ↓ contraction
				Smooth muscle: ↑ Contraction
				Peripheral nerves: Neural inhibition *via* autoreceptors and heteroreceptor ↓ Ganglionic transmission.
				CNS: Neural inhibition ↑ Tremors; hypothermia; analgesia
M_3	590 aa	Widely expressed in CNS (< than other mAChRs)	Activation of PLC; ↑ IP_3 and ↑DAG → ↑Ca^{2+} and PKC	*Smooth muscle*

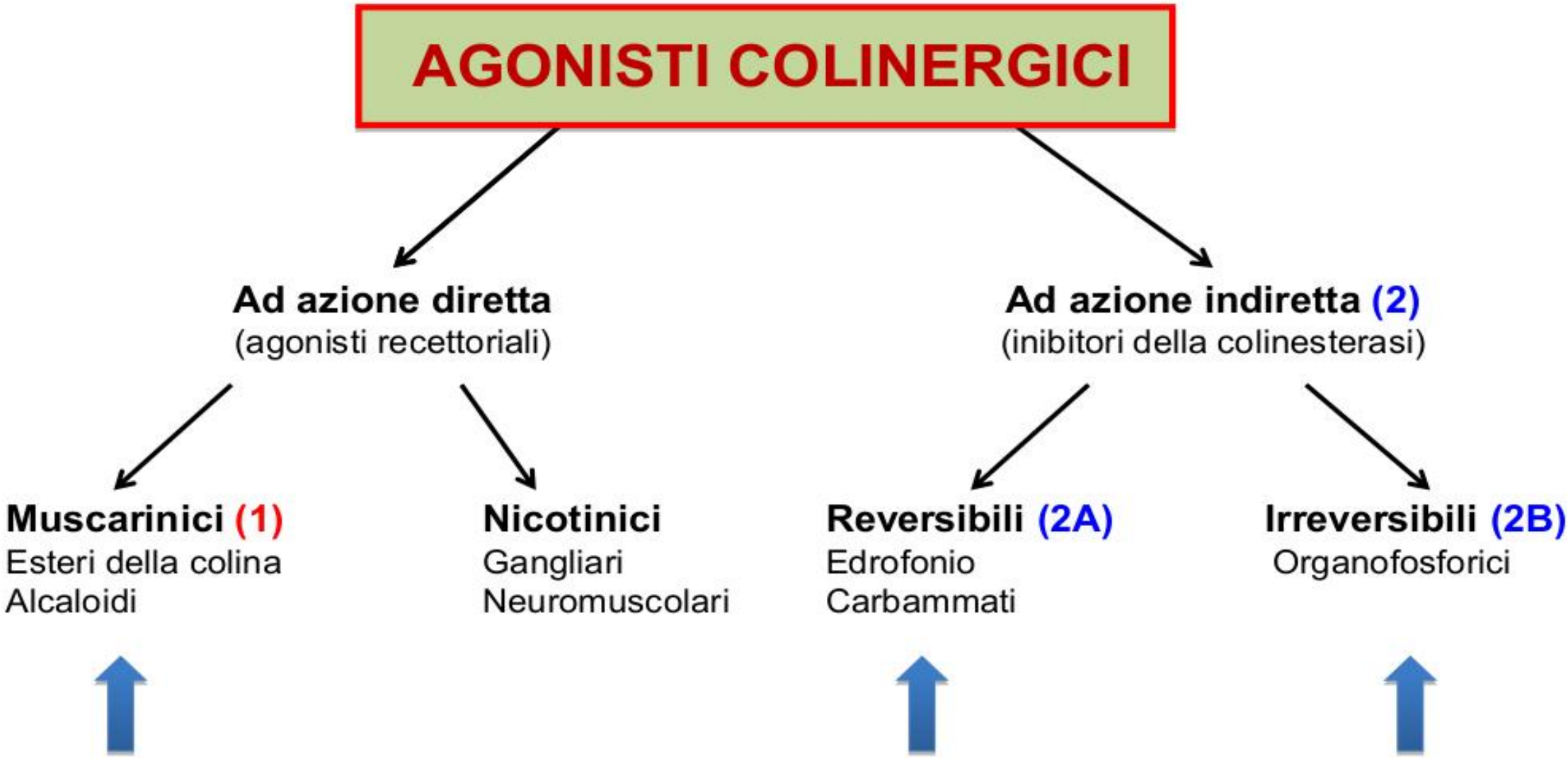
RECETTORI DELL'ACETILCOLINA



Neuropsychopharmacology Reviews advance online publication 28 September 2011.
doi:10.1038/npp.2011.199

ATTIVITÀ COLINERGICHE

- **OCCHIO**
  - Contrazione della pupilla e del muscolo ciliare (miosi), diminuzione della pressione intraoculare.
- **TRATTO GASTROINTESTINALE**
  - aumento della contrazione gastrica e della secrezione gastrica, aumento della motilità intestinale e del colon.
- **GIUNZIONI NEUROMUSCOLARI**
  - Contrazione muscolare
- **ALTRI SITI**
  - Aumento del responso secretorio delle ghiandole (lacrimali, salivari, gastriche), contrazione di fibre della muscolatura liscia, dei bronchi e dell'uretere, azioni cardiovascolari


AGONISTI COLINERGICI
Ad azione diretta
(agonisti recettoriali)
Ad azione indiretta (2)
(inibitori della colinesterasi)
Muscarinici (1)
Esteri della colina
Alcaloidi
Nicotinici
Gangliari
Neuromuscolari
Reversibili (2A)
Edrofonio
Carbammati
Irreversibili (2B)
Organofosforici

AGONISTI INDIRETTI (ANTICOLINESTERASICI)

•Due principali **colinesterasi** (ChE):

- acetilcolinesterasi (AChE): legata alla membrana, relativamente specifica per l'ACh, responsabile dell'idrolisi rapida di ACh nelle sinapsi colinergiche;
- pseudocolinesterasi: relativamente non selettive, si trovano nel plasma e in molti tessuti.

•I **farmaci anticolinesterasici** inibiscono l'AChE ➔ accumulo di ACh nello spazio sinaptico ➔ risposta a livello di tutti i recettori colinergici dell'organismo, sia muscarinici che nicotinici.

- a breve durata d'azione (edrofonio);
- a media durata d'azione (neostigmina, fisostigmina);
- irreversibili (organofosforici, isofluoropato, ecotiofato).

•Differiscono tra di loro per il tipo di interazione con il sito attivo della AChE.

•Gli effetti sono principalmente dovuti all'aumento della trasmissione colinergica nelle sinapsi colinergiche autonome e nella giunzione neuromuscolare.

- Gli **effetti autonomi** comprendono bradicardia, ipotensione, eccessive secrezioni, broncocostrizione, ipermotilità gastrointestinale, diminuzione della pressione intraoculare.
- L'azione **neuromuscolare** causa fascicolazioni e aumento della forza di contrazione e può determinare blocco da depolarizzazione.
- Gli anticolinesterasici che attraversano la barriera ematoencefalica (fisostigmina, organofosforici) hanno anche marcati **effetti sul SNC**.

ACETILCOLINESTERASE

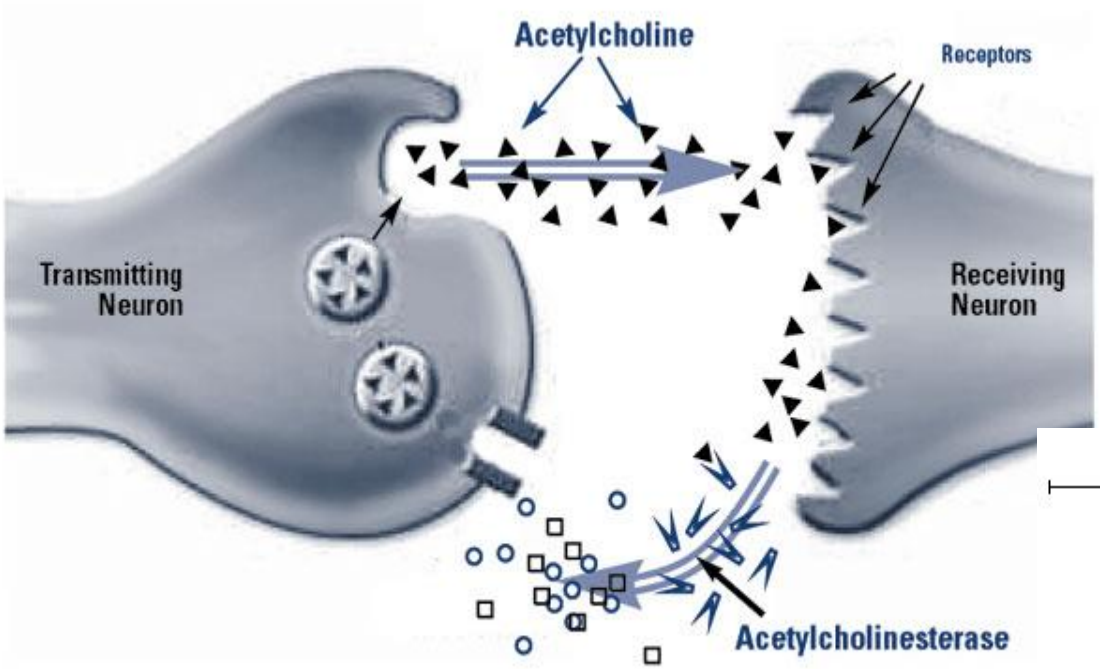
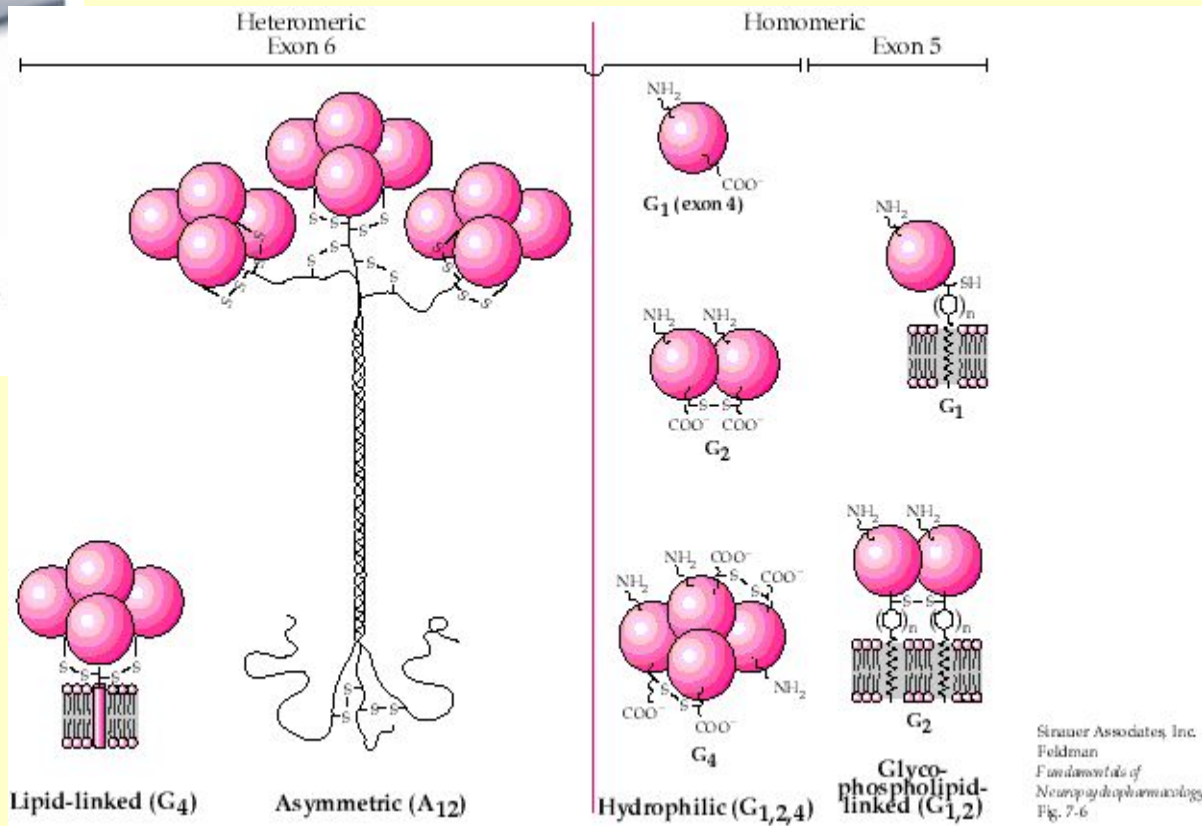
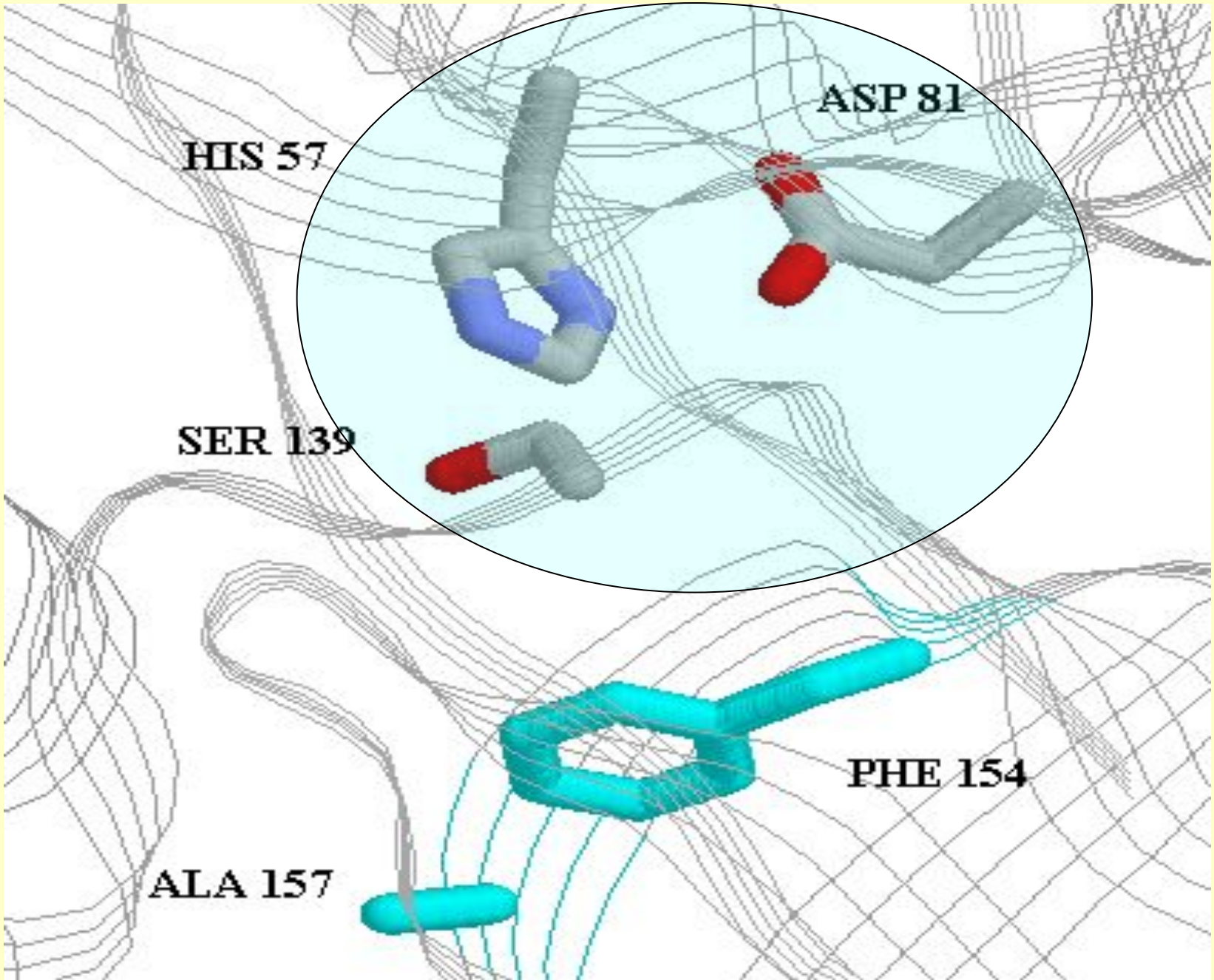


