Menù (turistico) del trimestre di CFTII

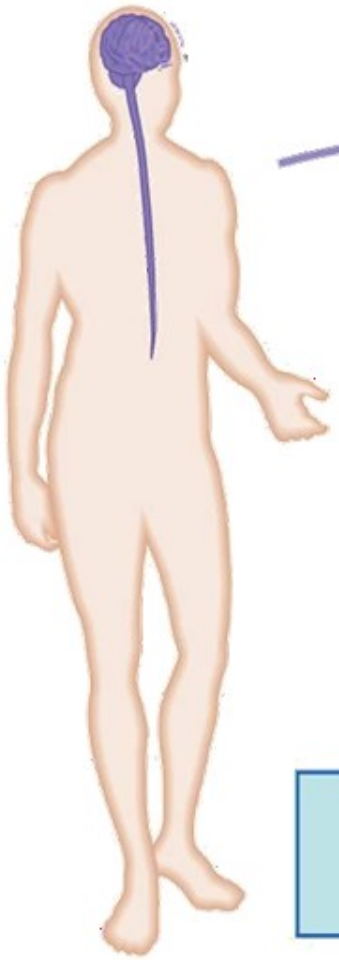
- **Parte prima: generale**

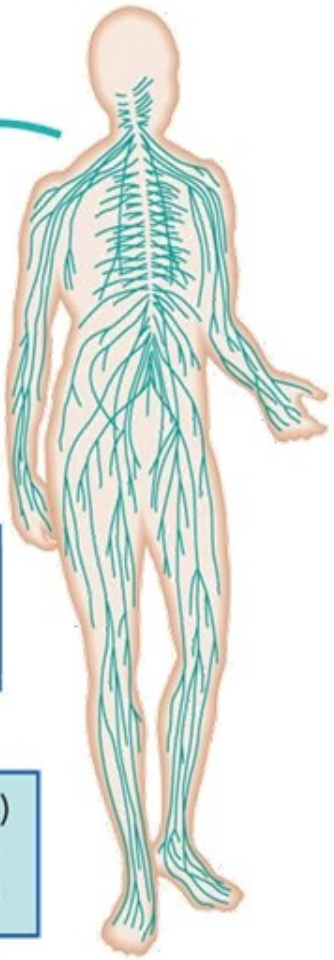
Le basi chimico-fisiche dell'interazione farmaco-bersaglio molecolare;
Sistemi di comunicazione cellulare

- **Parte seconda: sistematica**

Farmaci terapeuticamente rilevanti in patologie del SNC, dell'apparato cardiovascolare, del sistema immunitario e del sistema riproduttivo

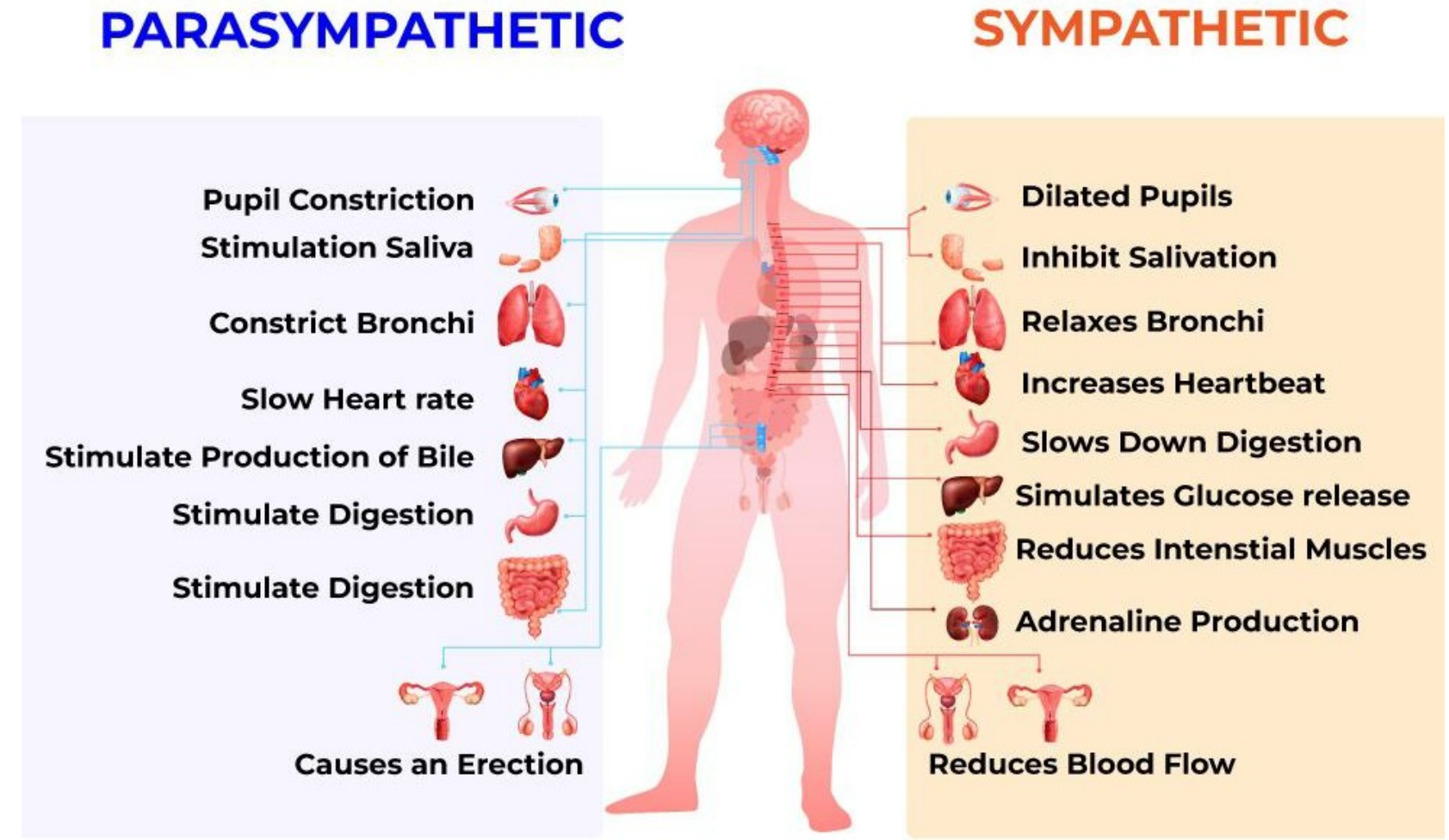
Before starting: propedeutic...

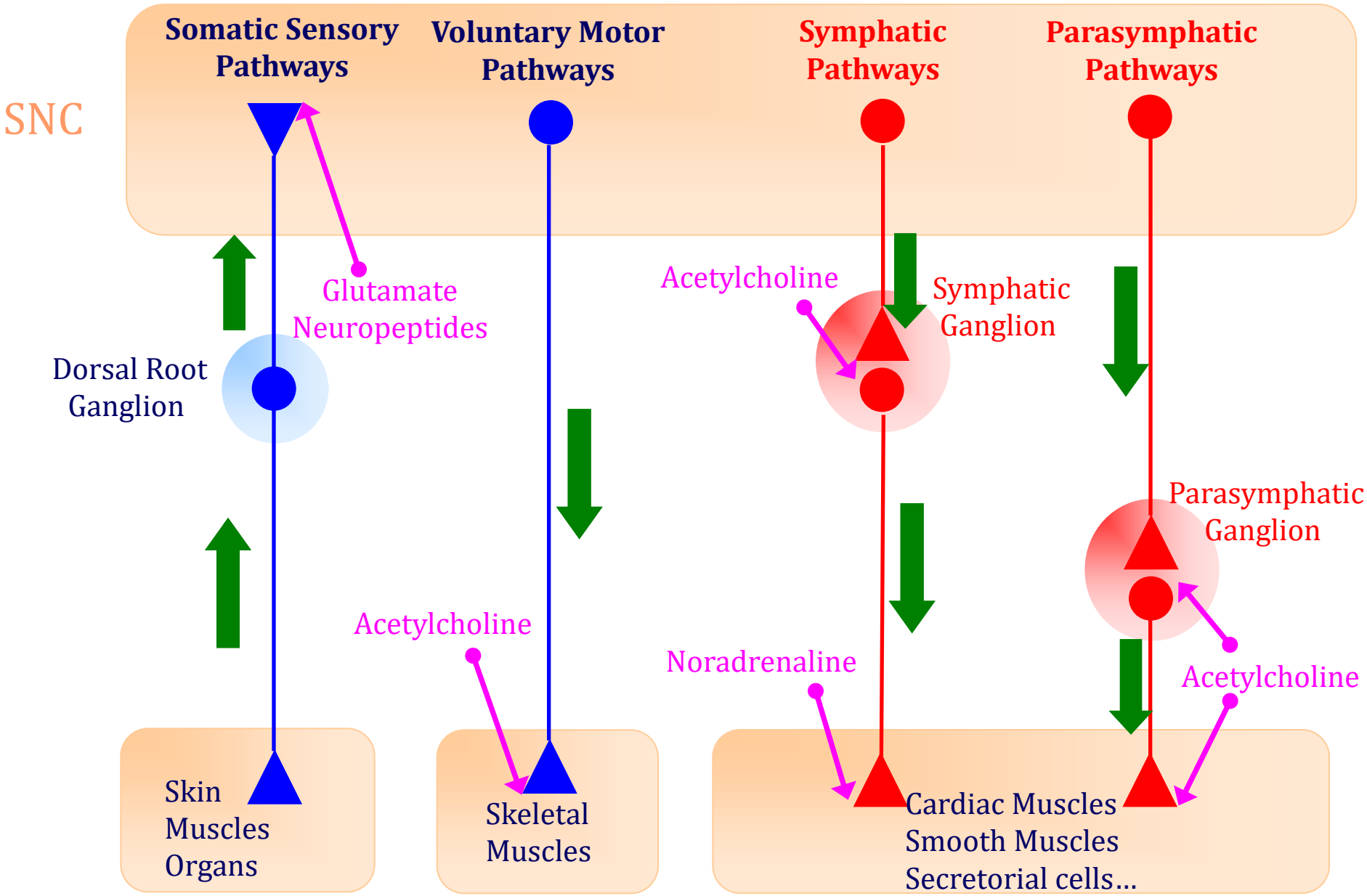




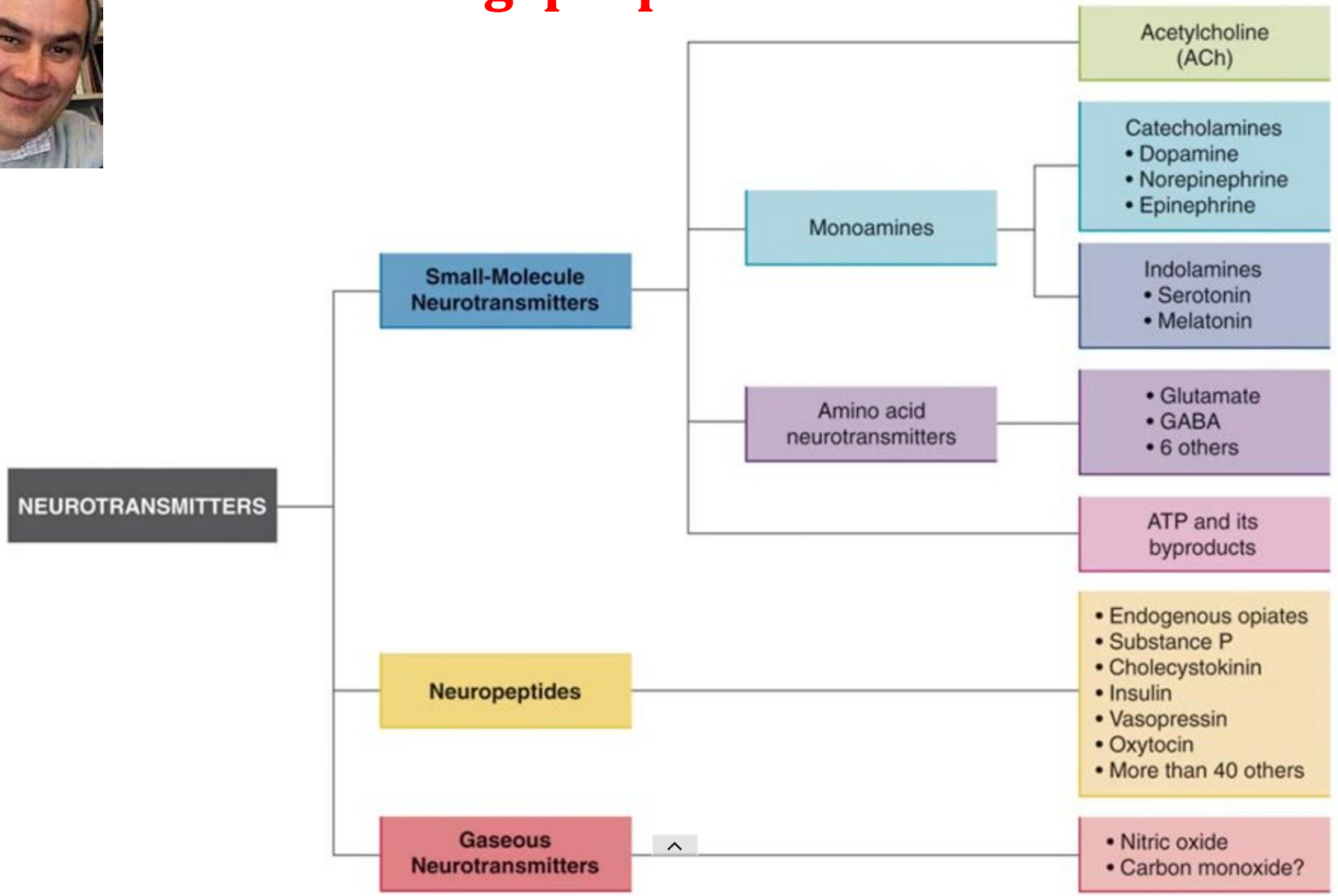
- Nervous system
  - Central nervous system (brain and spinal cord)
  - Peripheral nervous system
    - Autonomic nervous system (communicates with internal organs and glands)
      - Sympathetic division (arousing)
      - Parasympathetic division (calming)
    - Somatic nervous system (communicates with sense organs and voluntary muscles)
      - Sensory (afferent) nervous system (sensory input)
      - Motor (efferent) nervous system (motor output)

Before starting: propedeutic...