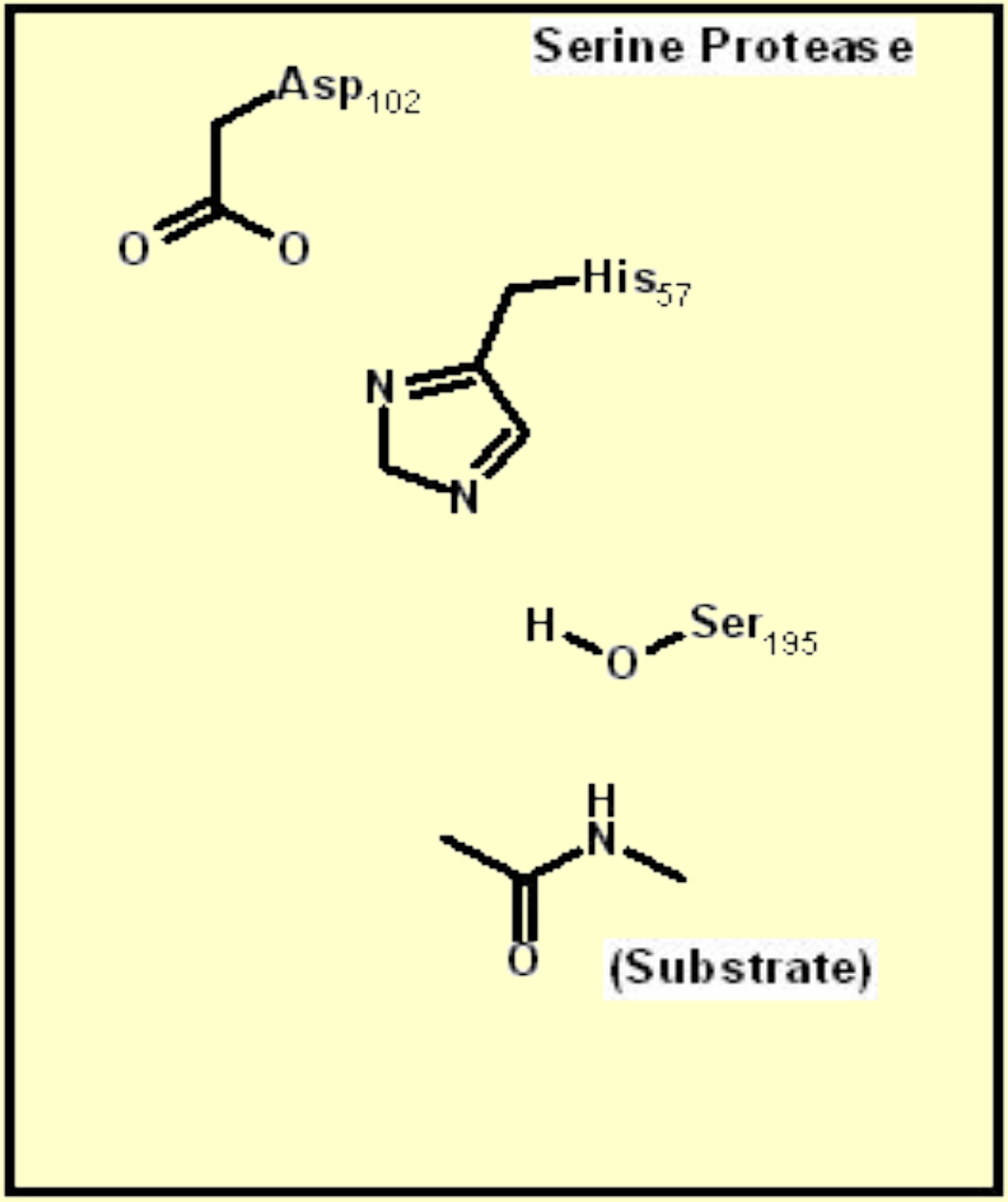
Fig. 1. After signalling, acetylcholine is released from receptors and broken down by acetylcholinesterase to be recycled in a continuous process.

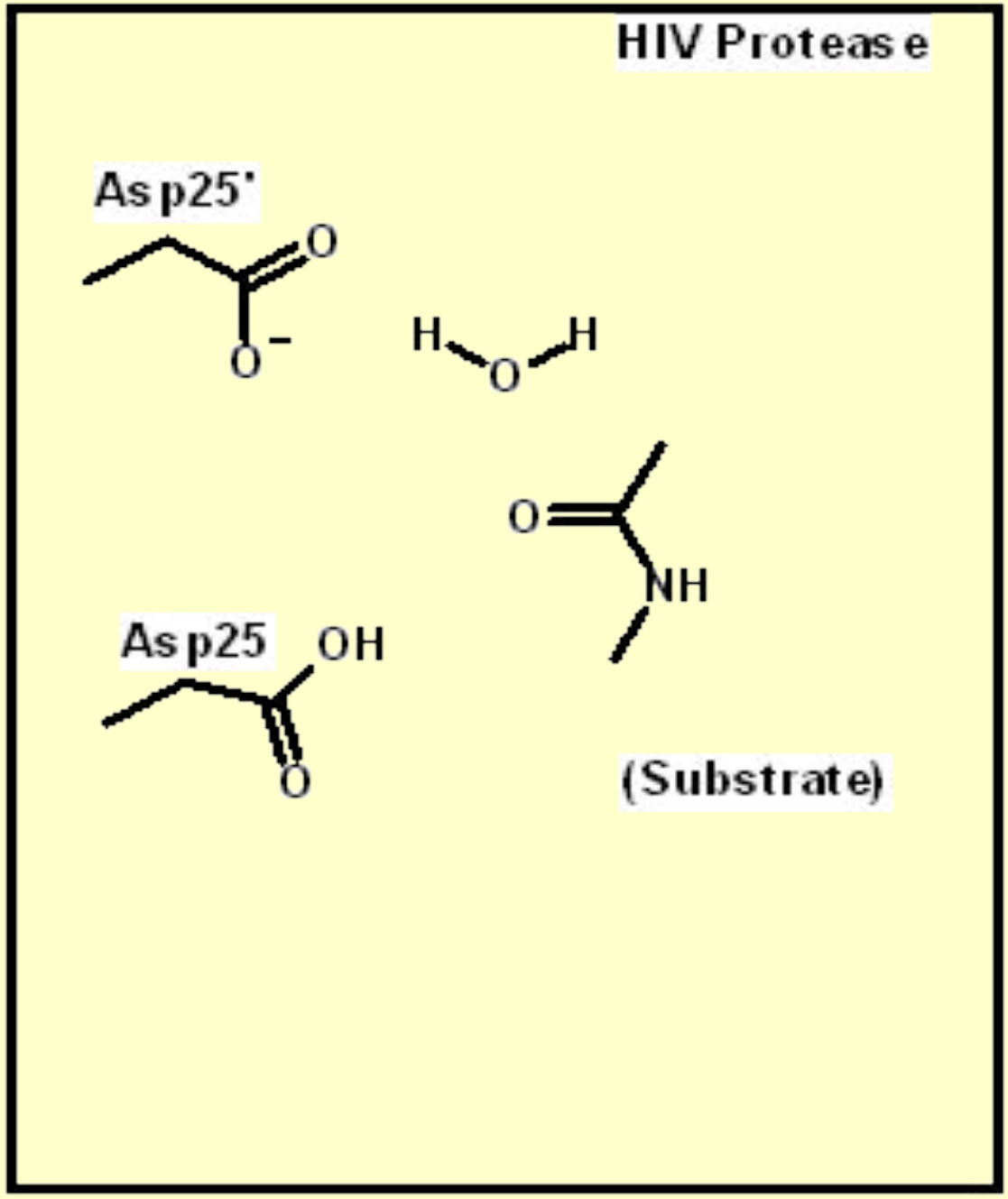


SITO ATTIVO DI PROTEASE SERINICA

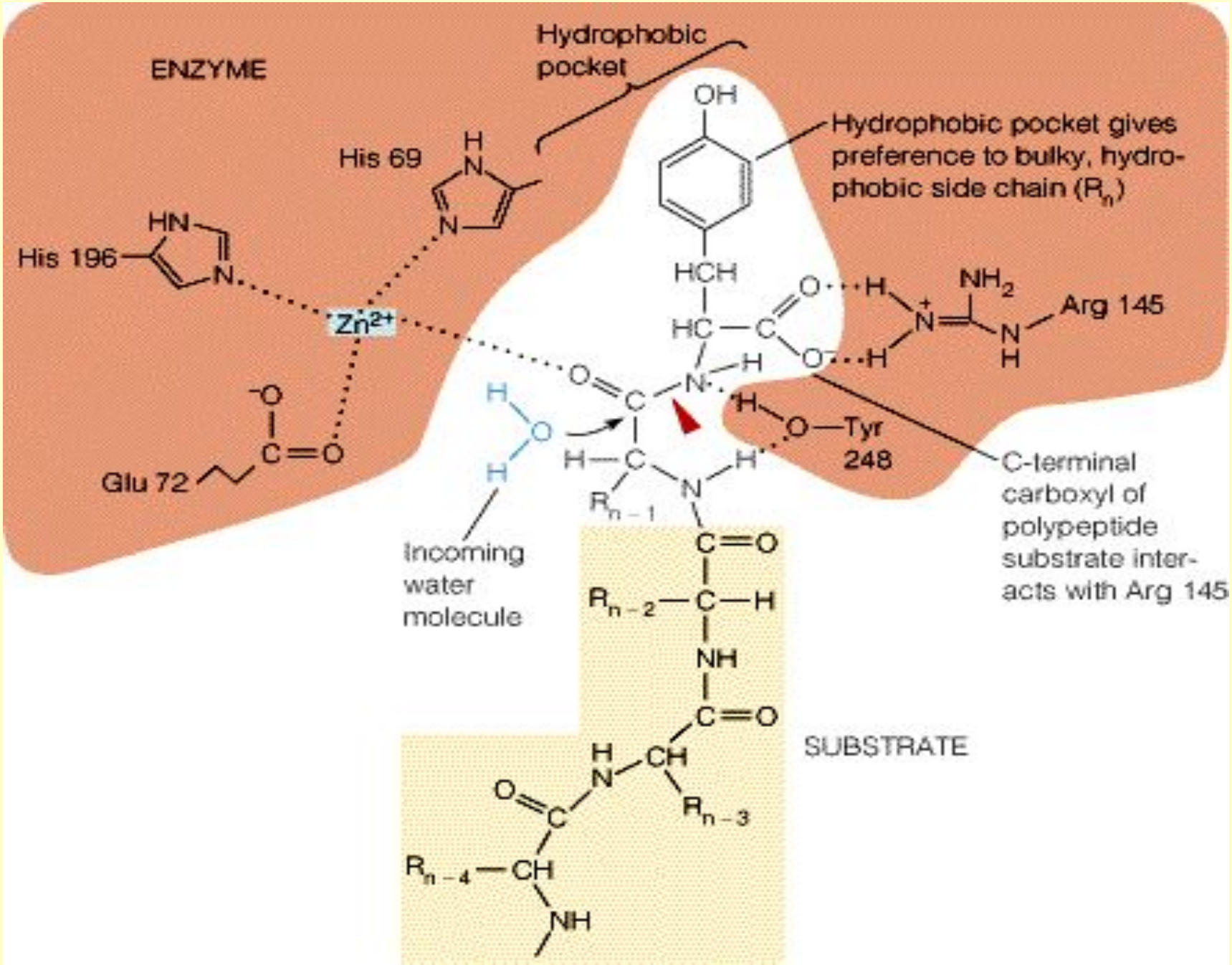


SITI ATTIVI DI PROTEASI SERINICHE E ACIDE





SITO ATTIVO DI PROTEASE METALLICA



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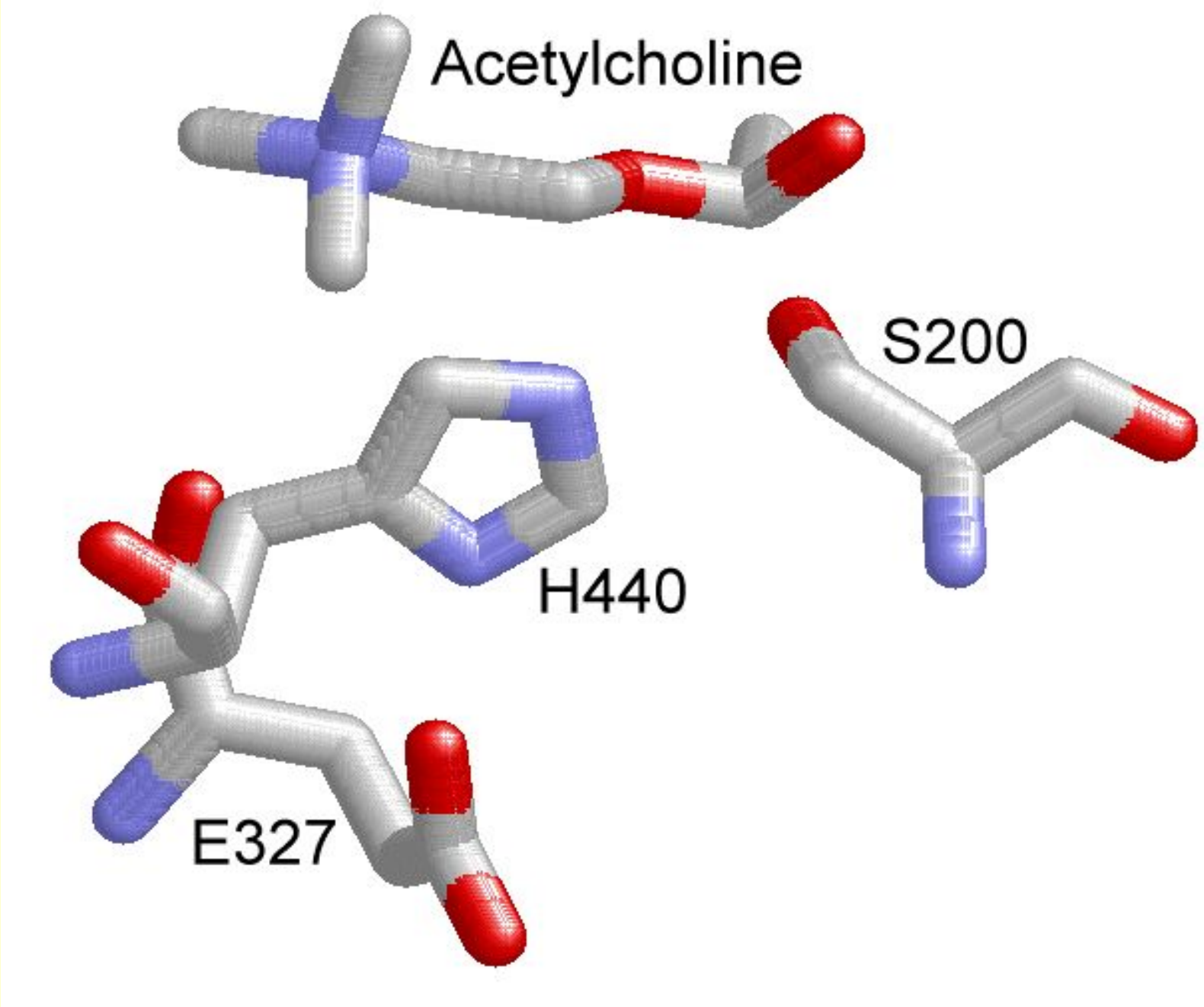
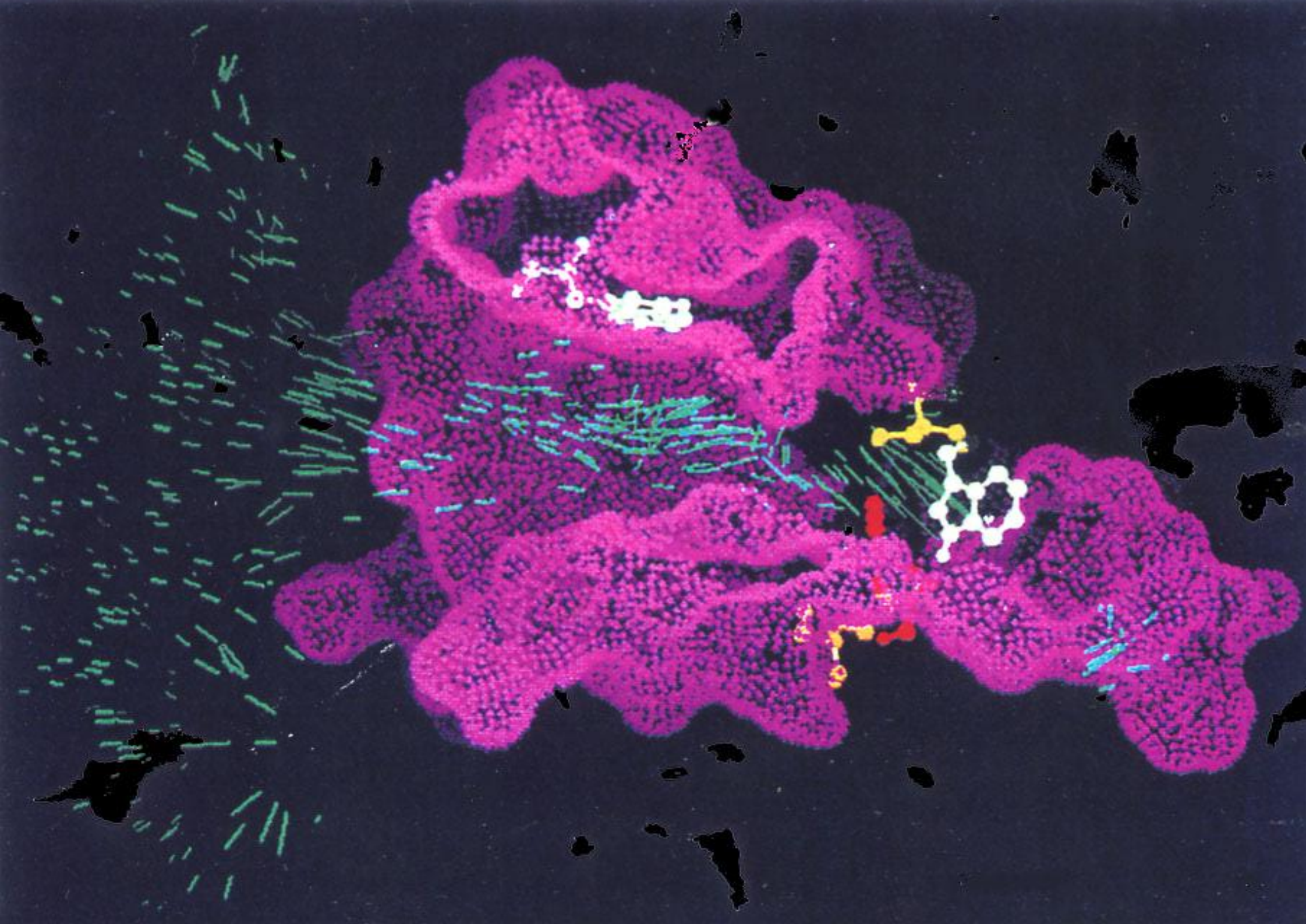
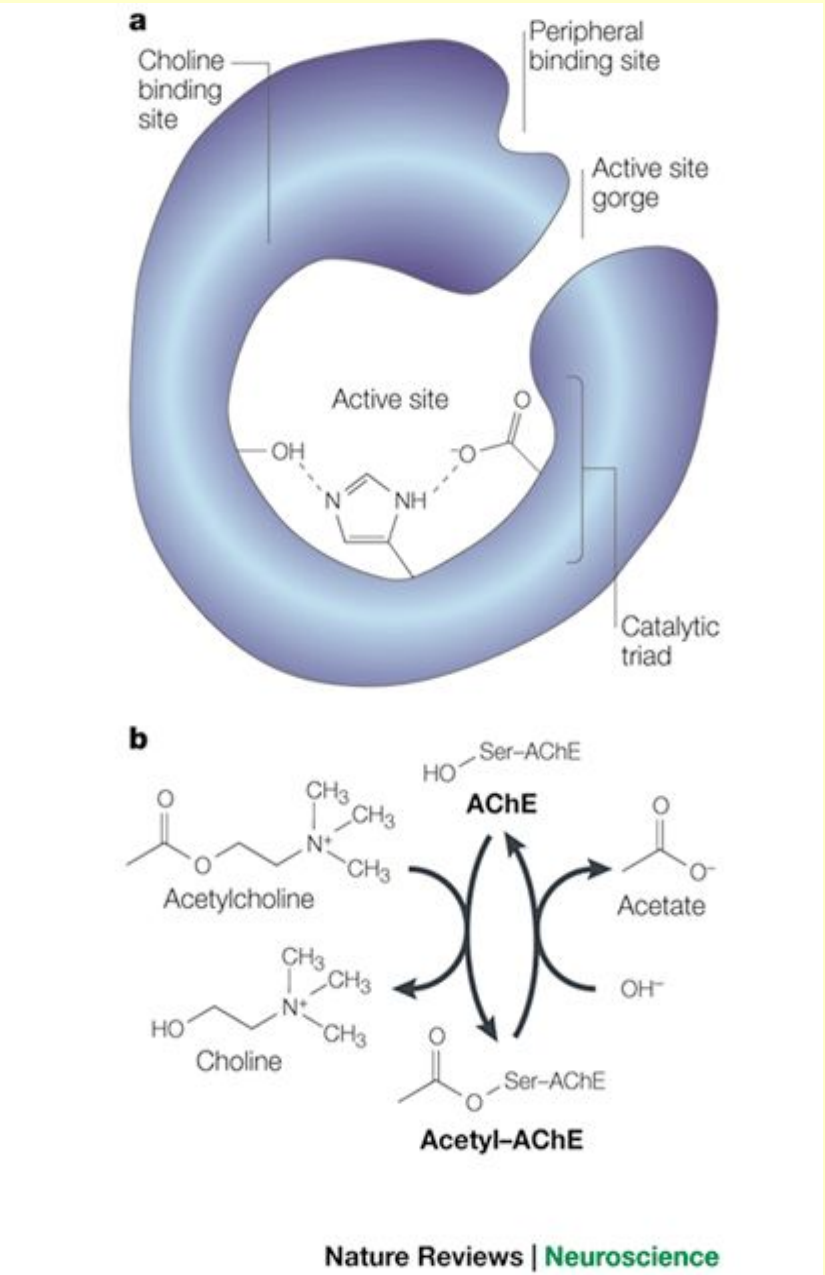
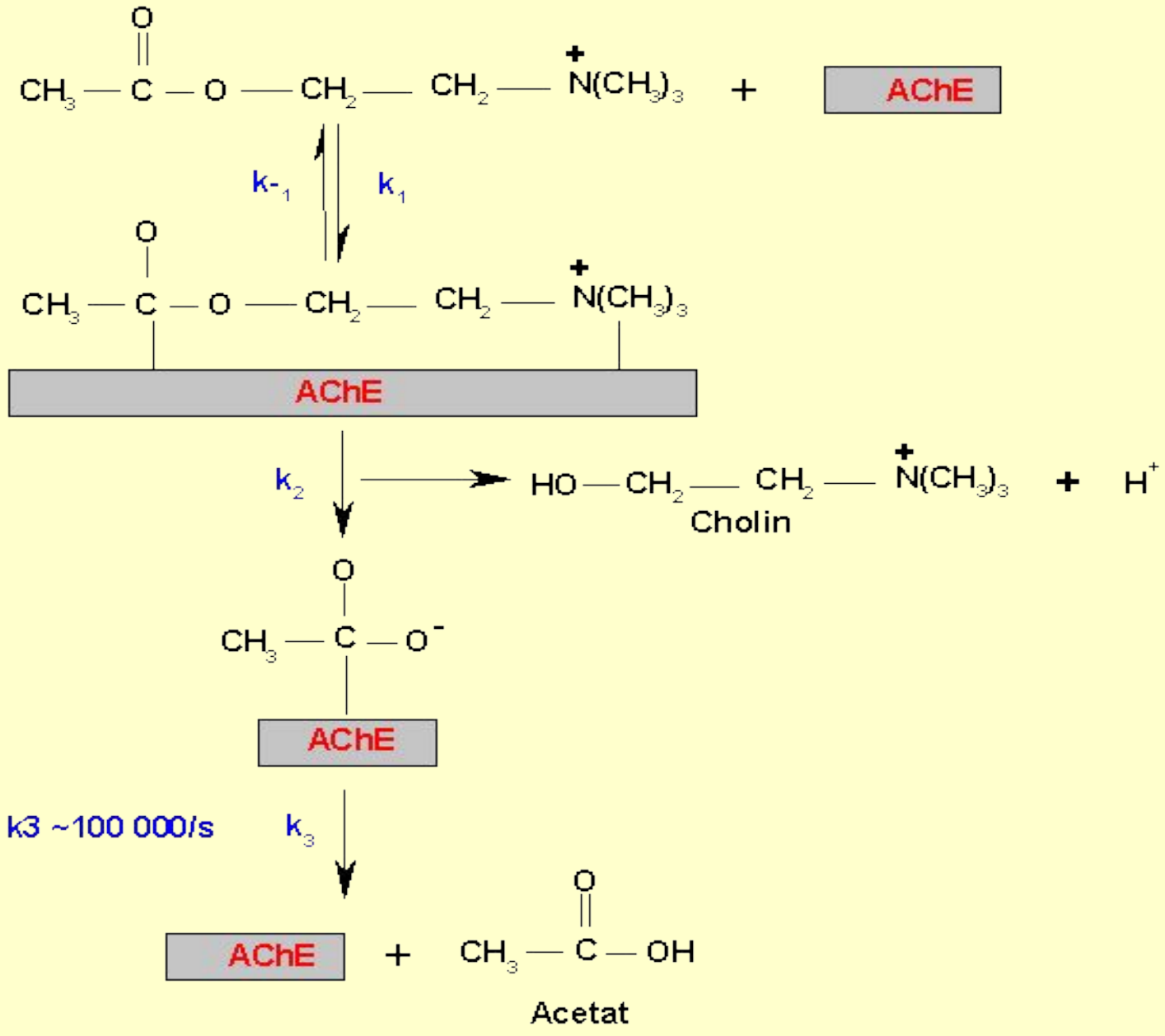