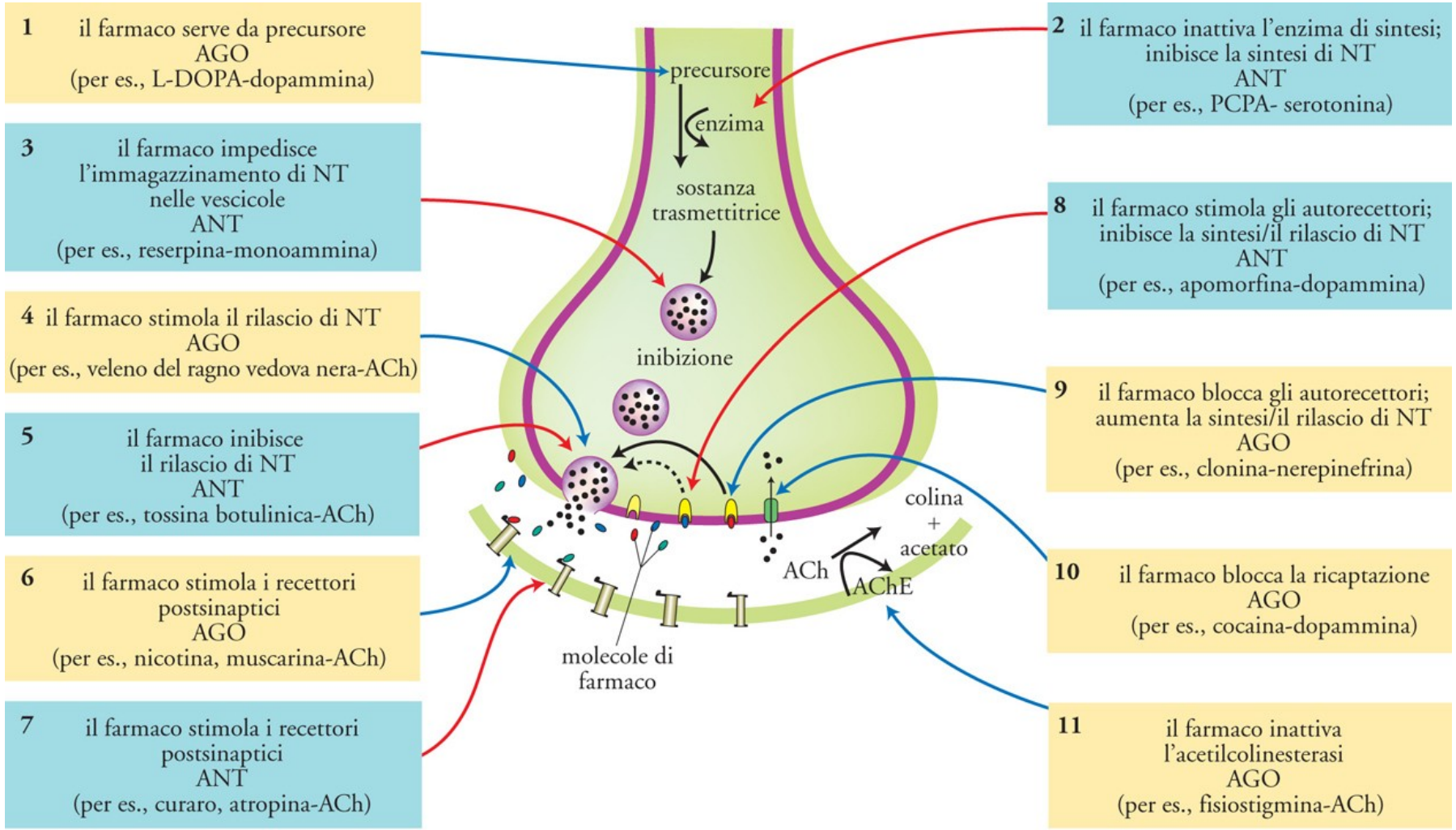


Before starting: propedeutic...



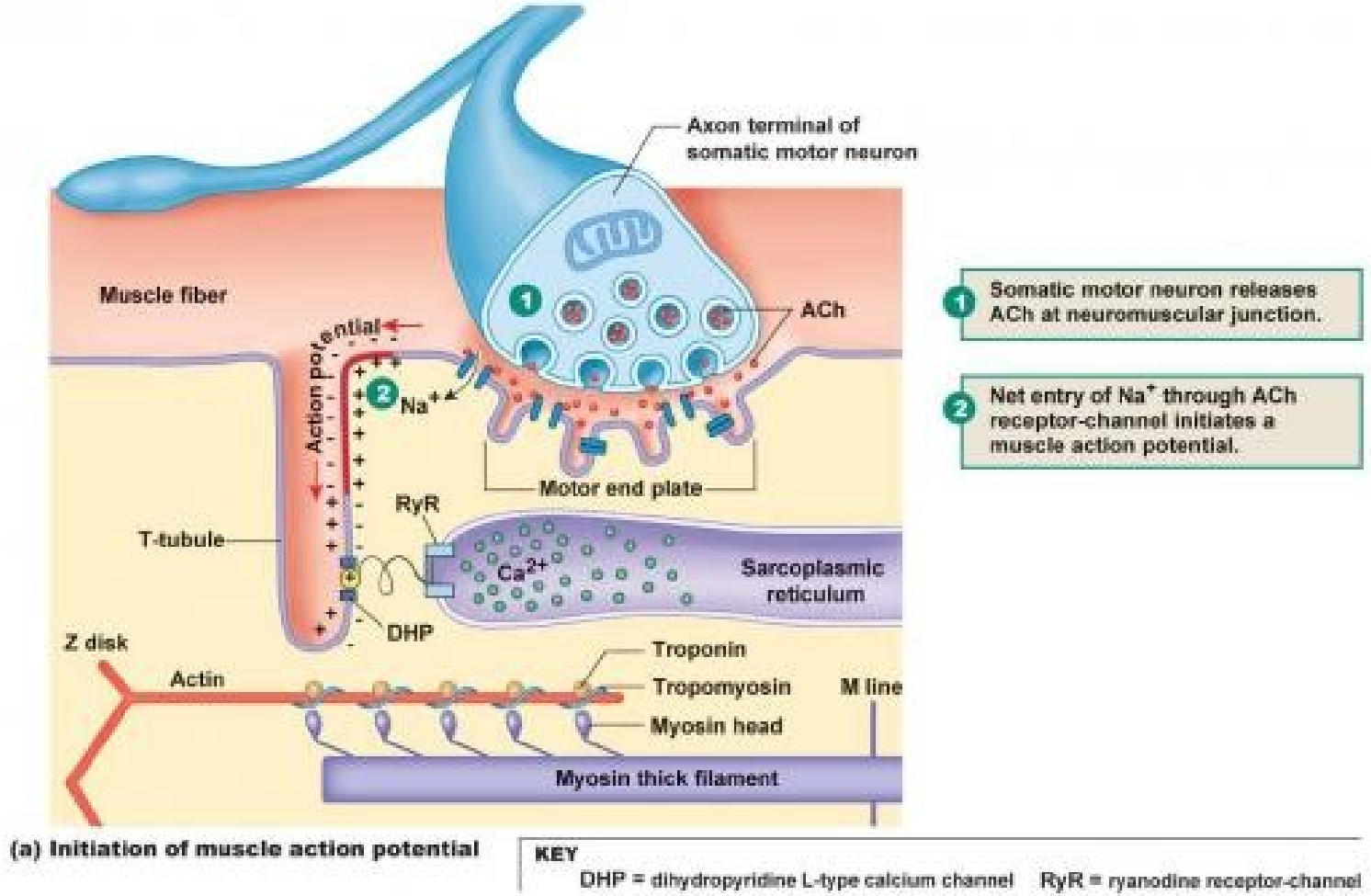
credits: https://slideplayer.com/slide/7815788/

A general overview of what we can do interfering with any communication mechanism:



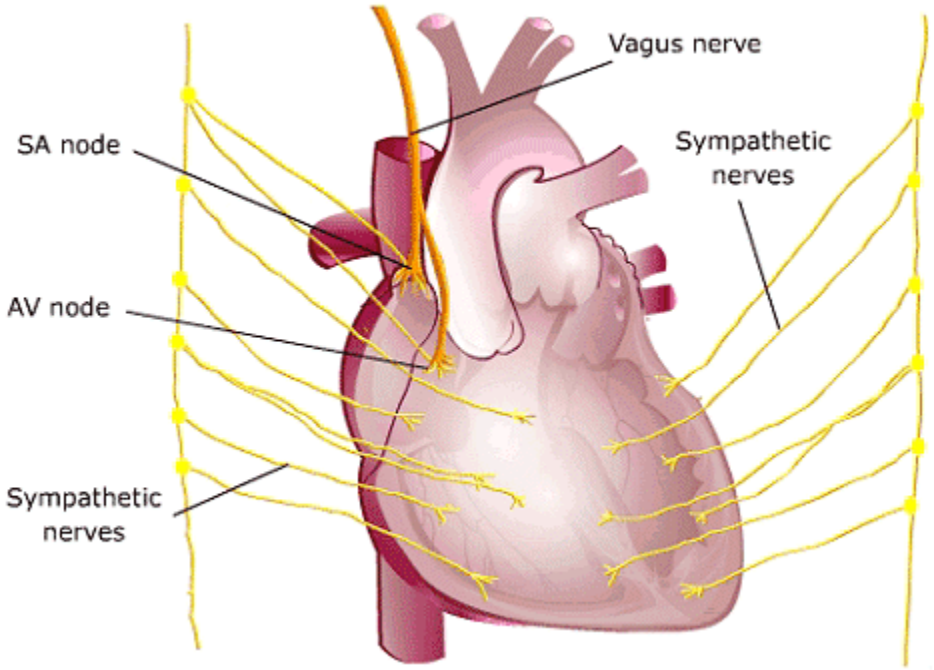
1. Nerve Transmission

Contraction of Skeletal muscle or "voluntary muscle"

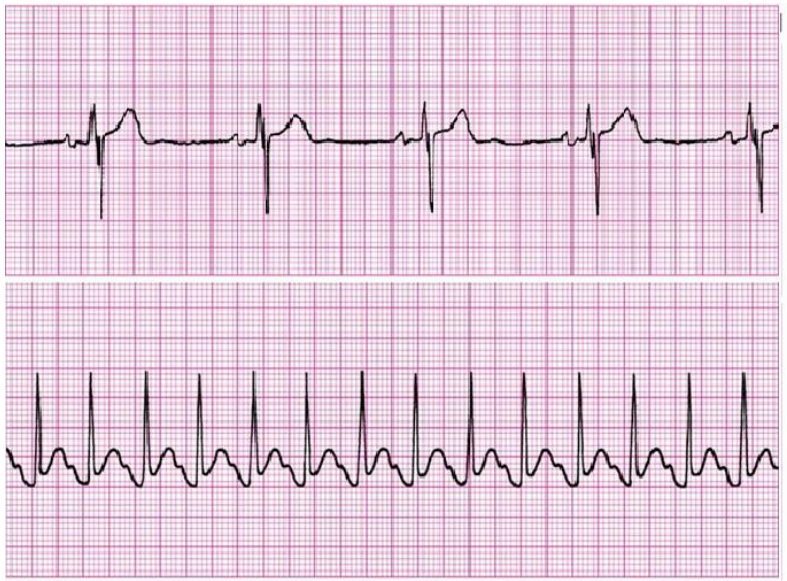


1. Nerve Transmission

The vagus nerve and the heart



Bradycardia with a heart rate less than 60 bpm.

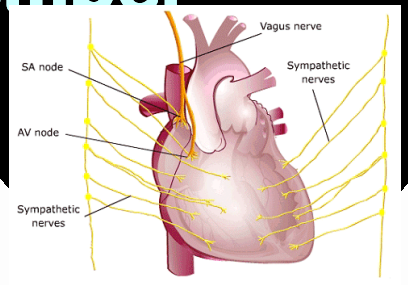


Tachycardia with a heart rate over 120 bpm

Atrioventricular node (abbreviated **AV node**)

Sinoatrial node (abbreviated **SA node)**

Do you remember



Ago

Ago

β1-receptor

M2-receptor

Gαs

AC

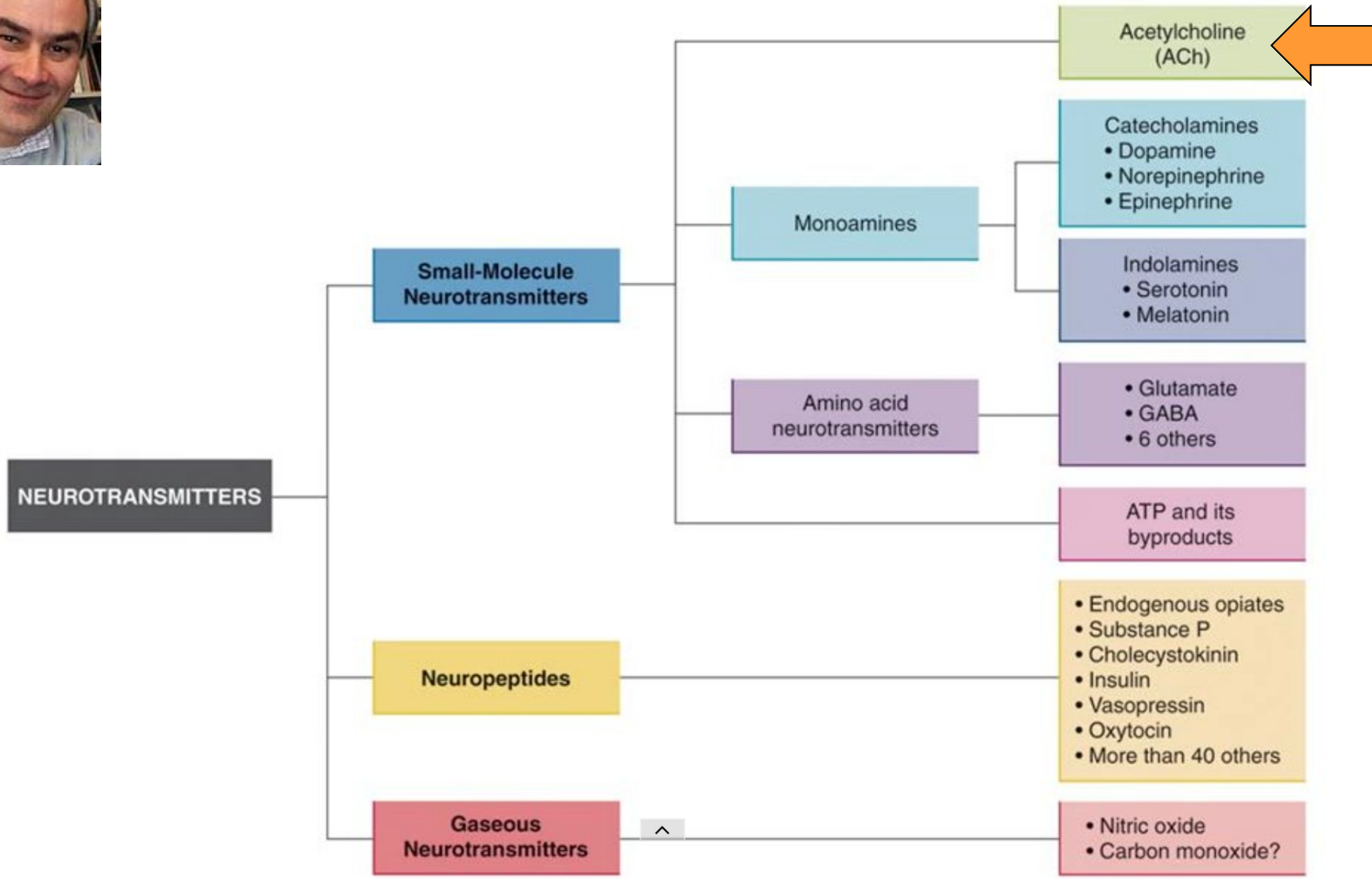
Gαi

\+

\-

cAMP -------> Ca^{2+}

It's time to start:

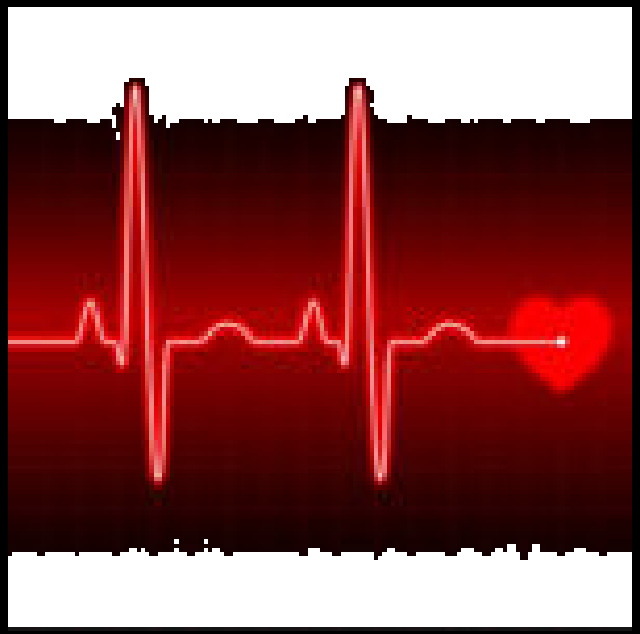


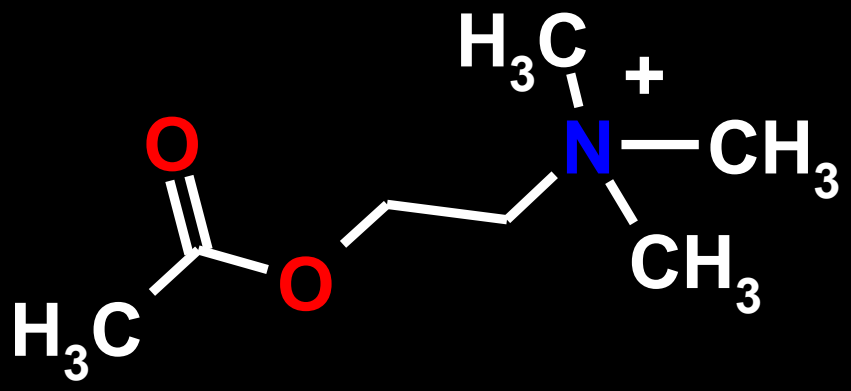
credits: https://slideplayer.com/slide/7815788/