ACETILCOLINESTERASE





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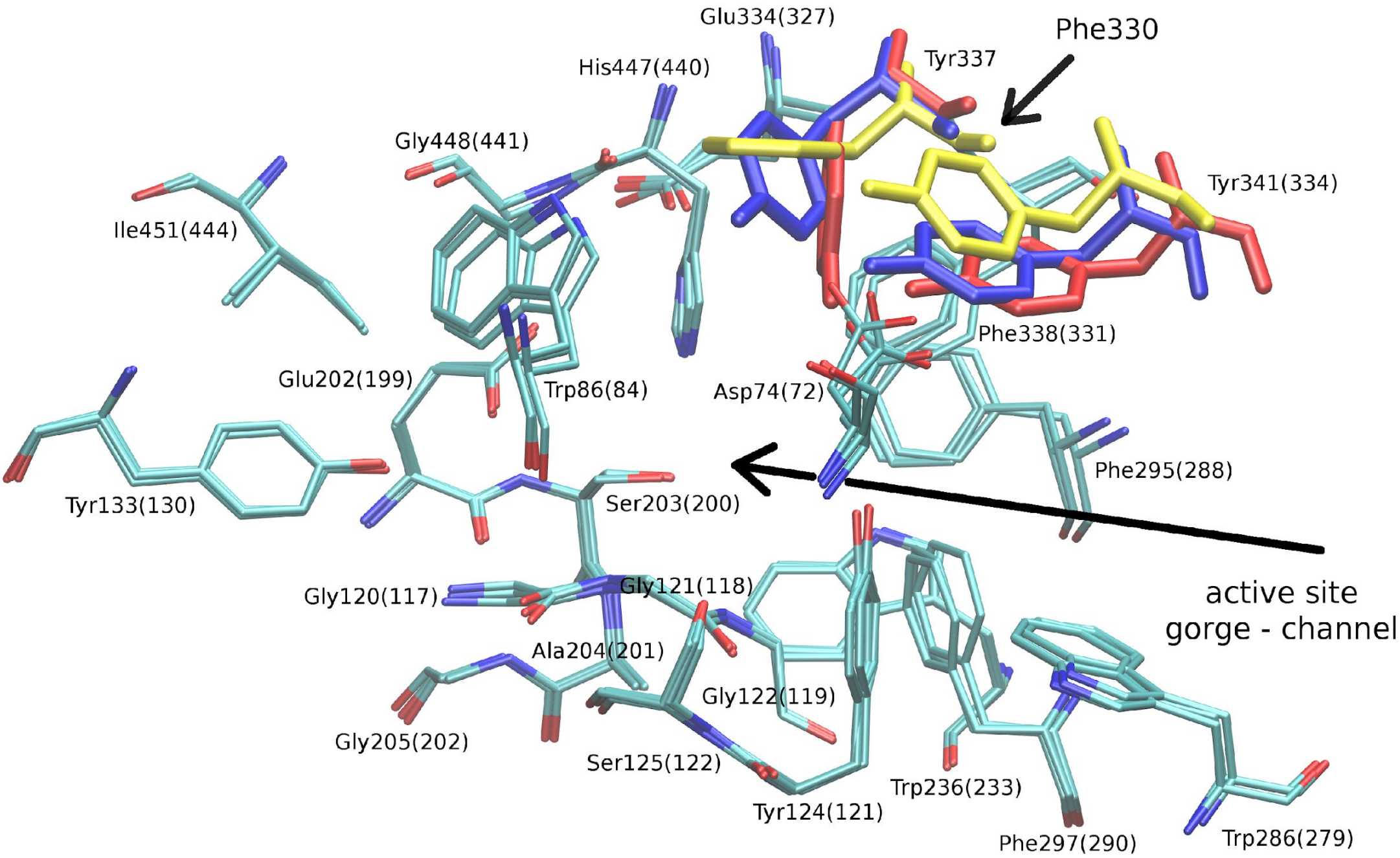
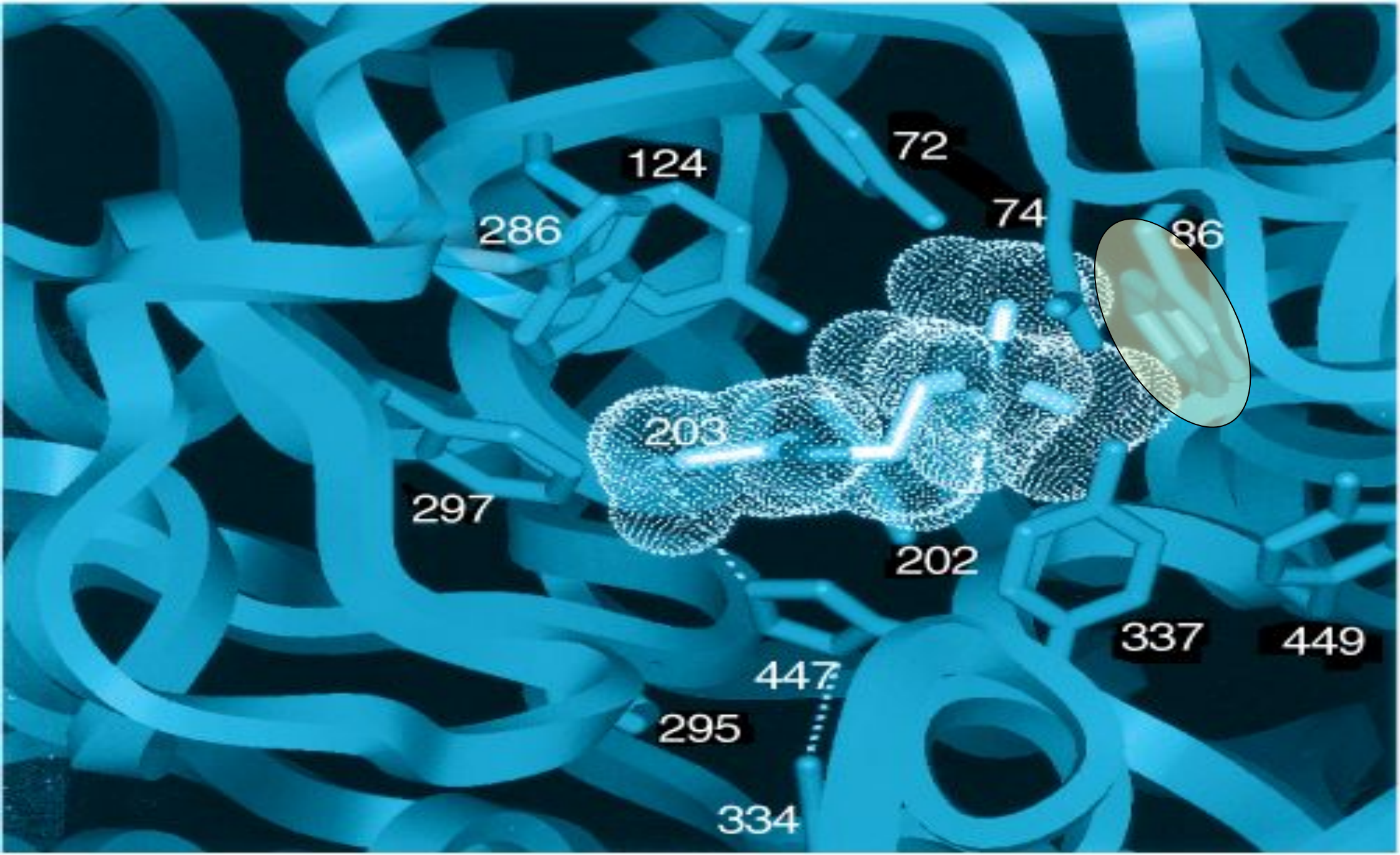
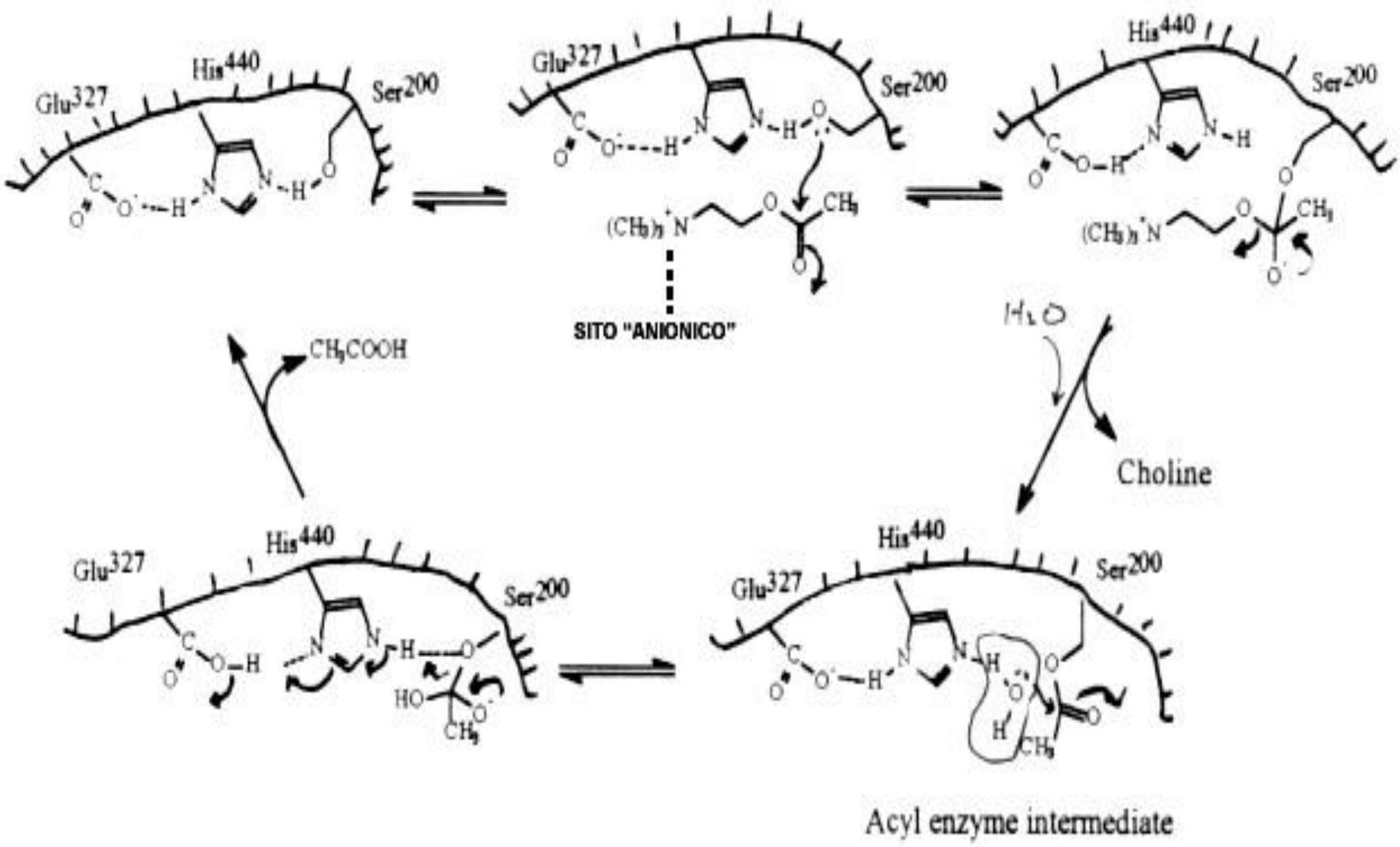