Lecture number 0… the most important for us:

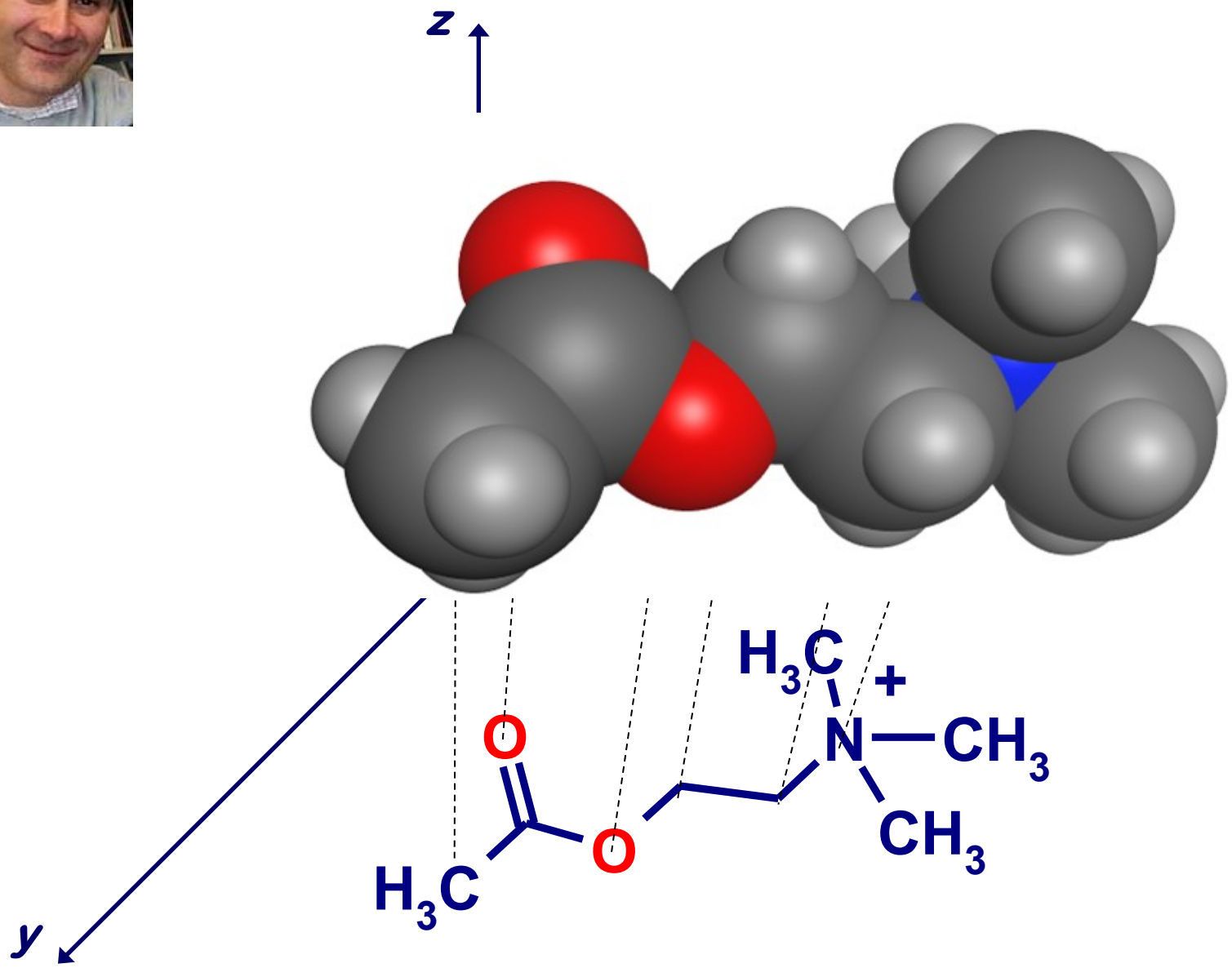
NON CONFONDEREMO MAI LA *CALCOLATRICE* CON LE *CIFRE* CHE ESSA PRODUCE!!!

We



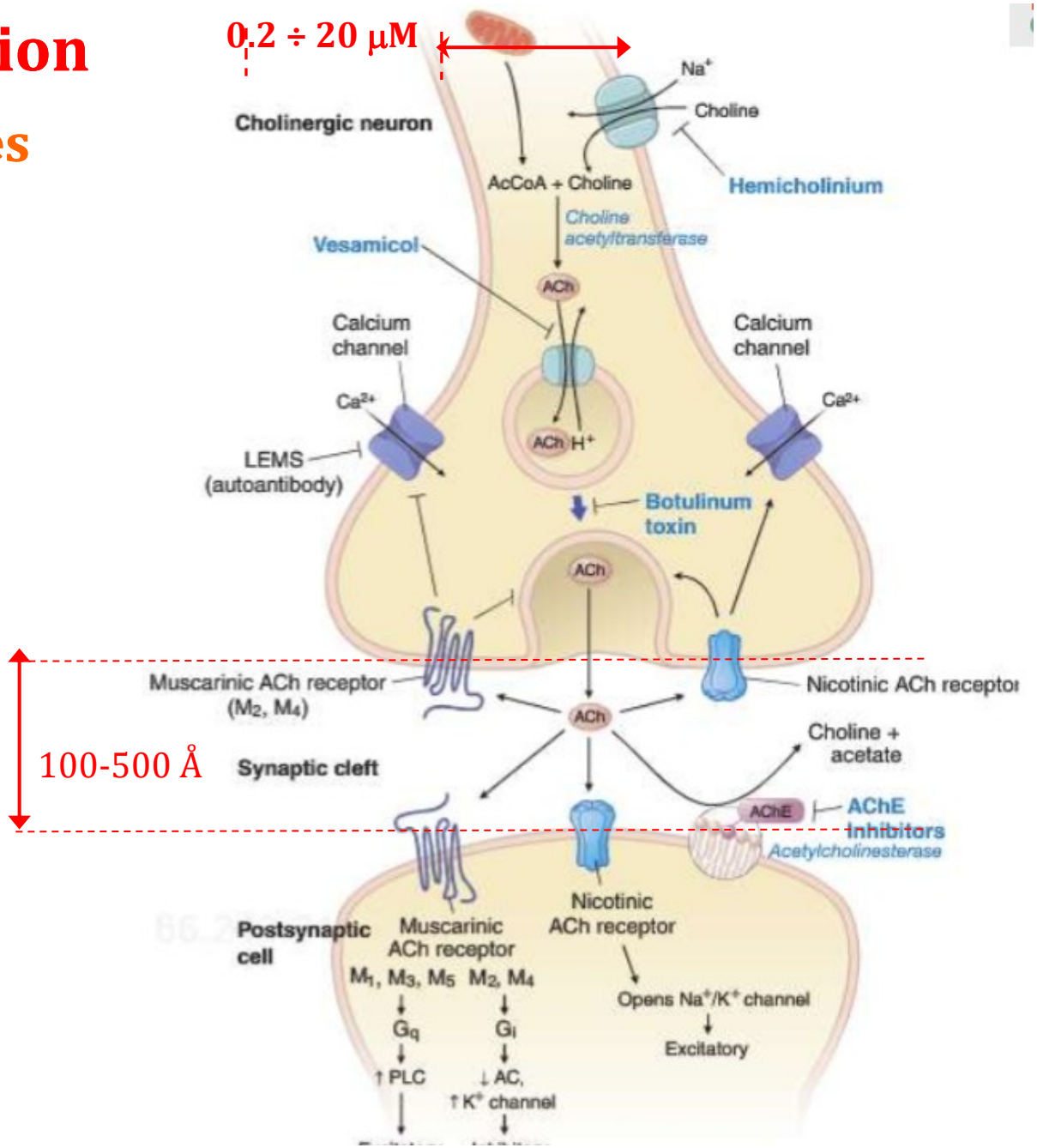


Now in 30 seconds…



1. Nerve Transmission

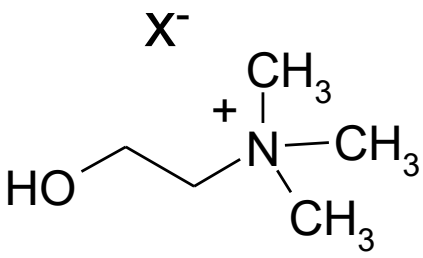
Cholinergic Synapses

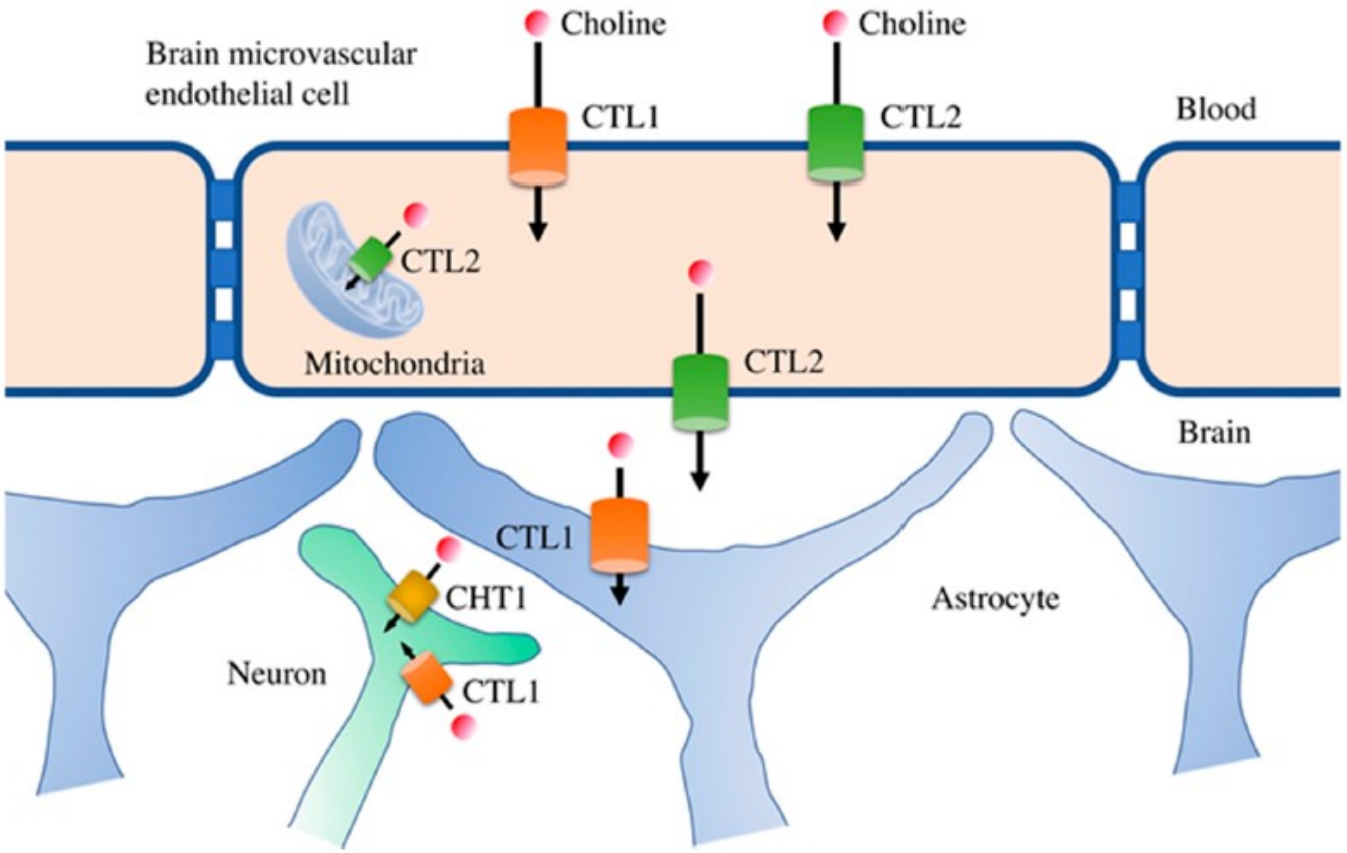


1. Nerve Transmission

Cholinergic Synapses: Choline Transporters

Sodium- and chloride-dependent transporter proteins with a high affinity for choline (CHT1) and intermediate-affinity (CTL1 and CTL2). **The uptake of choline by this transporter is the rate-limiting step for the synthesis of ACh.**

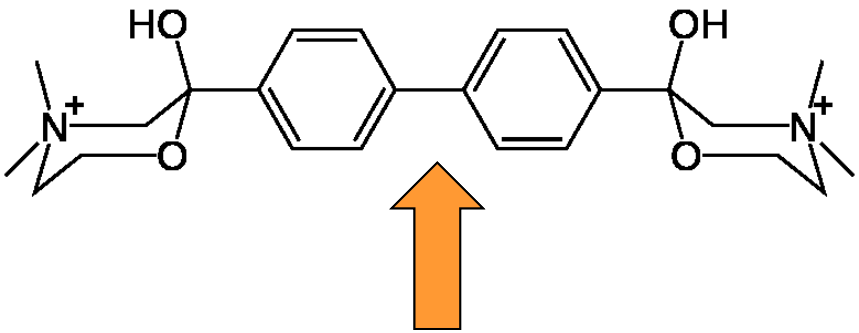


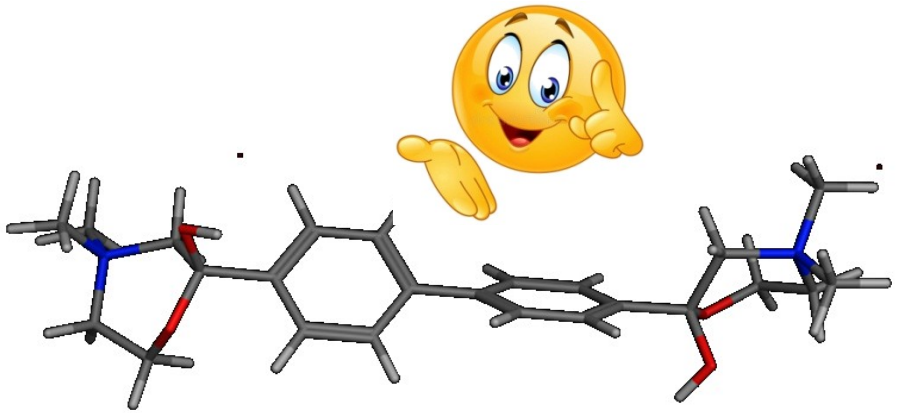


1. Nerve Transmission

Cholinergic Synapses: Choline Transporter

Hemicholinium-3 is a highly specific inhibitor of choline uptake by the CHT (Ki = 0.05–0.10 M). Choline is present in plasma at a concentration of about 10 m*M*. Moreover, more than 50% of choline hydrolyzed by Ach is re-uptaken by a ***high-affinity choline transporter , CHT1***.



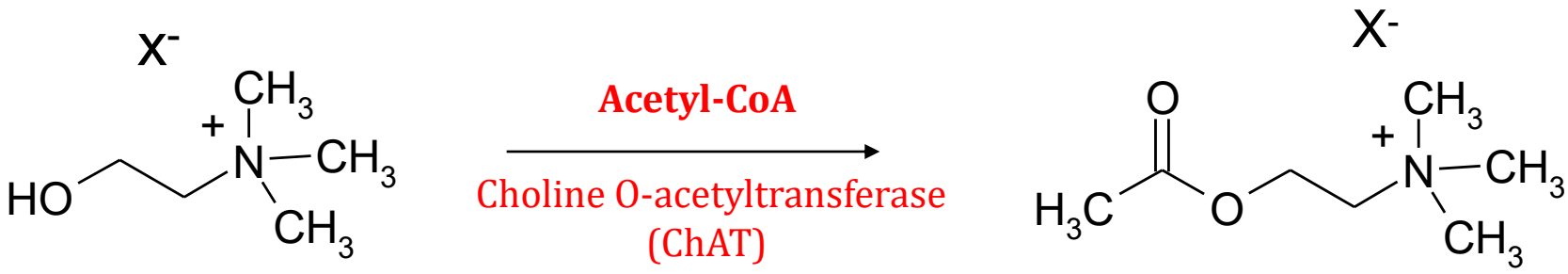


≈ 50 °

Hemicholinium-3 (hemicholine)

1. Nerve Transmission

Cholinergic Synapses: Acetylcholine biosynthesis



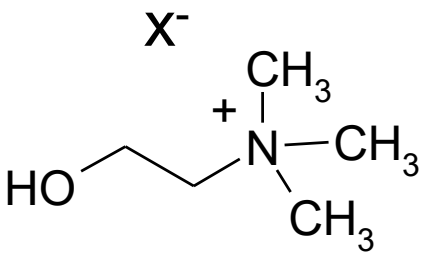
2-hydroxy-N,N,N-trimethylethanaminium

2-Acetoxy-N,N,N-trimethylethanaminium

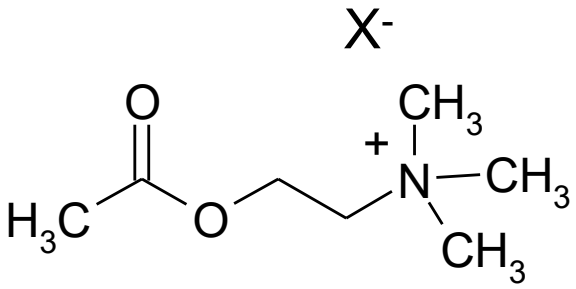
A. **Choline** is a water soluble quaternary amine that is widely distributed in foods. It is a **dietary component essential for normal function of all cells**. Choline ensures the structural integrity and signaling functions of cell membranes; it is the major source of methyl groups in the diet; and it is required for lipid transport and metabolism. Most choline in the body is found in phospholipids such as phosphatidylcholine and sphingomyelin. Phosphatidylcholine (*lecithin*) is the predominant phospholipid (>50%) in most mammalian membranes.

B. **Choline acetyltransferase** (ChAT, E.C. 2.3.1.6) catalyzes the transfer of an acetyl group from acetyl-CoA to choline to form the neurotransmitter acetylcholine. Communication between cholinergic neurons and their target cells and tissues is dependent on functional **ChAT**, with the loss of ChAT expression and activity found in several neurological and psychiatric disorders, such as *Alzheimer's disease, schizophrenia , and neuromuscular diseases.*

This is the most important thing to remember:



2-hydroxy-N,N,N-trimethylethanaminium



2-Acetoxy-N,N,N-trimethylethanaminium

Find the differences…

Where can we find Choline?

Foods Rich in Choline (mg/100g)

- Salmon –smoked– 220mg/100g
- Chicken –roasted- 79mg/100g
- Salmon –cooked- 91mg/100g
- Tilapia – 83mg/100g
- Soy protein powder – 86mg/100g
- Peanut Butter – 66mg/100g
- Cocoa powder – 115mg/110g
- Skim Milk – 38mg/cup

- Fried egg – 270/100g
- Hard-boiled egg – 230/100g
- Large Egg (one) – 120mg
- Beef Liver – 350mg/100g
- Chicken Liver – 330mg/100g
- Almonds – 52mg/100g
- Broccoli – 40mg/100g
- Brussels sprouts – 41mg/100g
- Cauliflower – 39mg/100g

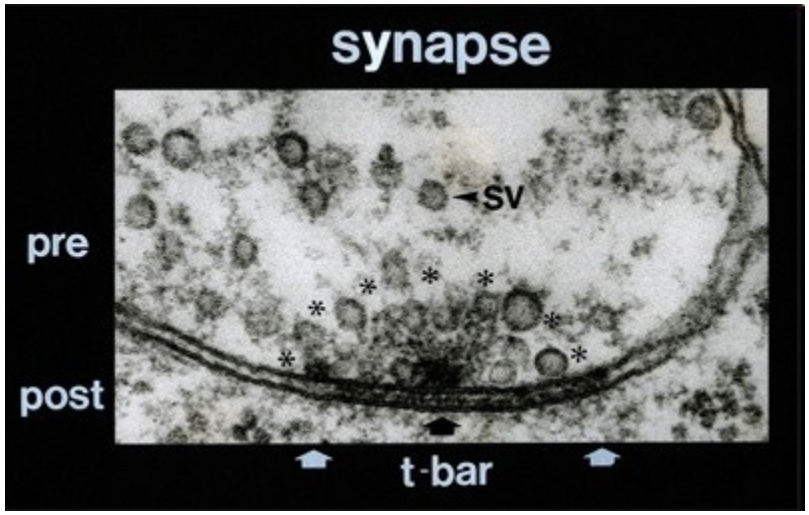
USDA Database for Choline in Common Foods, Release Two, USDA-ARS, Jan 2008.

Choline Requirements by Age (mg/day)

Infants/Children	Pregnancy	Lactation	Men/Woman
Infants • 0-6 months **125mg/day** • 7-12 months **150mg/day** **Boys** • 9-13 Years **375 mg/day** • 714-18 Years **550 mg/day** **Girls** • 9-13 Years **375 mg/day** • 714-18 Years **400 mg/day**	14-18 Years **450 mg/day** 19-30 Years **450mg/day** 31-50 Years **450 mg/day**	14-18 Years **550 mg/day** 19-30 Years **550mg/day** 31-50 Years **550 mg/day**	**Men** 19-30 Years **550 mg/day** 31-50 Years **550 mg/day** 51-70 Years **550 mg/day** >70 Years **550 mg/day** **Women** 19-30 Years **425 mg/day** 31-50 Years **425 mg/day** 51-70 Years **425 mg/day** >70 Years **425 mg/day**

1. Nerve Transmission

Cholinergic Synapses: 2_ Synaptic Vesicle



Synaptic vesicles are relatively simple because only a limited number of proteins fit into a sphere of 40 nm diameter. Purified vesicles have a protein:phospholipid ratio of 1:3 with a lipid composition of 40% phosphatidylcholine, 32% phosphatidylethanolamine, 12% phosphatidylserine, 5% phosphatidylinositol, and 10% cholesterol.

Synaptic vesicles contain two classes of obligatory components: ***transport proteins*** involved in neurotransmitter uptake, and ***trafficking proteins*** that participate in synaptic vesicle exocytosis, endocytosis, and recycling.

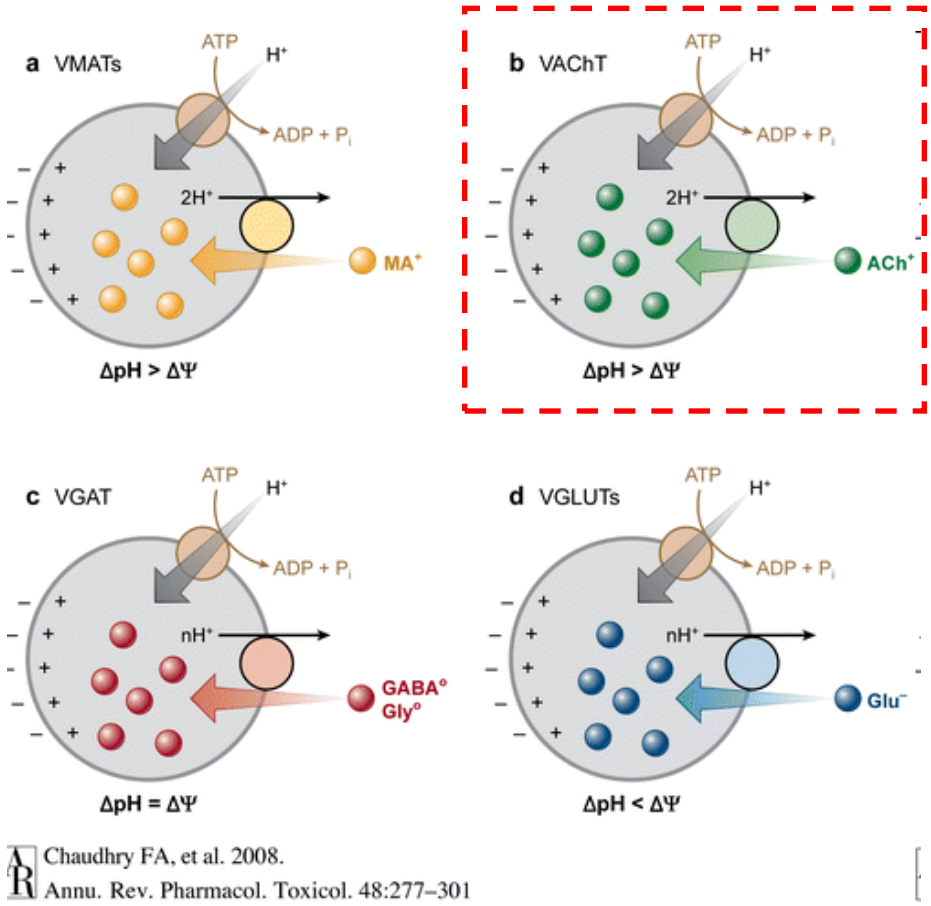
5000 ÷ 100000 synapses per neuron

≈ 300000 vesicles per synapses

1000 ÷ 50000 Ach molecules per vesicle

1. Nerve Transmission

Cholinergic Synapses: Synaptic Vesicle

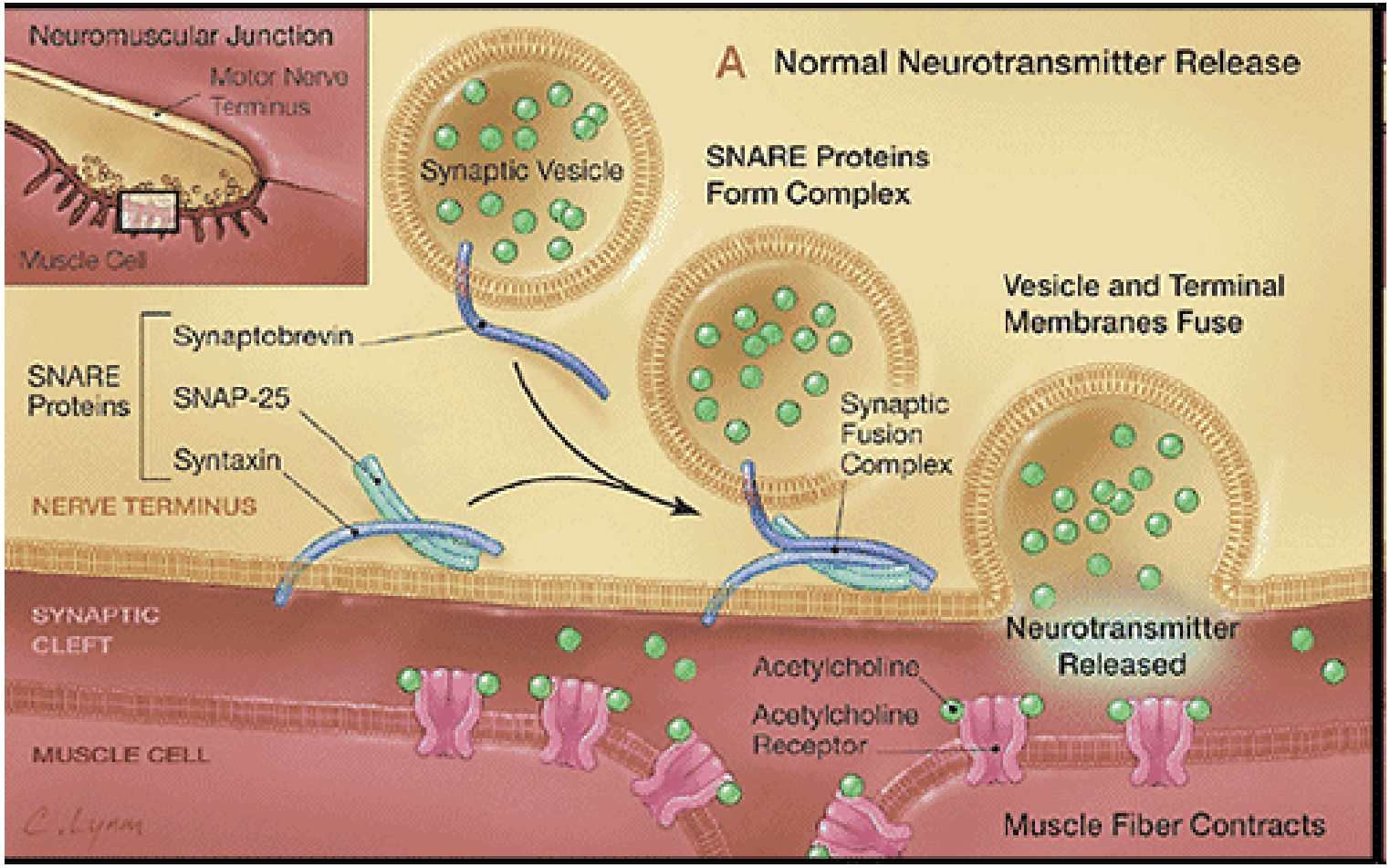


Chaudhry FA, et al. 2008.
Annu. Rev. Pharmacol. Toxicol. 48:277–301

The **Vesicular acetylcholine transporter** (**VAChT**) is a neurotransmitter transporter which is responsible for loading acetylcholine into synaptic vesicles in neurons making acetylcholine available for secretion. Transport proteins are composed of proton pumps that generate electrochemical gradients, which allow for neurotransmitter uptake, and neurotransmitter transporters that regulate the actual uptake of neurotransmitters. The necessary proton gradient is created by V-ATPase, which breaks down ATP for energy.