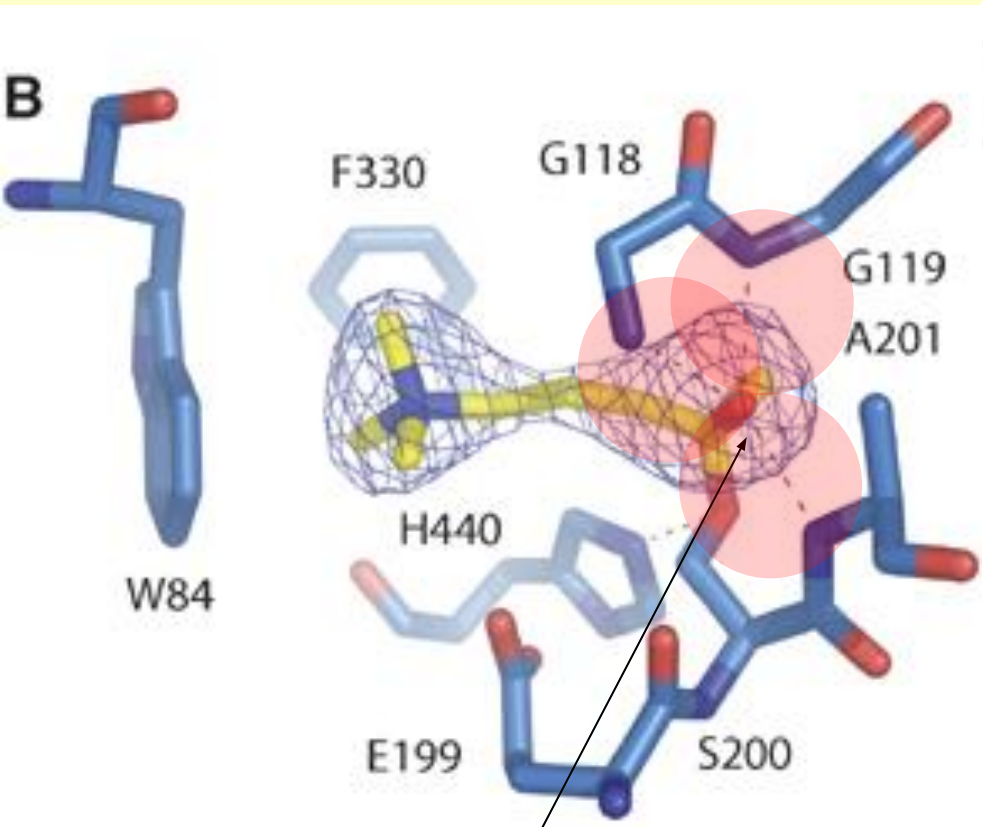


Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

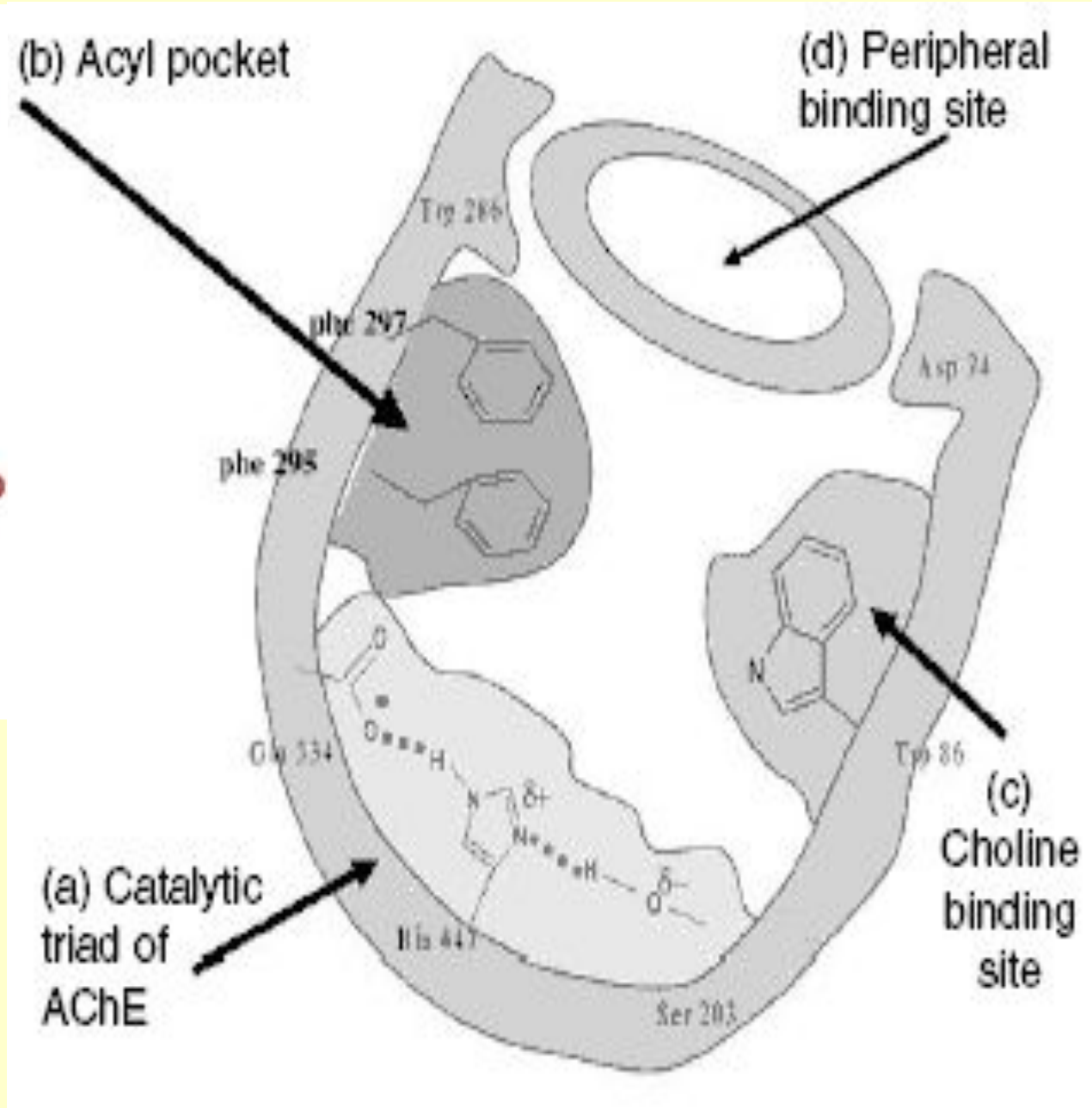
MECCANISMO DI IDROLISI DELL'ACETICOLINA



SITO ATTIVO DELL'ACETICOLINESTERASE

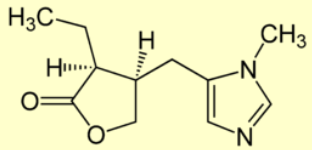


OXYANION HOLE

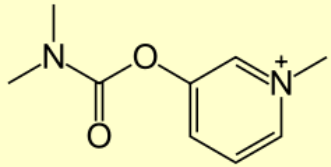


FARMACI COLINERGICI
USI TERAPEUTICI

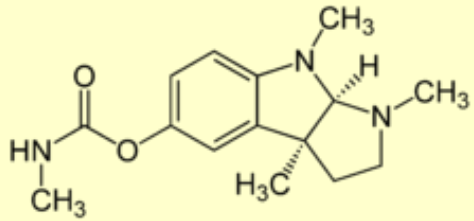
- GLAUCOMA (Pilocarpina)



- ILEO PARALITICO E ATONIA
- MIASTENIA GRAVIS (Piridostigmina)