1. Nerve Transmission

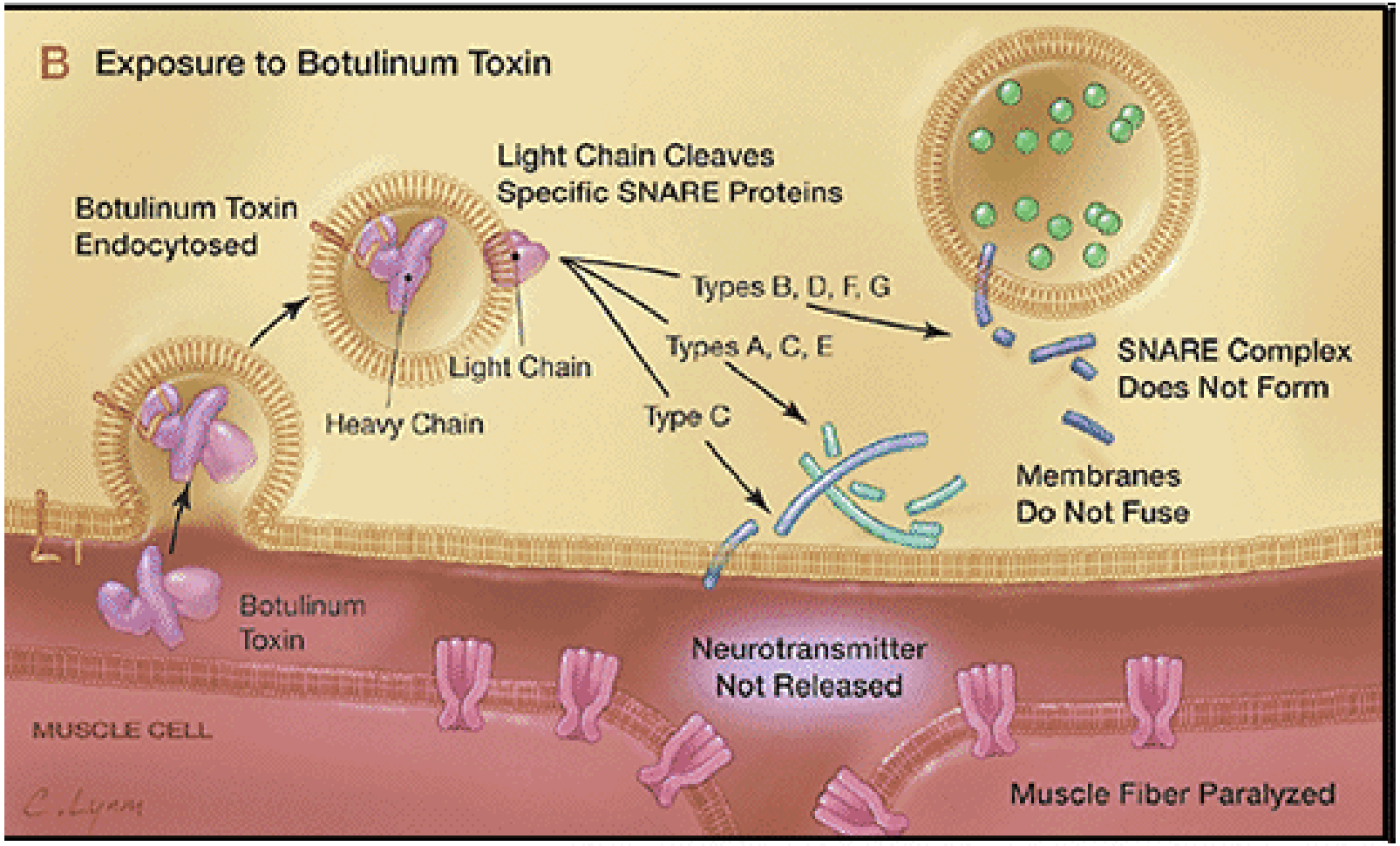
Cholinergic Synapses: 2_ Synaptic Vesicle



SNAP-25 = synaptosomal-associated protein of 25 kd.
SNARE = soluble NSF-attachment protein receptor
NSF= N-ethylmaleimide-sensitive fusion protein.

1. Nerve Transmission

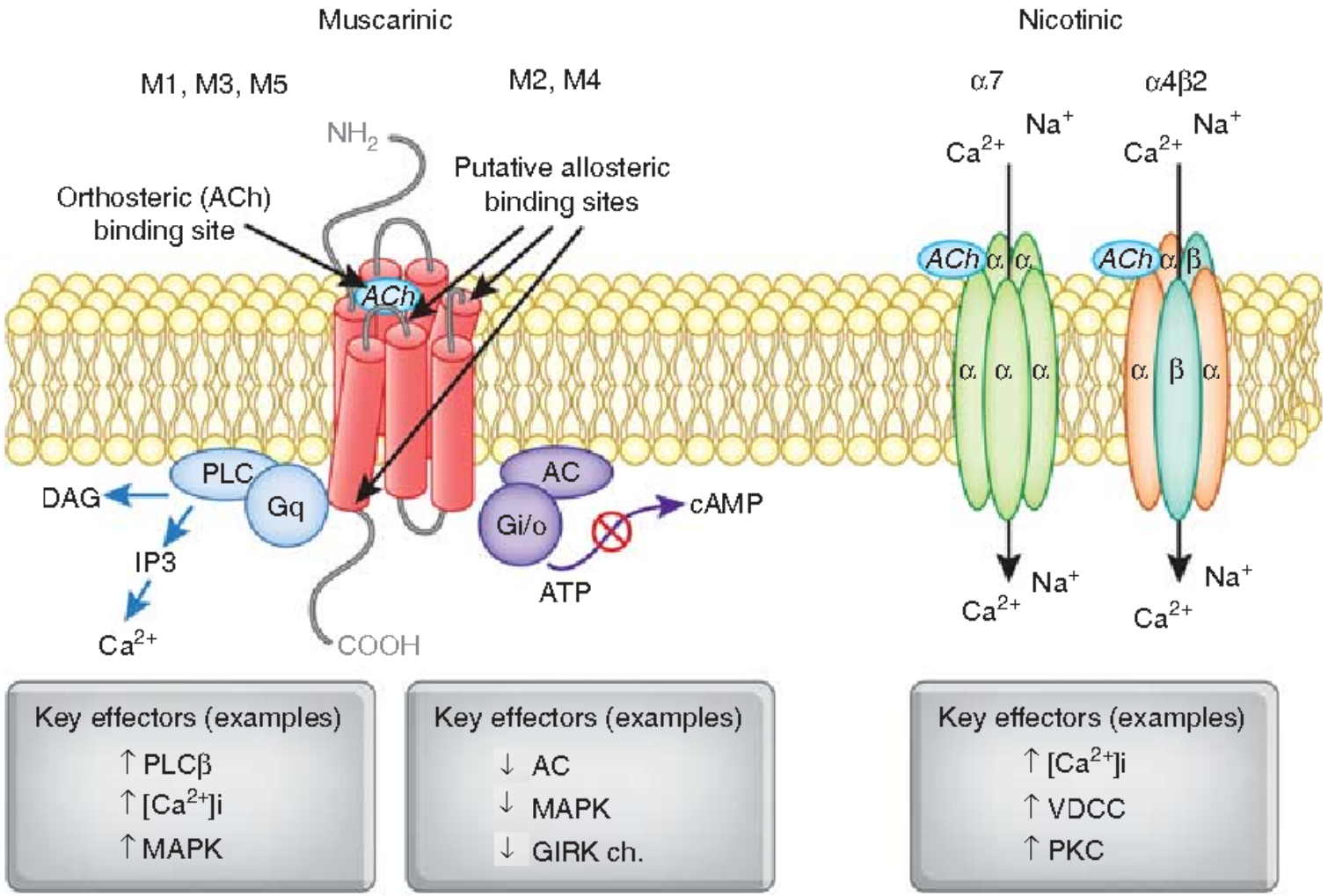
Cholinergic Synapses: 2_ Synaptic Vesicle



JAMA. 2001;285:1059-1070. © American Medical Association

2. Cholinergic receptors

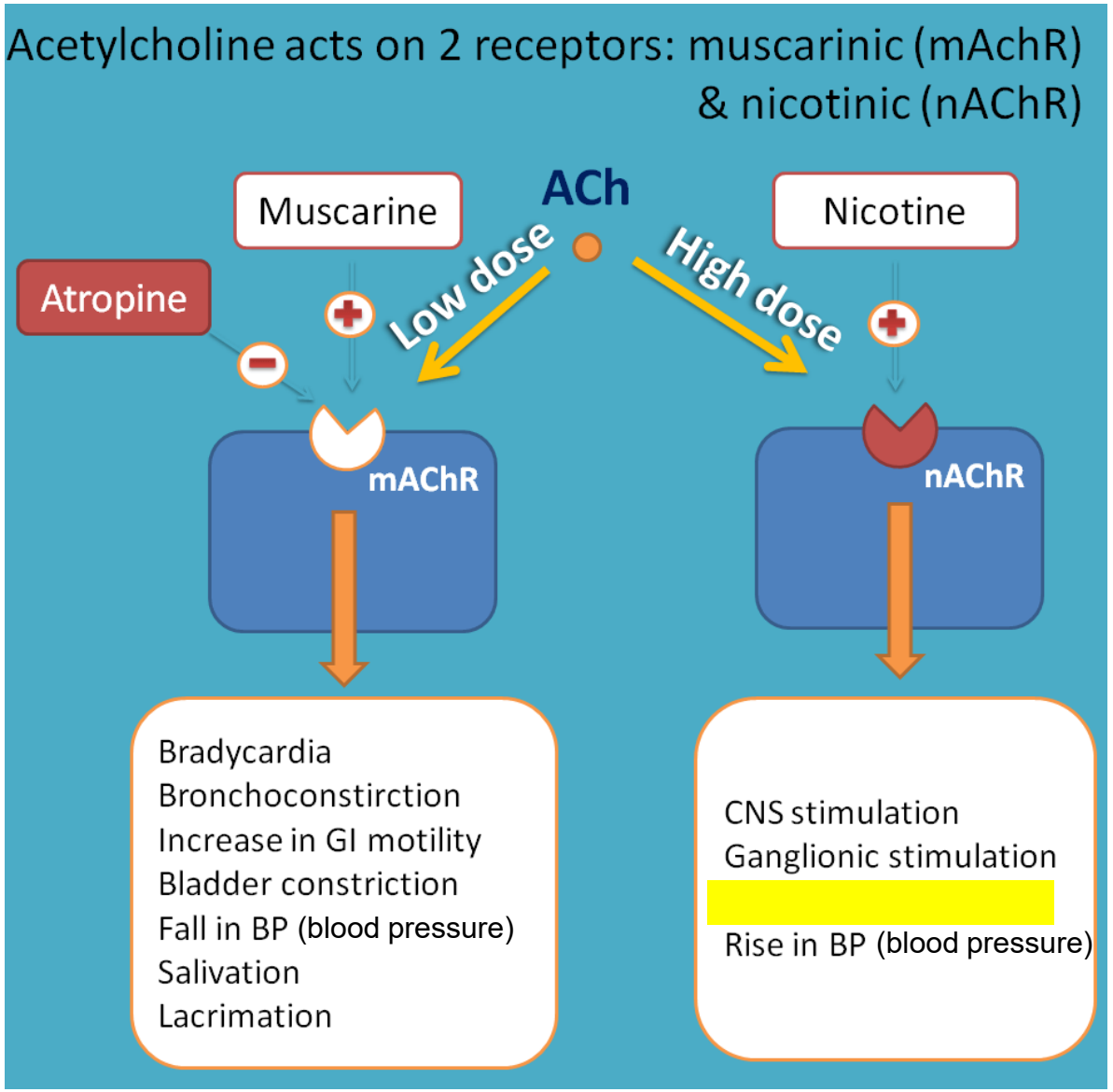
Receptor types:



credits: https://egpat.com/tutorials/cholinergic-agonists/introduction

2. Cholinergic receptors (classification)

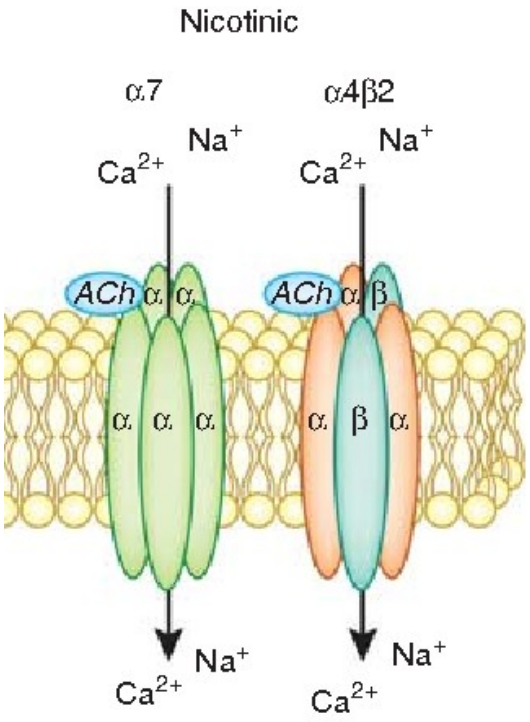
Receptor types:



credits: https://egpat.com/tutorials/cholinergic-agonists/introduction

2. Cholinergic Nicotinic receptors

Receptor types:



Nicotinic acetylcholine receptors

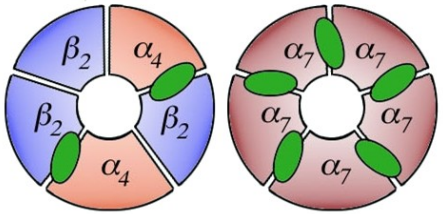
Nicotinic receptors are classified as N,G and M types.

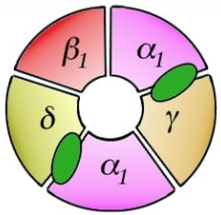
N_N	N_G	N_M
CNS Adrenal medulla	Autonomic ganglia	Skeletal muscle
CNS Excitation Release of adrenaline	Ganglionic transmission	Skeletal muscle contraction

All nicotinic receptors are ionotropic receptors and fast acting

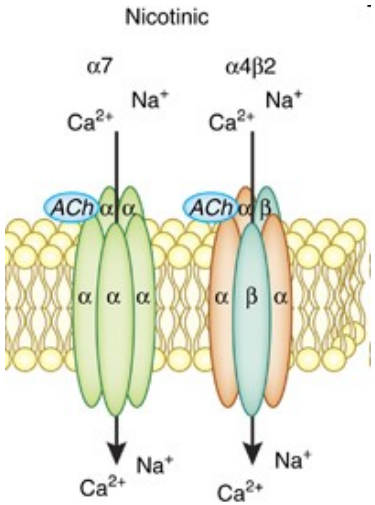
credits: https://egpat.com/tutorials/cholinergic-agonists/introduction

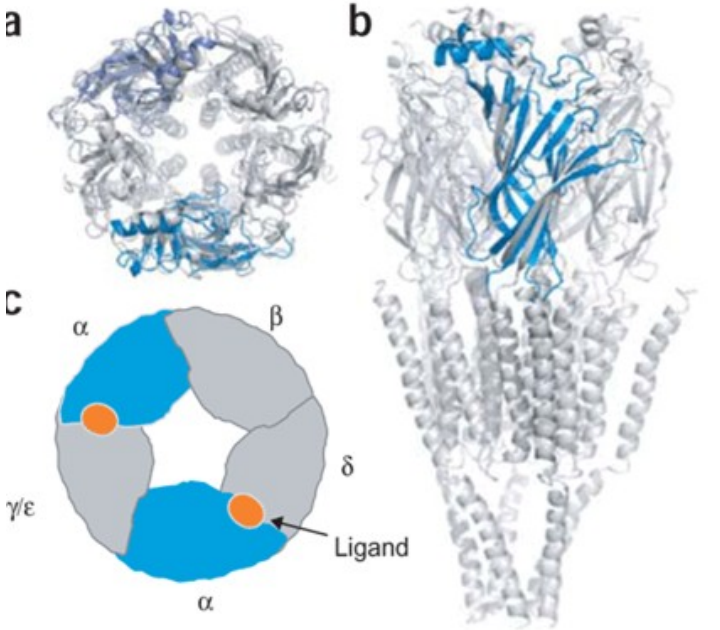
2. Cholinergic nicotinic receptors (classification)

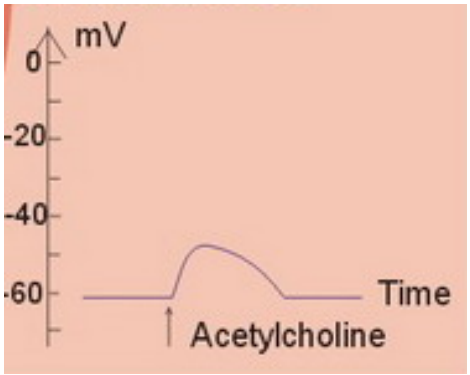




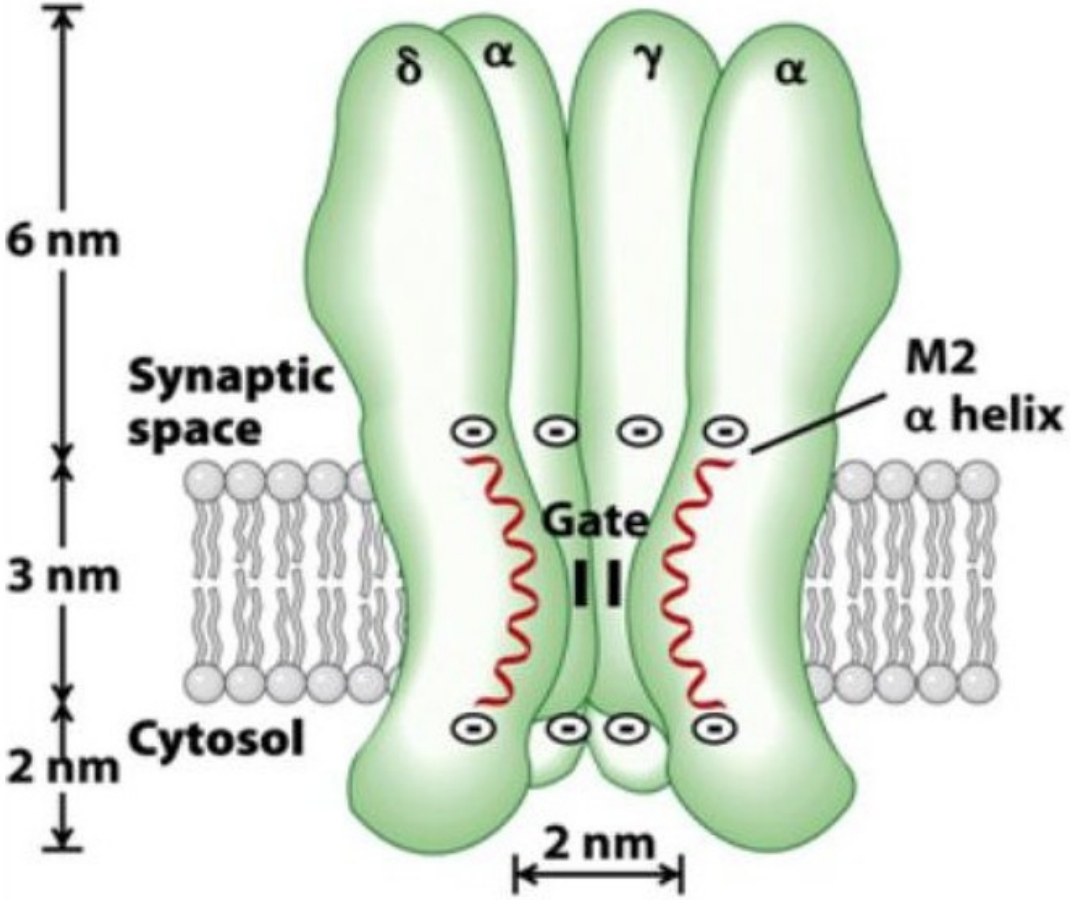
Tipo neuronale					Tipo muscolare
I	II	III			IV
α9,	α7, α8	1	2	3	α1, β1, δ, γ, ε
		α2, α3, α4, α6	β2, β4	β3, α5	

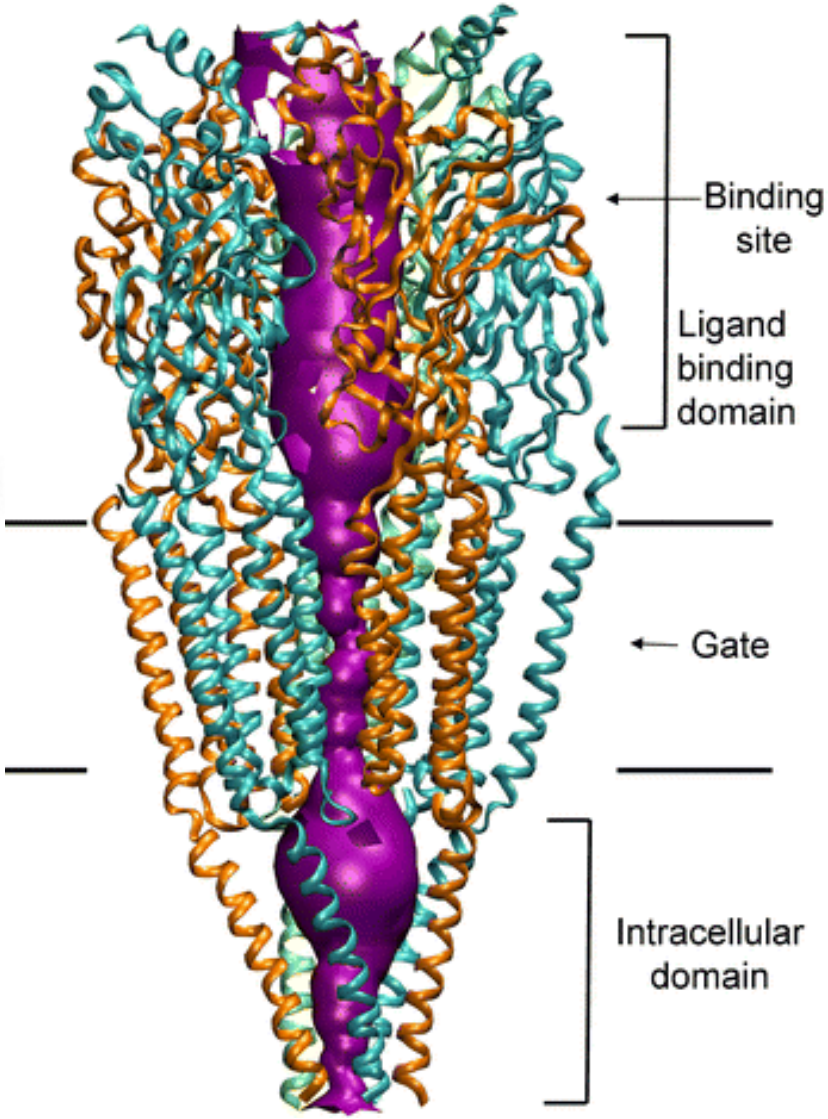




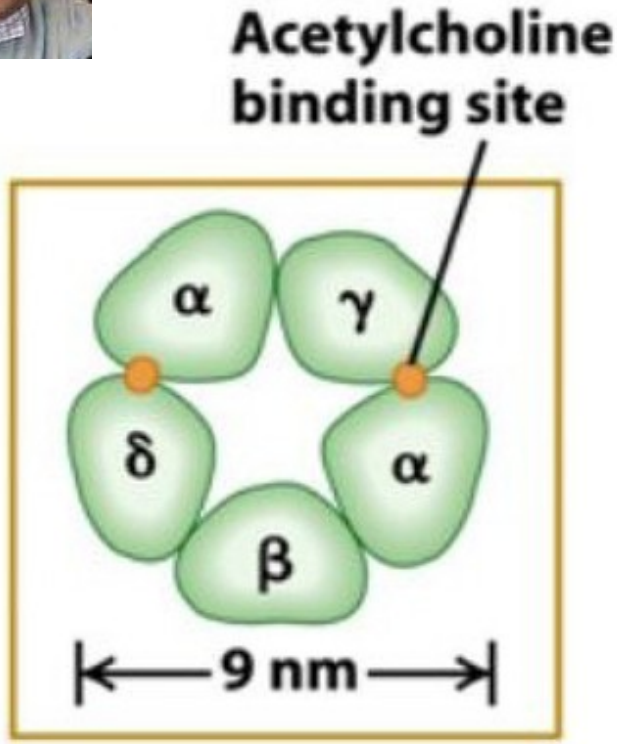


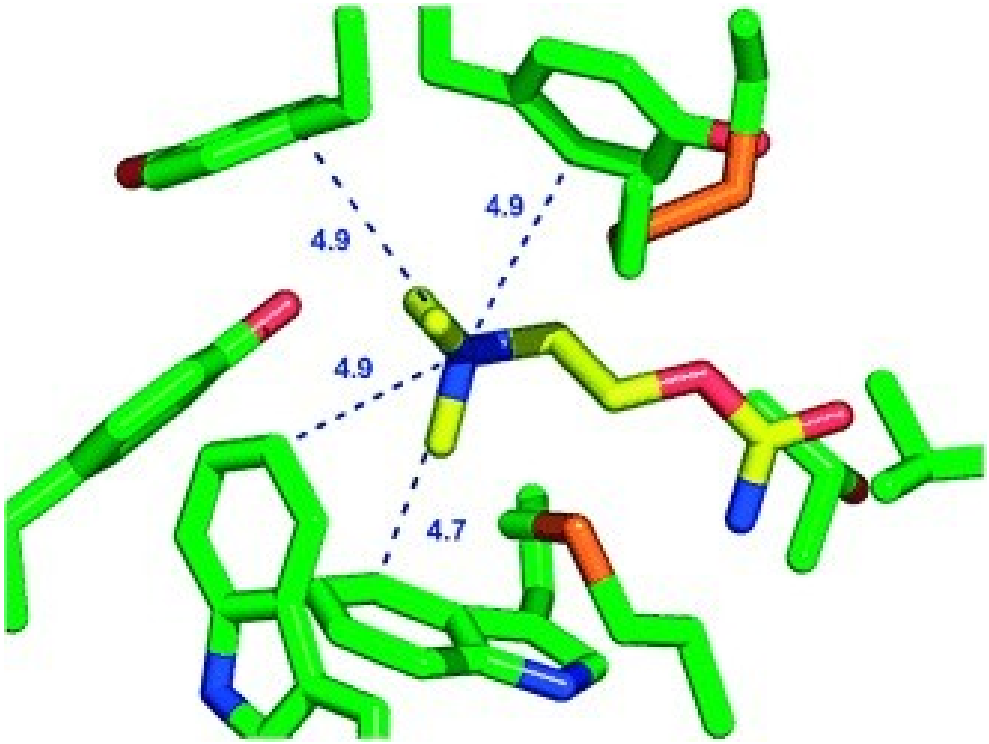
Nicotinic receptor… a beautiful machinery!





Do you remember *cation-π* interactions?

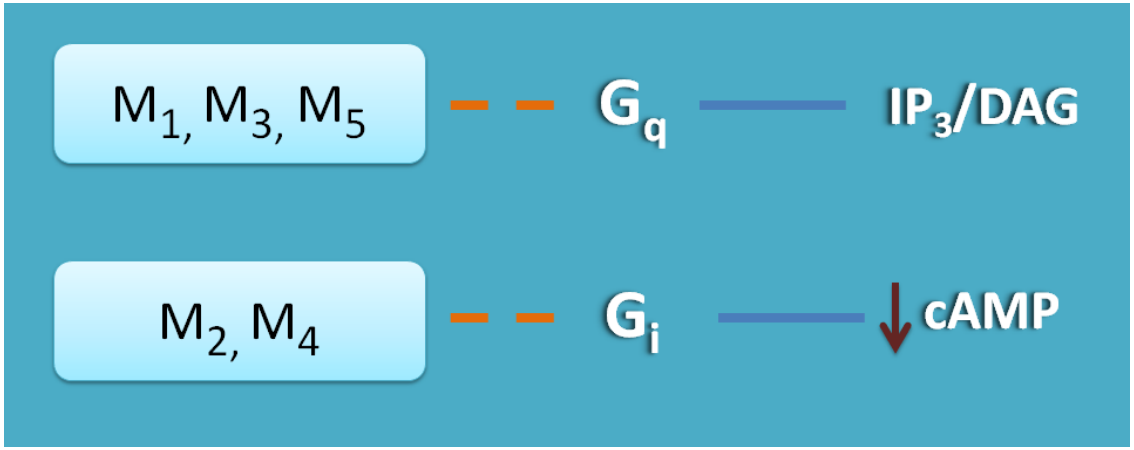


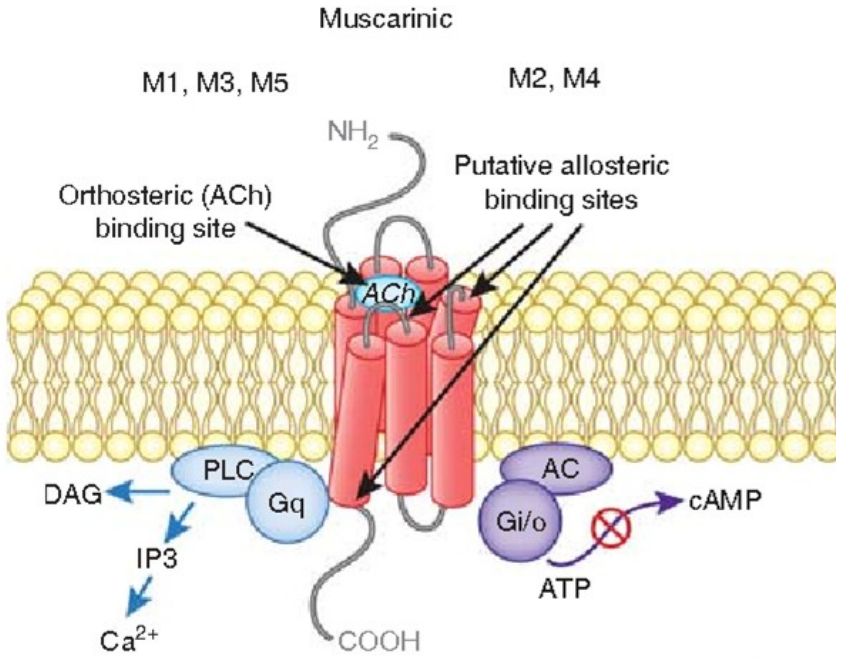


Acetylcholine binding to nicotinic acetylcholine receptor; the cation–π interaction distances (Å) which stabilize the acetylcholine head group are highlighted.