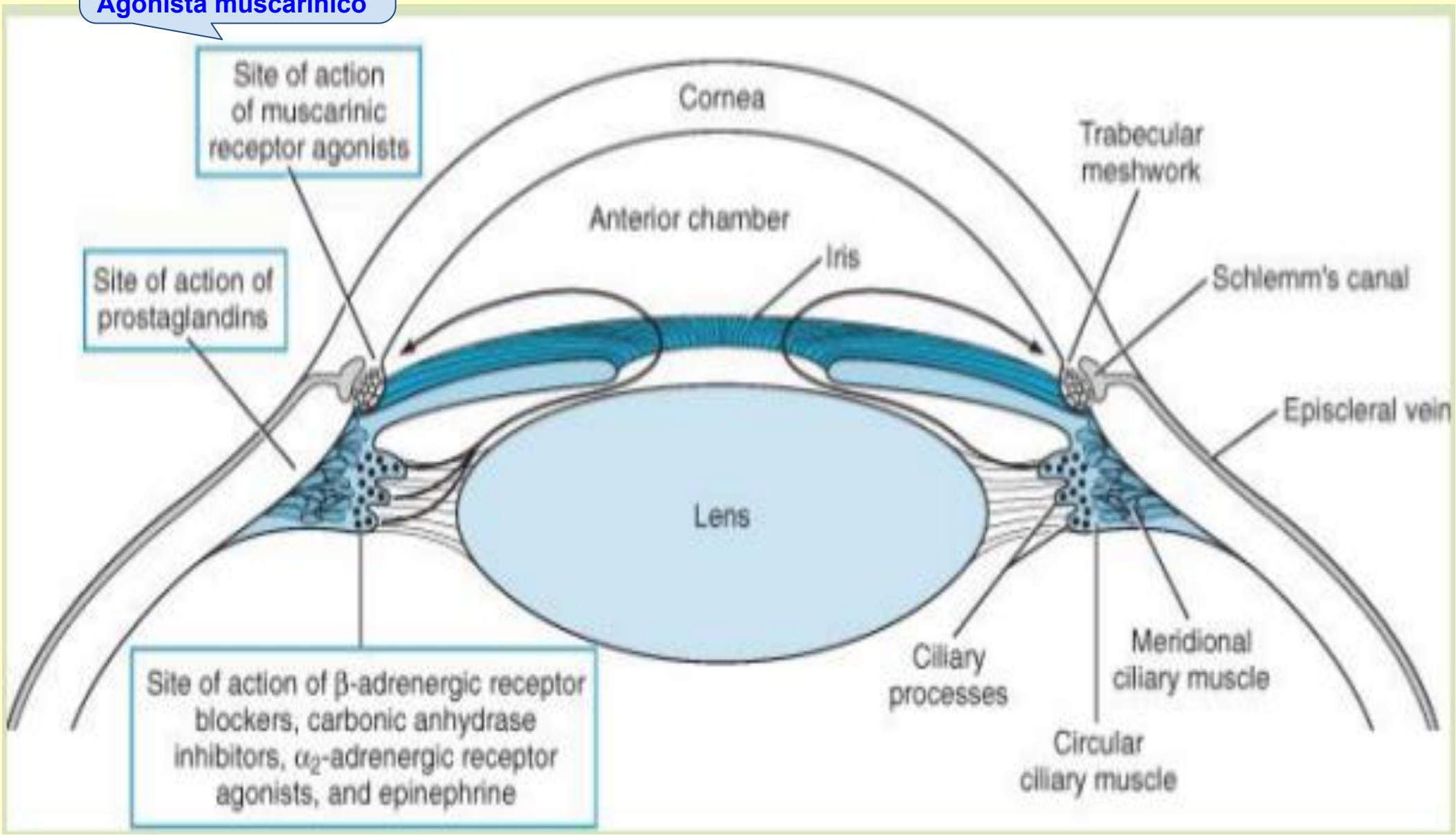


- INTOSSICAZIONE DA AGENTI ANTICOLINERGICI
- MORBO DI ALZHEIMER (Fisiostigmina)

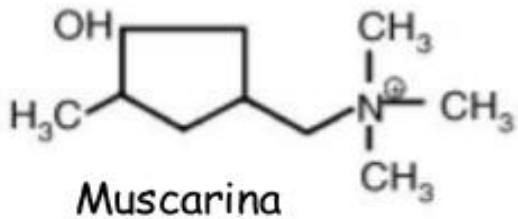


GLAUCOMA

PILOCARPINA
Azione colinergica
Agonista muscarinico

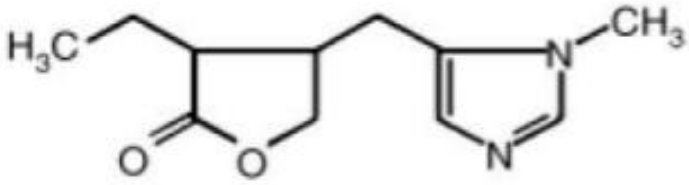


ALCALOIDI



Muscarina

Bene assorbiti.
Escreti prevalentemente per via renale.

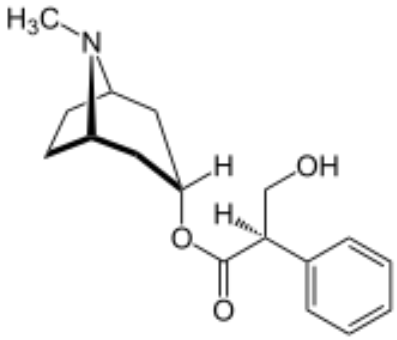


Pilocarpina

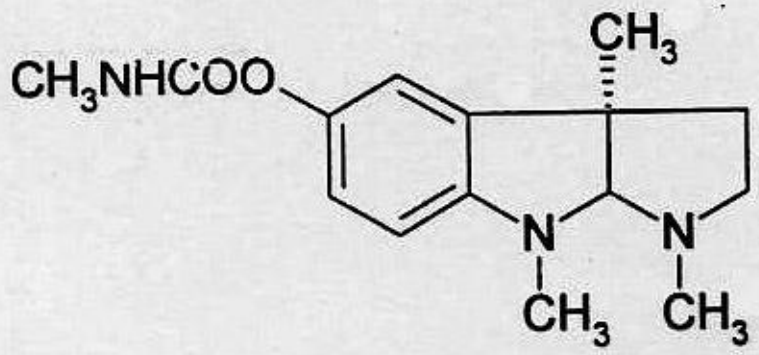
Muscarina

Pilocarpina
-Attività prevalentemente muscarinica.
-Alcaloide; non influenzato dalla colinesterasi.
-Effetti di interesse terapeutico: miosi.
-Stimola la secrezione di sudore.