2. Cholinergic muscarinic receptors (classification)

Receptor types:

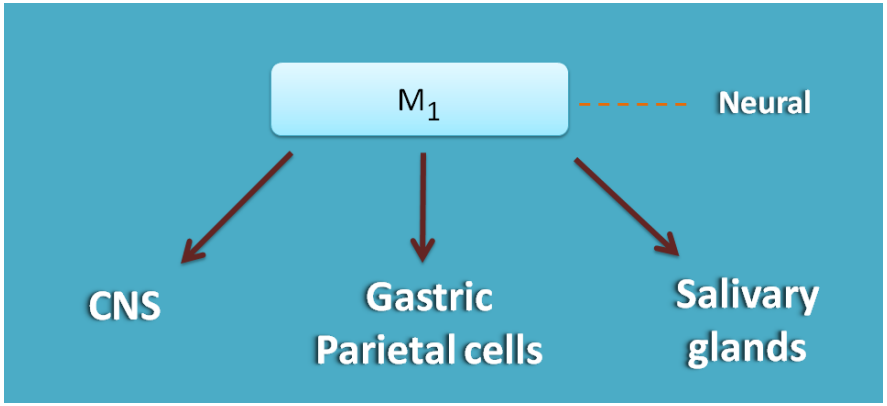


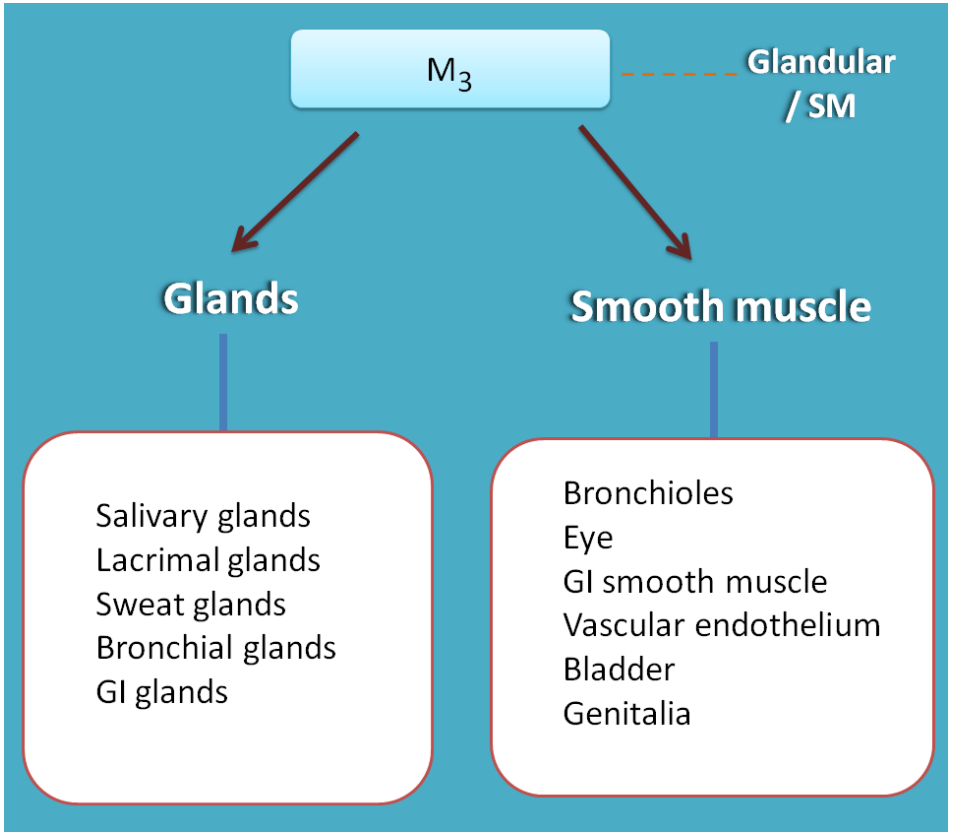


credits: https://egpat.com/tutorials/cholinergic-agonists/introduction

2. Cholinergic receptors

Receptor types:





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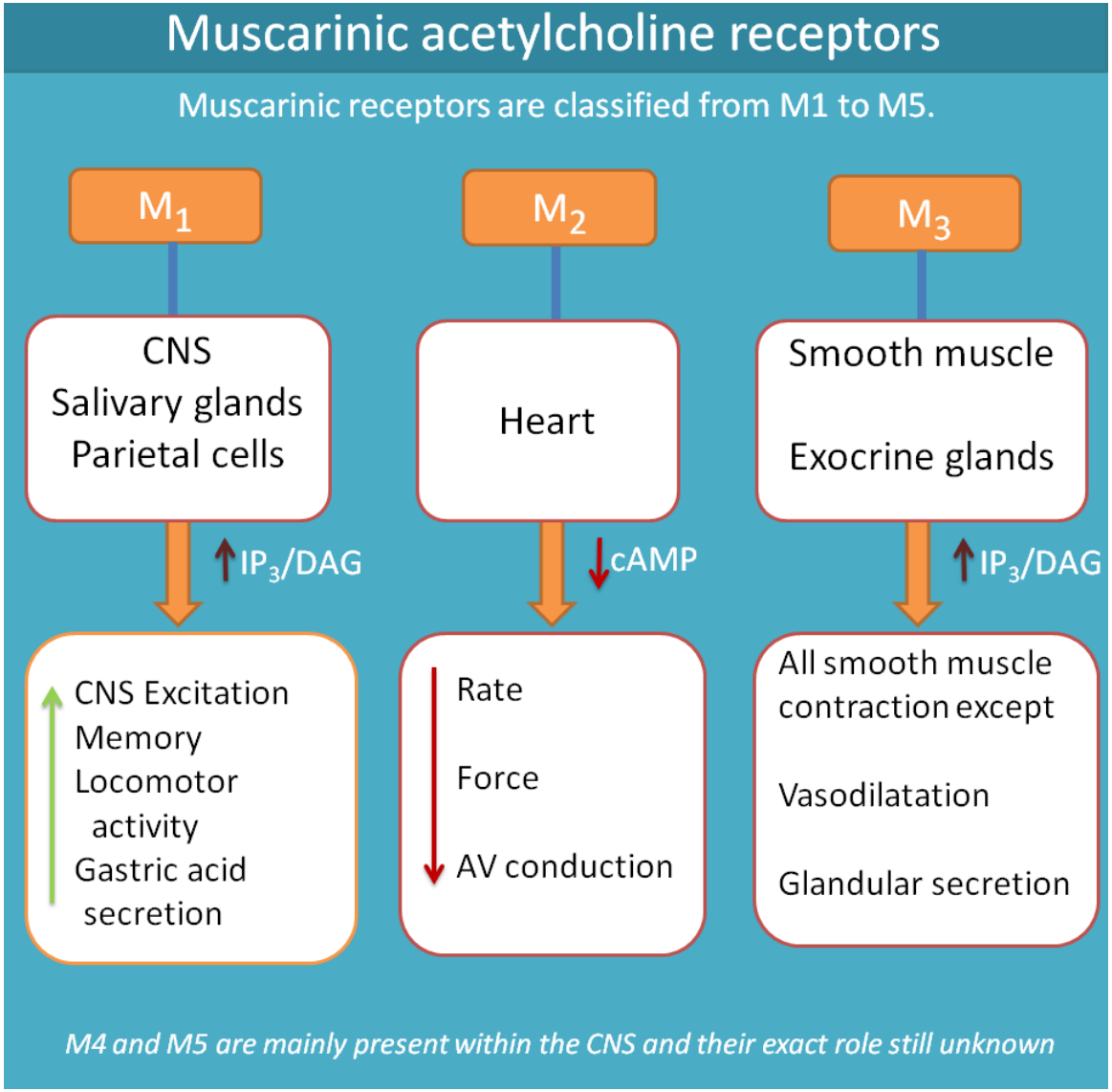
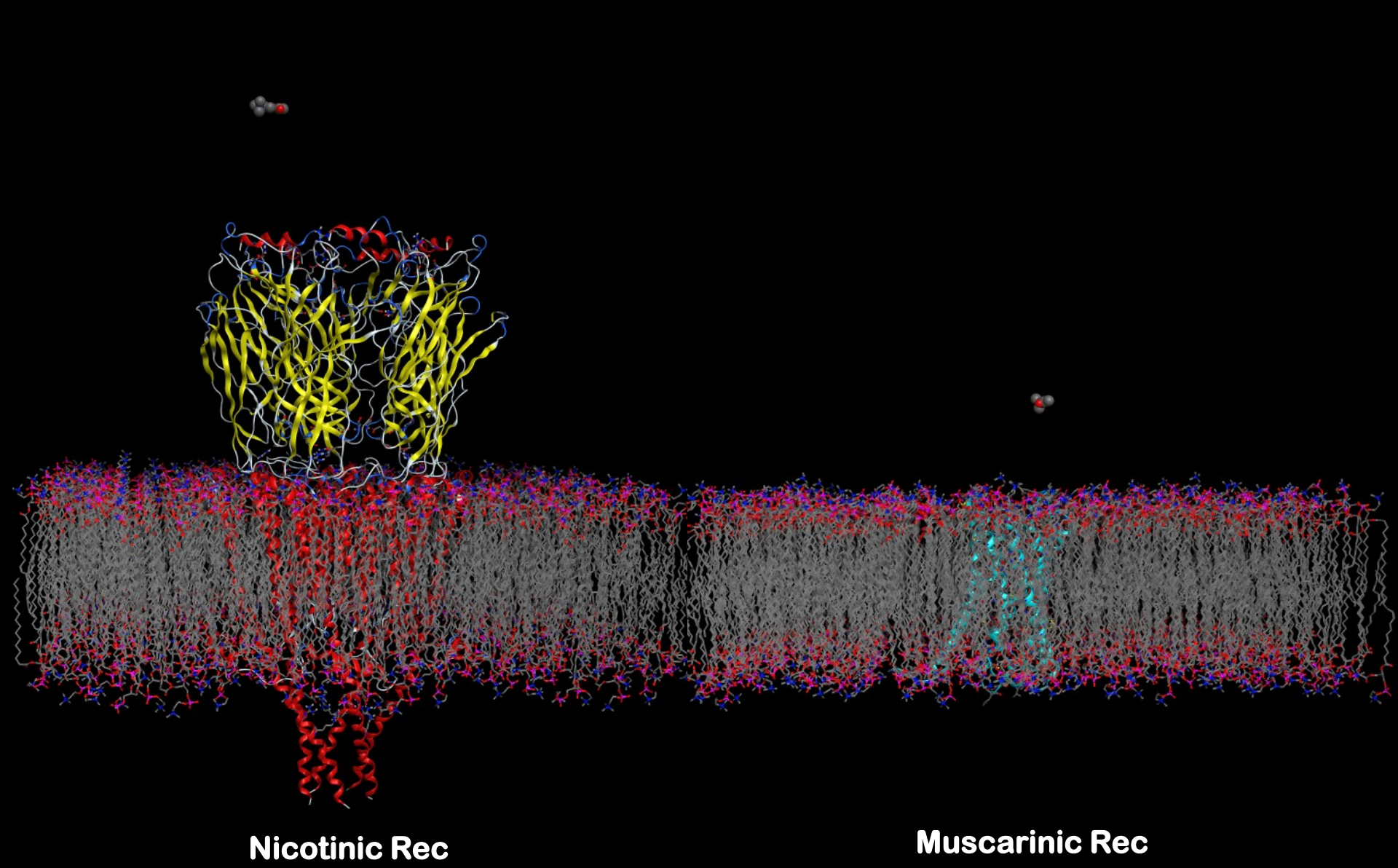
2. Cholinergic receptors

Receptor types:



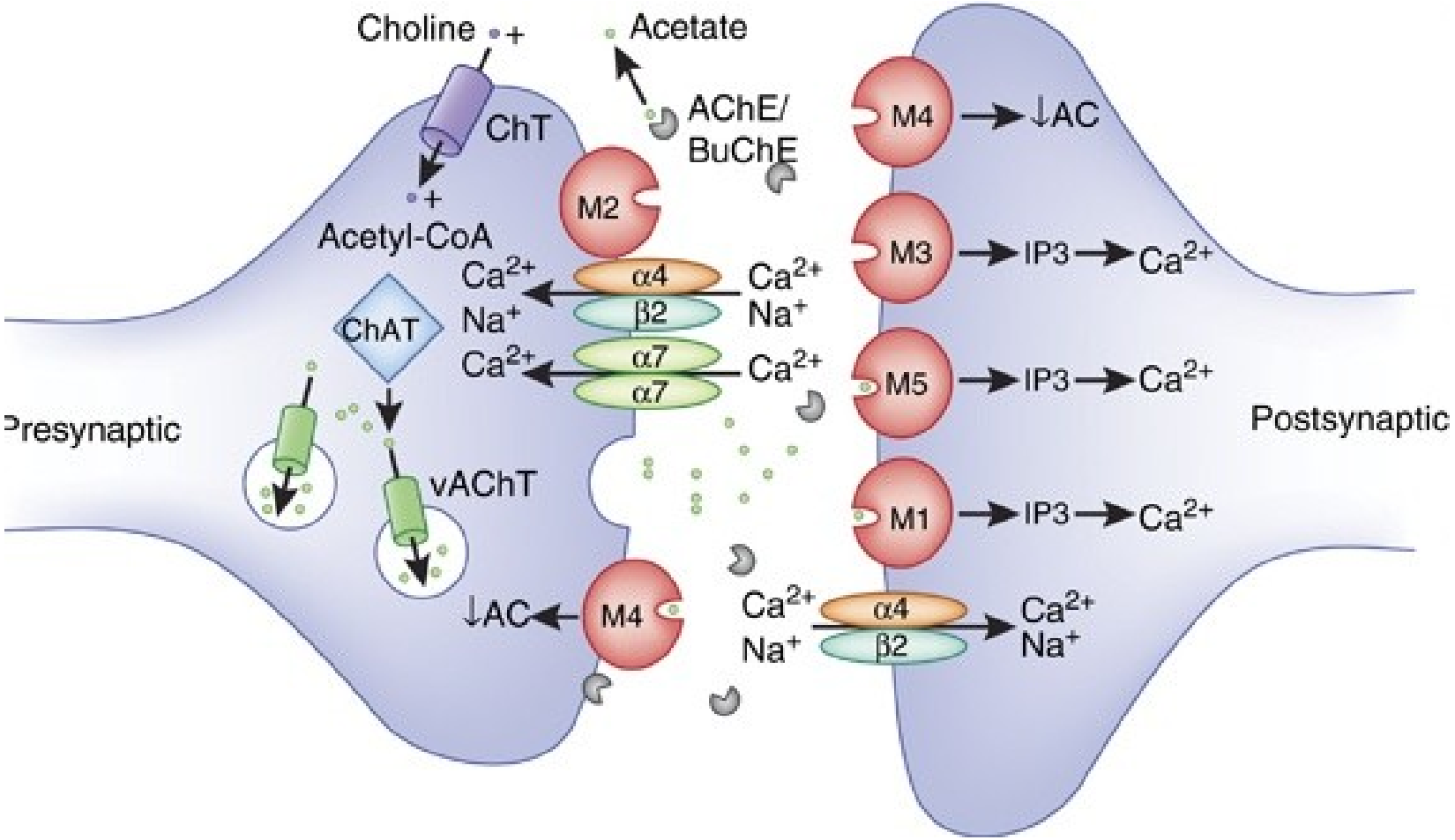
credits: https://egpat.com/tutorials/cholinergic-agonists/introduction



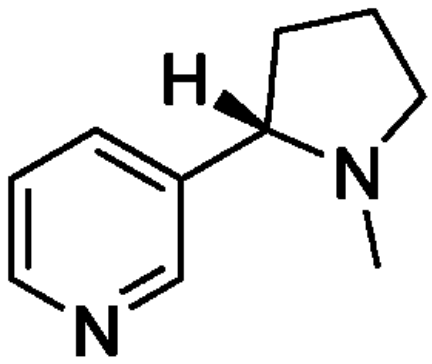
Credits: Gianluca Novello – MMS (2025)

2. Cholinergic receptors

Cholinergic Synapses: signalling integration



Nicotine (or Ach)… in the CNS



S(-)-Nicotine

Acetylcholine
(enhances concentration)

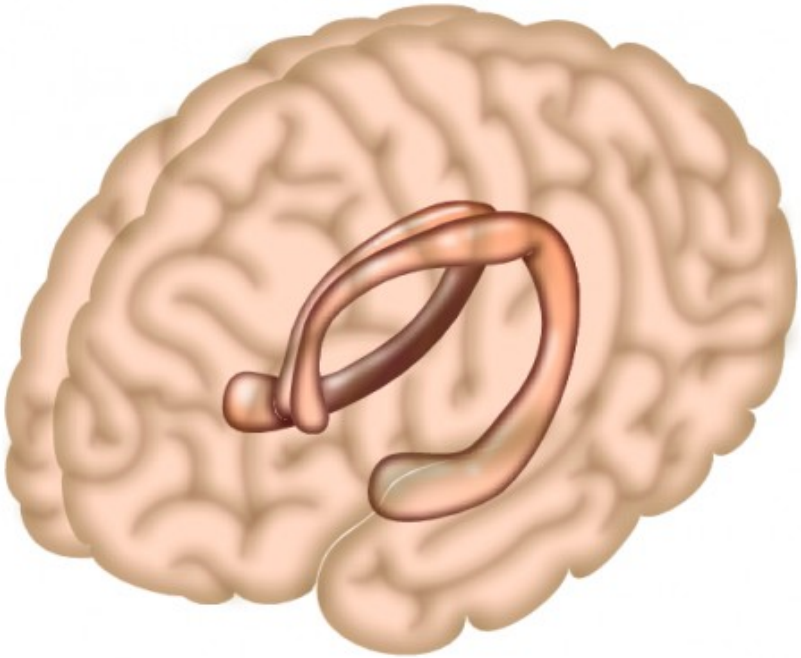
Noradrenaline
(enhanced alertness and arousal)

Dopamine
(enhanced gratification)

Beta-endorphin
(reduce anxiety and modulate the pain perception)

***Nicotine** has an estimated oral LD50 of 6.5 - 13 mg/kg in humans, which is much lower than many other common stimulants. It is unlikely that overdose can be achieved by smoking tobacco, however, coadministration with other sources of nicotine such as patches or gum may potentially be dangerous.*

2. Cholinergic muscarinic receptors (classification)



The hippocampus is a region of the brain largely responsible for memory formation. *Credit: Salk Institute*

Meet the hippocampus: A seahorse-shaped structure in the cerebral cortex's medial temporal lobe, it's part of the limbic system, generally believed to be involved in spatial navigation and establishing long-term memories. However, it's been unclear which specific memory functions the hippocampus manages - ***recall***, which is the ability to retrieve memory; or ***recognition***, which is the ability to identify a stimulus as new.