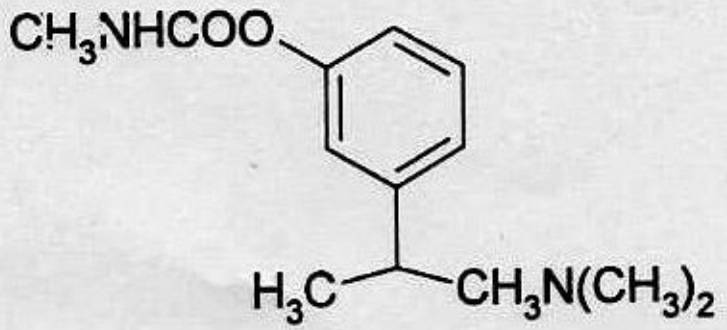
Atropina



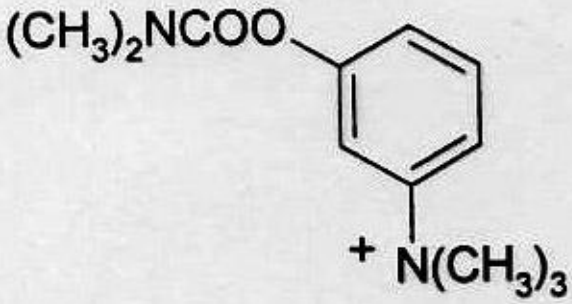
INIBITORI ACETILCOLINESTERASE



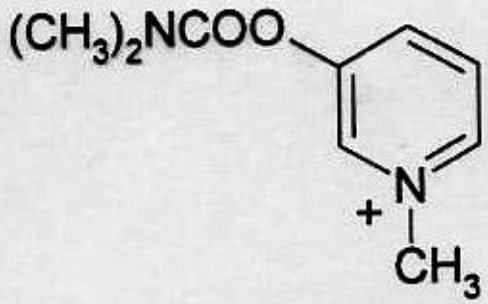
Fisostigmina



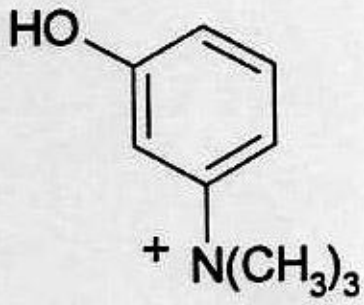
Miotina



Neostigmina

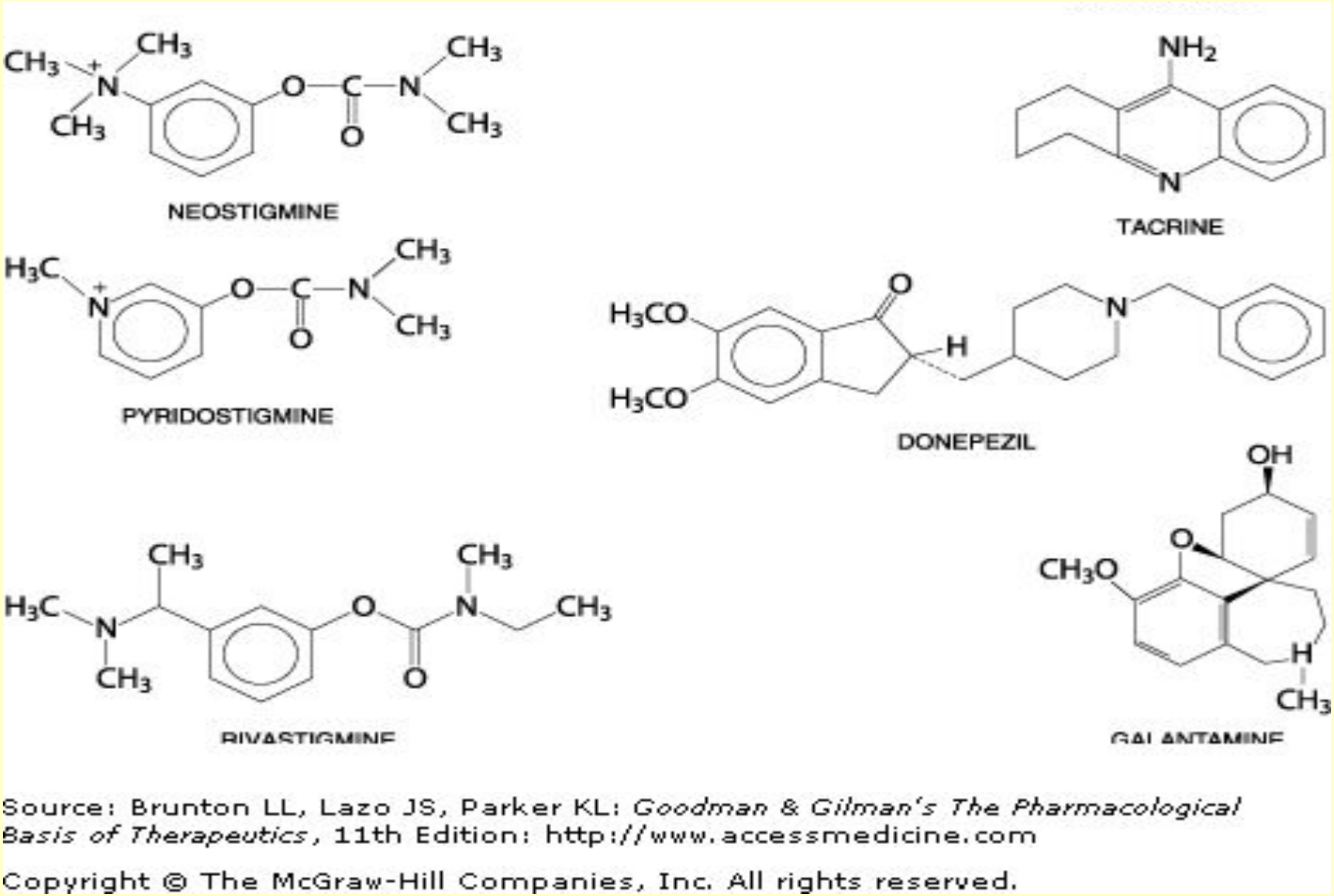


Piridostigmina



Edrofonio

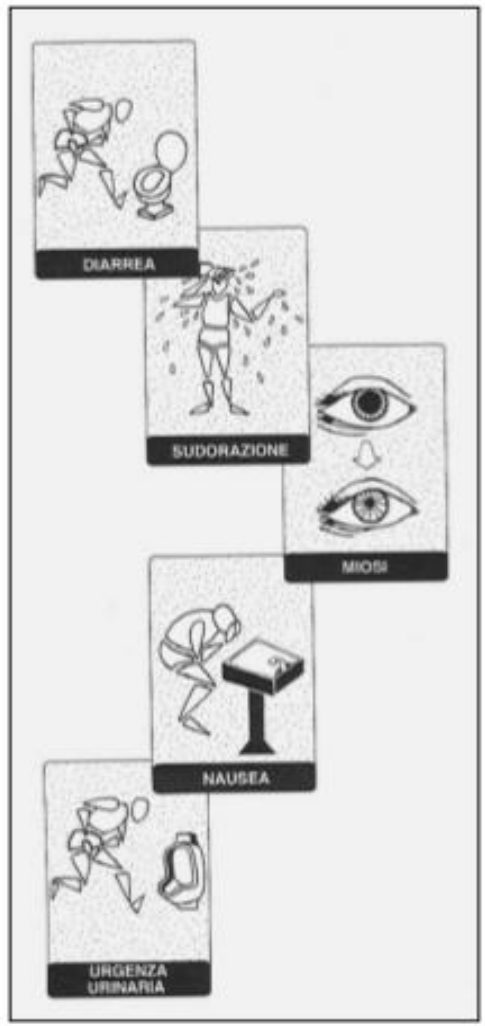
INIBITORI ACETILCOLINESTERASE



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

Effetti

ORGANI EFFETTORI	RISPOSTE COLINERGICHE
Occhio	
Muscolo sfintere dell'iride	Contrazione (miosi forte)
Muscolo ciliare	Contrazione (forte) per la visione da vicino
Cuore	
Nodo seno/atriale	↓ della frequenza (effetto cronotropo negativo)
Atri	↓ della forza di contrazione (effetto inotropo negativo).
Nodo atrio/ventricolare	↓ della velocità di conduzione (effetto dromotropo negativo)
Ventricoli	↓ lieve della forza di contrazione
Vasi sanguigni	
Arterie	Dilatazione
Vene	Dilatazione
Polmoni	
Muscoli lisci bronchiali	Contrazione
Ghiandole bronchiali	Stimolazione
Stomaco e intestino	
Motilità e tono	↑ (forte)
Sfinteri	Rilassamento (di solito)
Secrezioni	Stimolazione
Vescica	
Muscolo detrusore	Contrazione
Trigono e sfintere	Rilassamento
Ghiandole:	
sudoripare, salivari, lacrimali, nasofaringee	Secrezione



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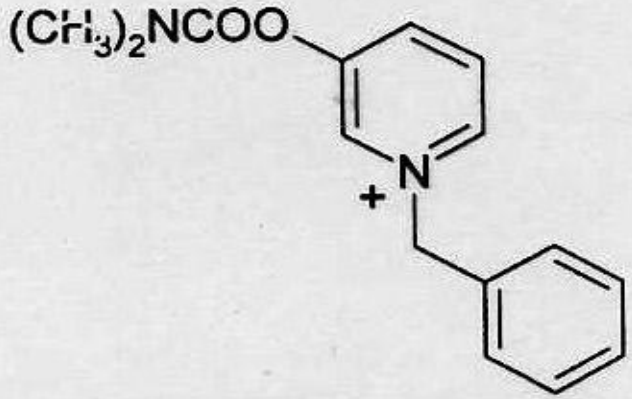
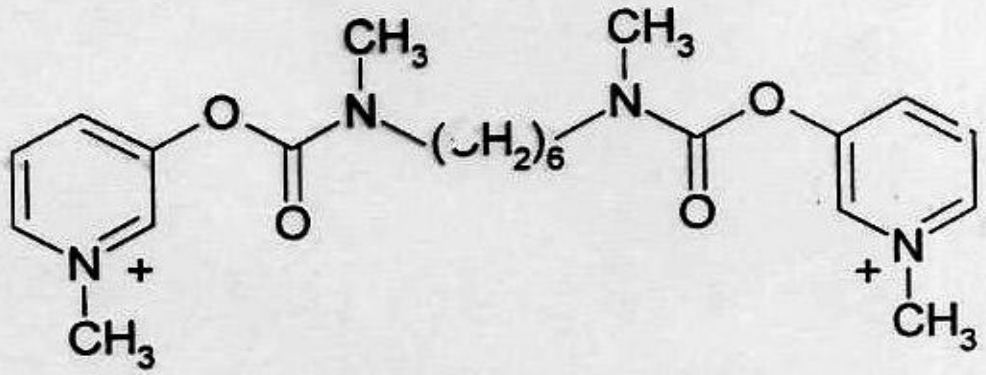
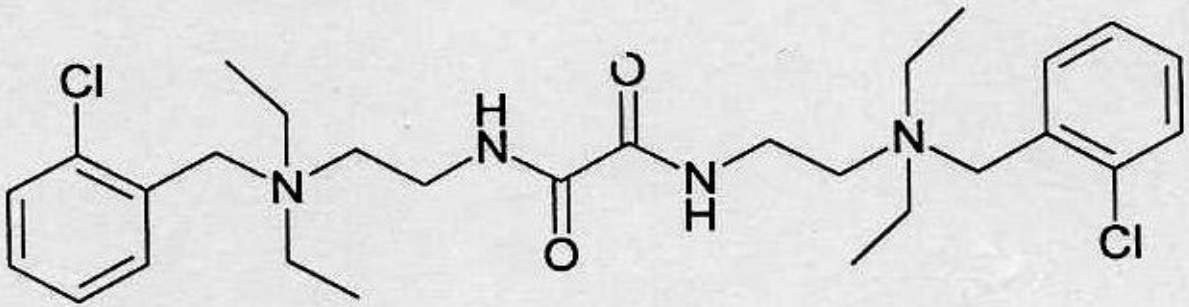


Benzopirinio

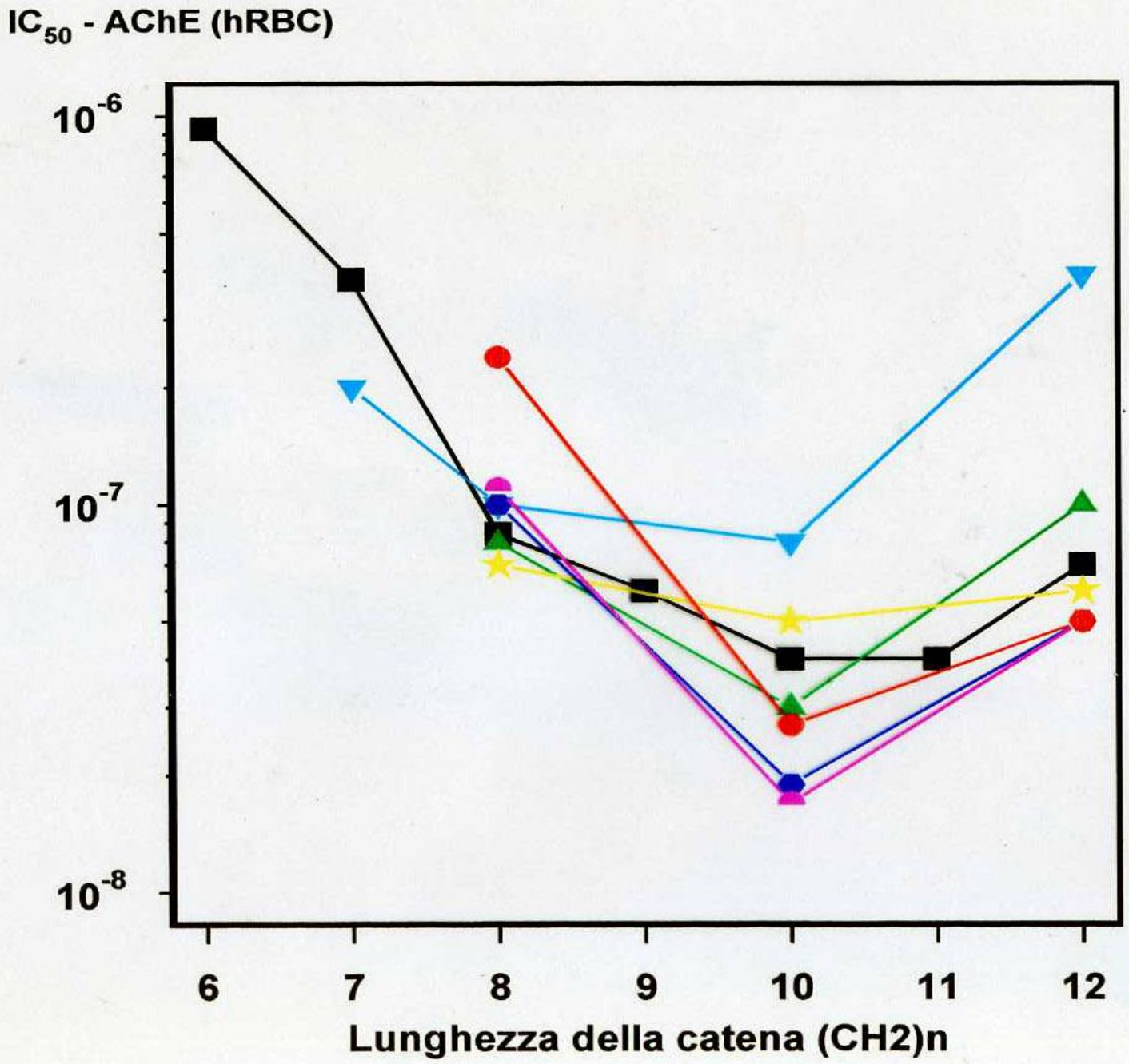


Distigmina



Ambemonio

Rapporto tra IC_{50} e lunghezza della catena dei derivati delle serie amminoalchilcarbammiche



Serie morfolina (■)

Serie o-metossifenil piperazina (▼)

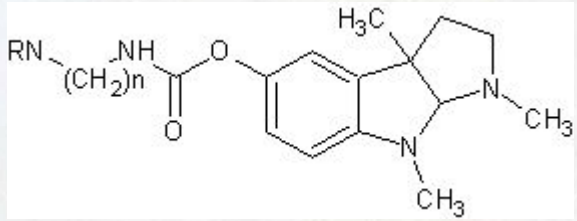
Serie piperidina (⬢)

Serie N-metilpiperazina

Serie N,N-dietilammina

Serie N,N-dipropilammin

Serie N-acetilpiperazina



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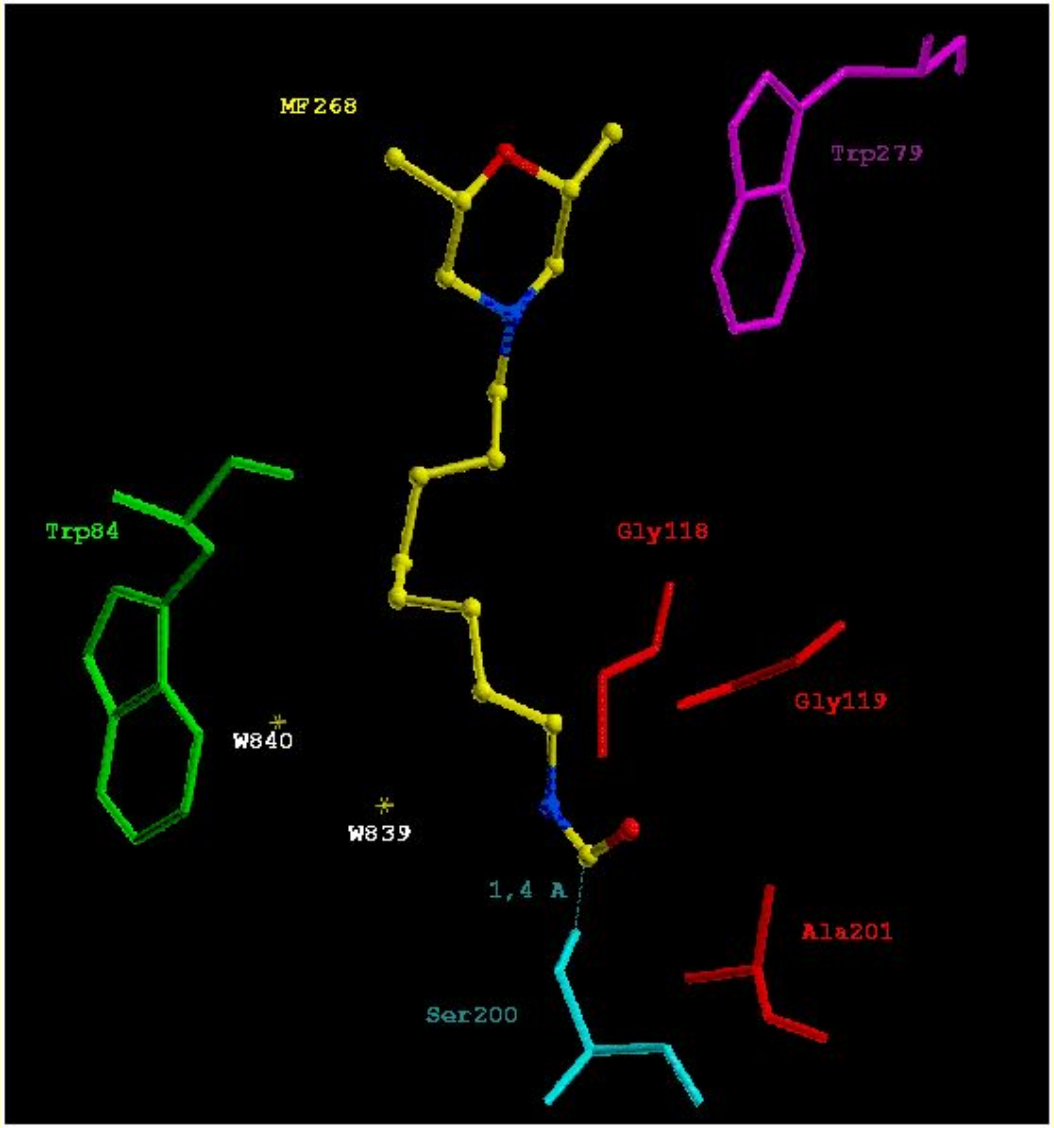
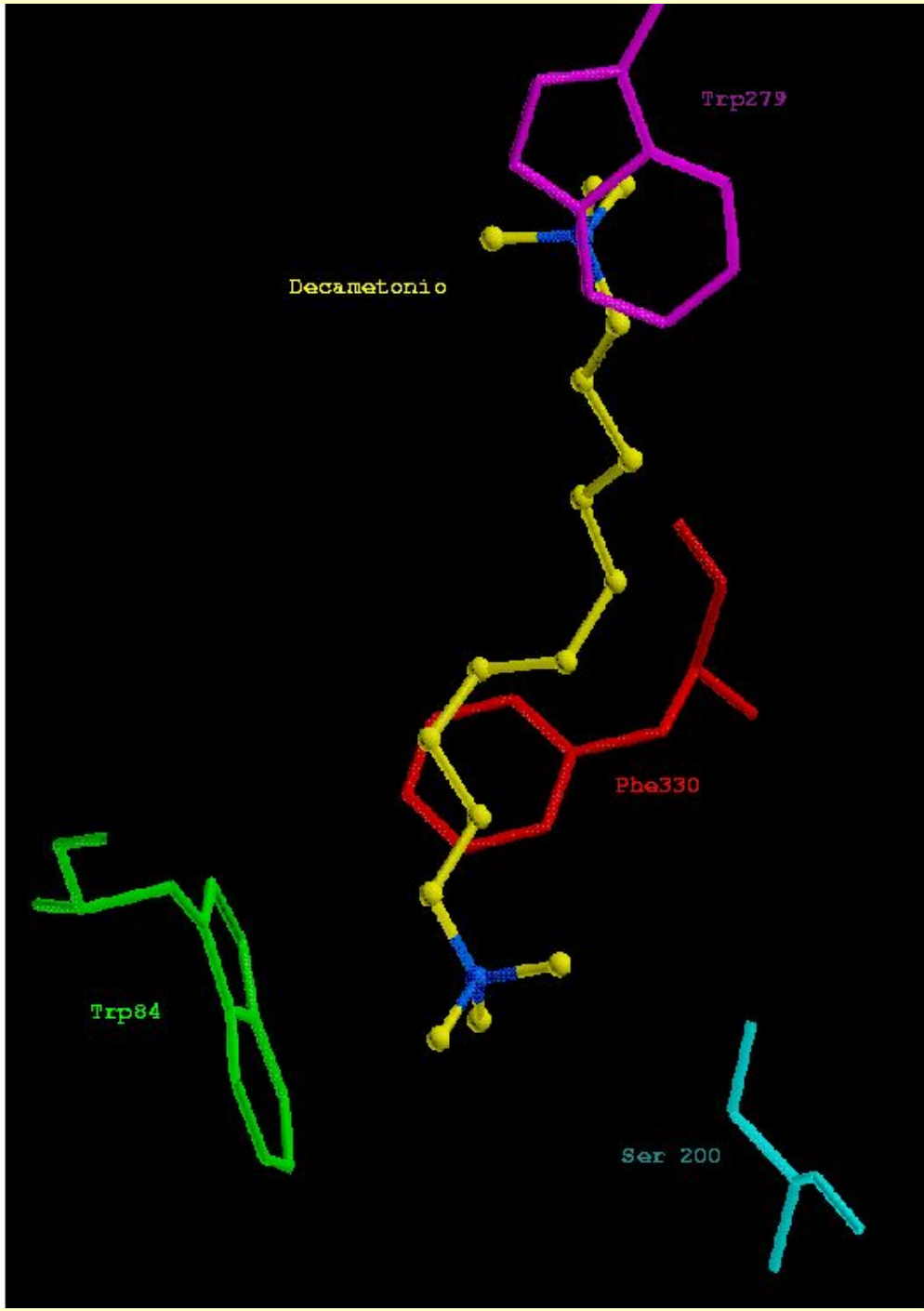
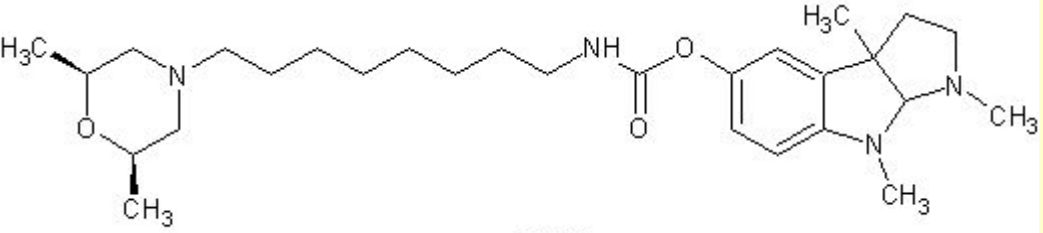


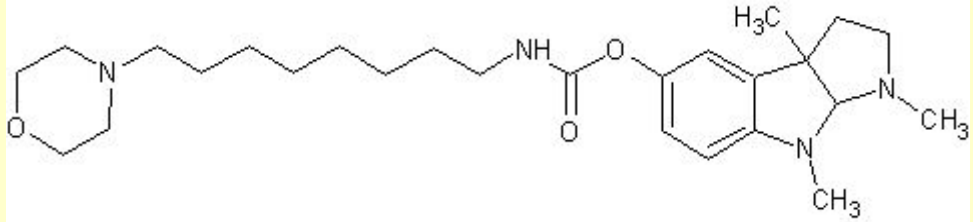
AchE con MF268



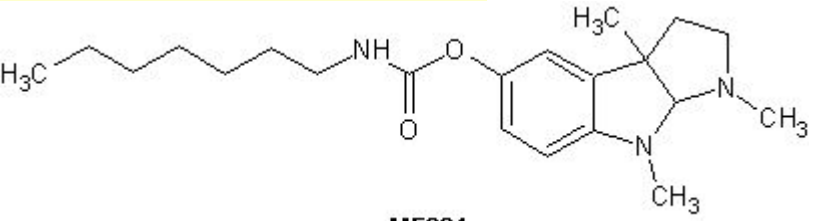
AchE con Decametonio



MF268

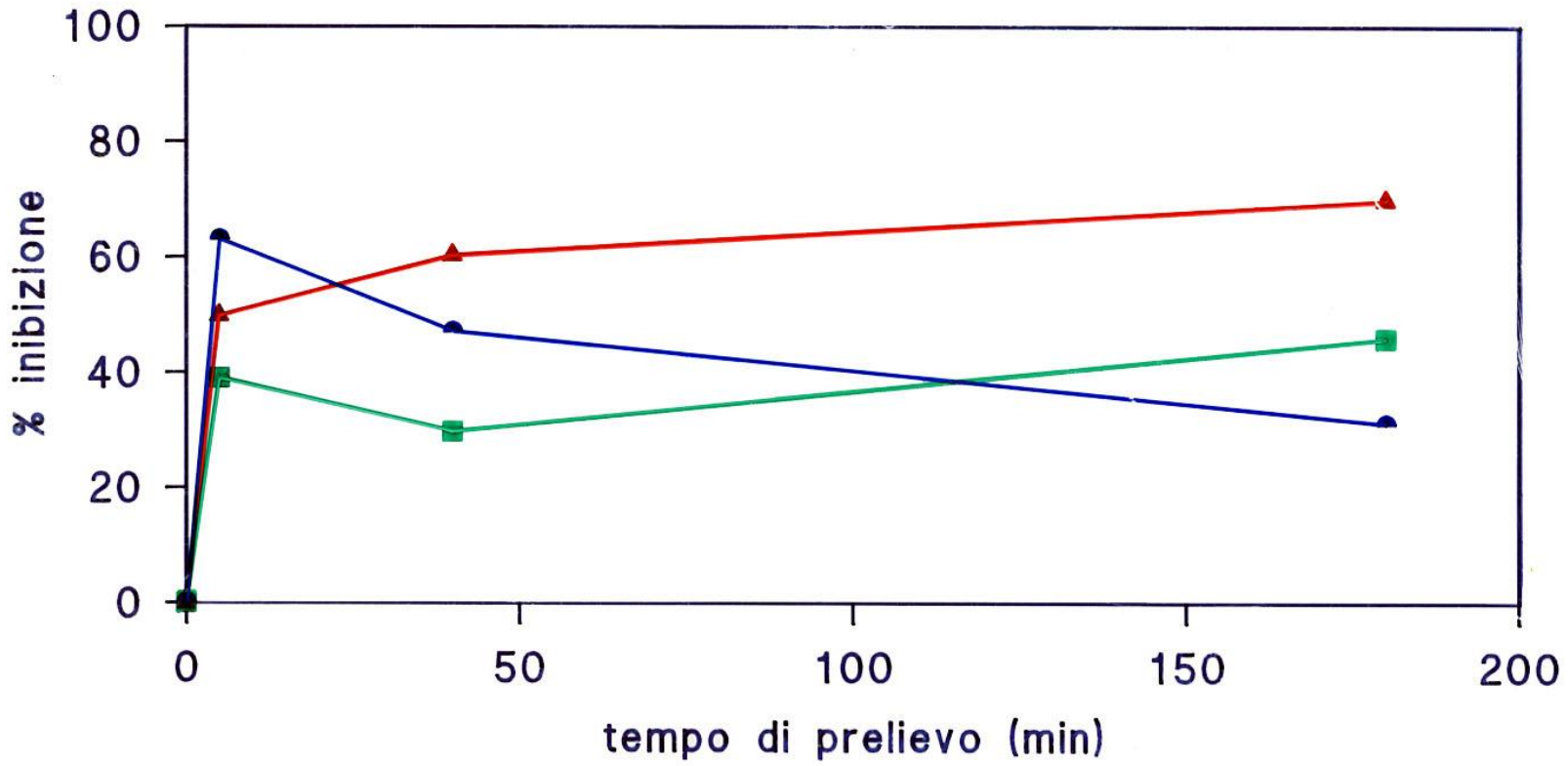


MF217



MF201

ATTIVITA' ANTICOLINESTERASICA NEL CERVELLO DI TOPO



dopo somministrazione i.v.