2. Nerve Transmission

Memory processes:

1. **Memory encoding**: is the crucial first step to creating a new memory. It allows the perceived item of interest to be converted into a **construct** that can be stored within the brain, and then recalled later from ***short-term*** or ***long-term memory***.

2. **Memory consolidation**: is the processes of stabilizing a memory trace after the initial acquisition.

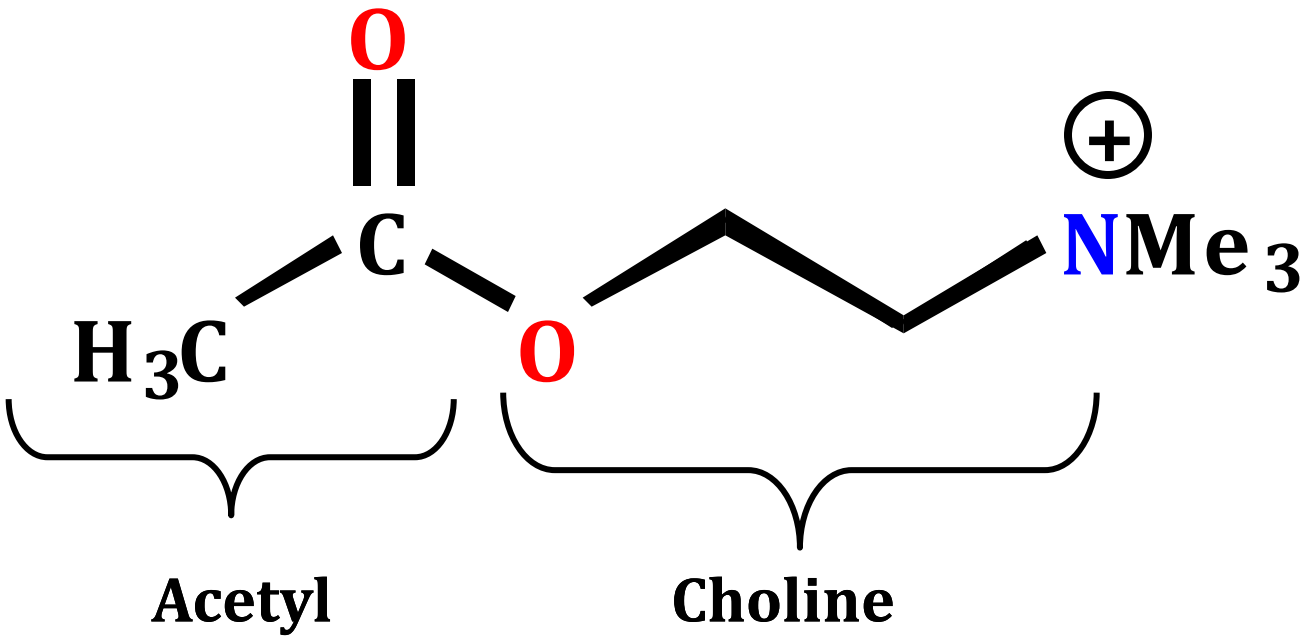
3. **Memory storage**: is the more or less passive process of **retaining information** in the brain, whether in the sensory memory, the short-term memory or the more permanent long-term memory.

4. **Memory recall/retrieval:** recall or retrieval of memory refers to the subsequent **re-accessing** of events or information from the past, which have been previously encoded and stored in the brain. In common parlance, it is known as **remembering**.

Remembering it looks a lot more to revise a theatrical representation that a movie!

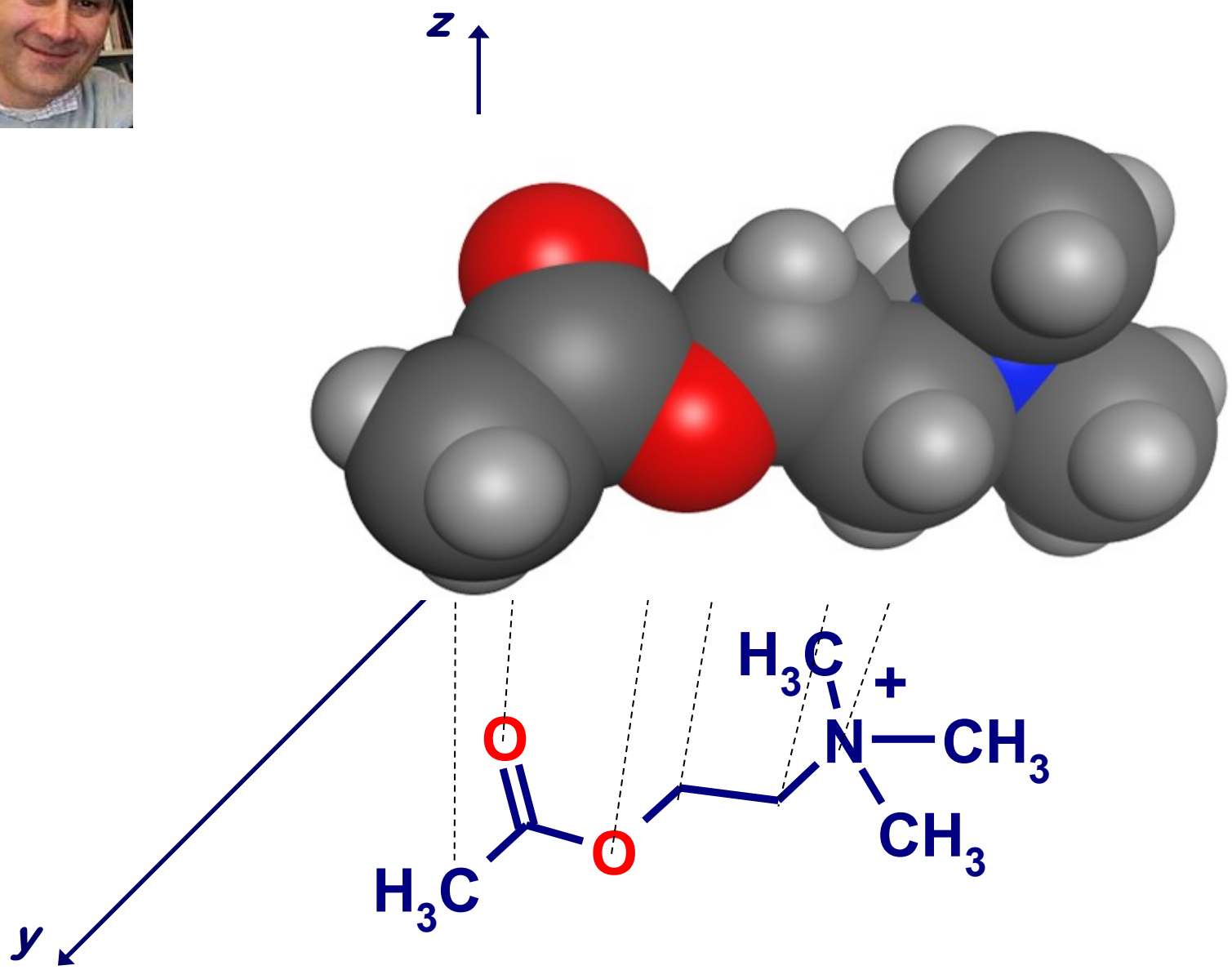
2. Neurotransmitter

Acetylcholine (Ach)

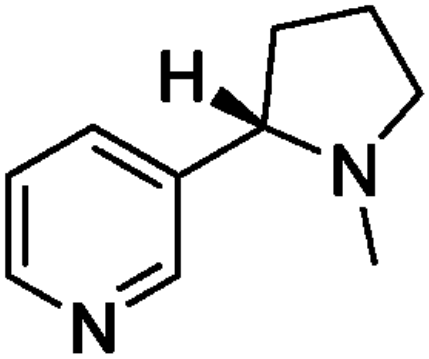


2-Acetoxy-N,N,N-trimethylethanaminium

The shadow of reality:



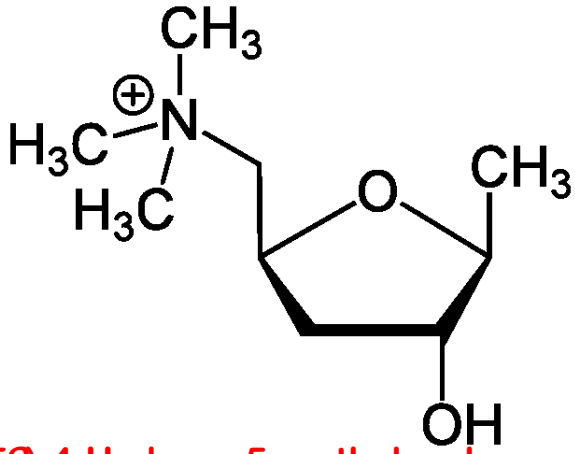
2. Cholinergic receptors



***S*-(-)Nicotine**

3-[(2*S*)-1-methylpyrrolidin-2-yl]pyridine

Activates cholinergic receptors at nerve synapses and on skeletal muscle

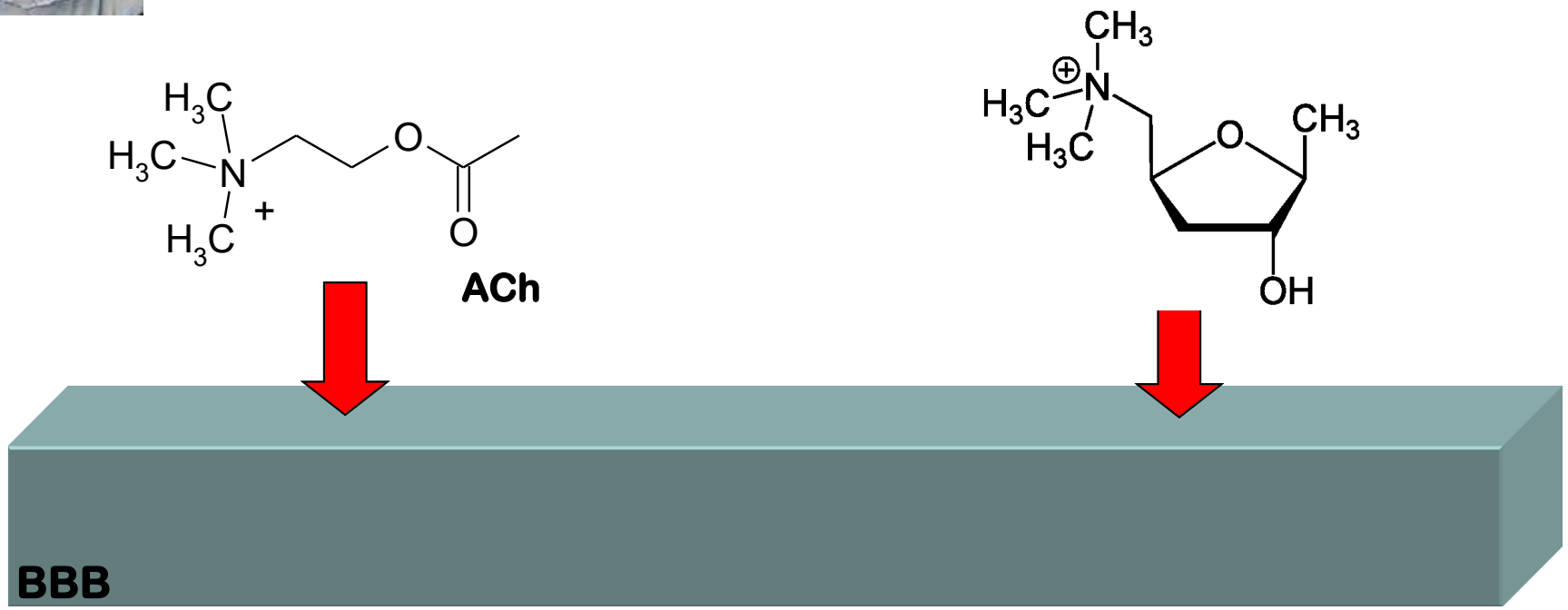


(*2S,4R,5S*)

1-[(*2S,4R,5S*)-4-Hydroxy-5-methyloxolan-2-yl]-N,N,N-trimethylmethanaminium

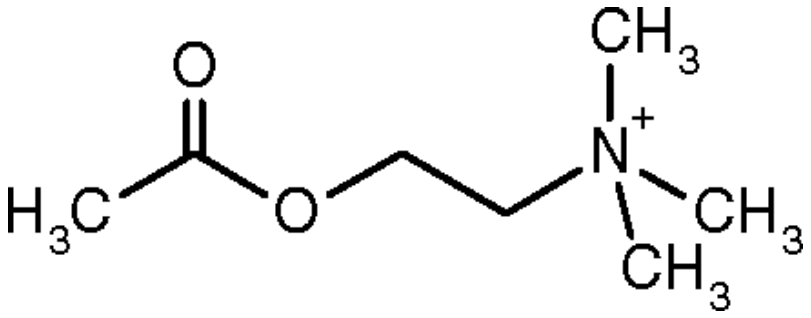
Activates cholinergic receptors on smooth muscle and cardiac muscle

Remember?

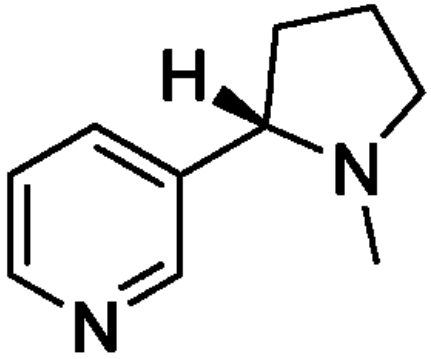


Muscarine does not directly cause CNS symptoms because it does not cross the blood-brain barrier due to its chemical nature as an ionized quaternary amine. On the contrary, nicotine acts on the nicotinic acetylcholine receptors, specifically the ganglion type nicotinic receptor and one CNS nicotinic receptor. Why?

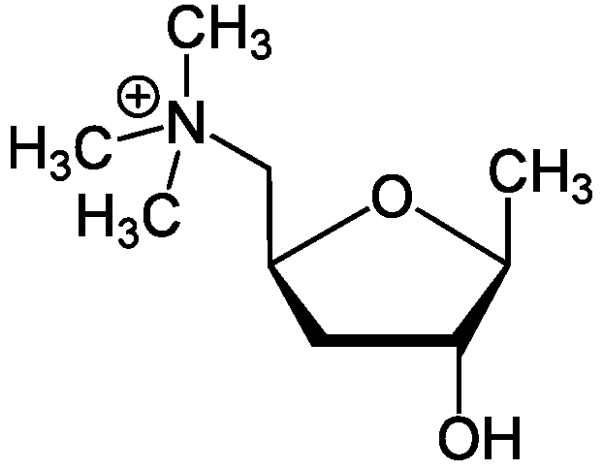
Very interesting: do you see similarities in Flatland?



Acetylcholine (Ach)



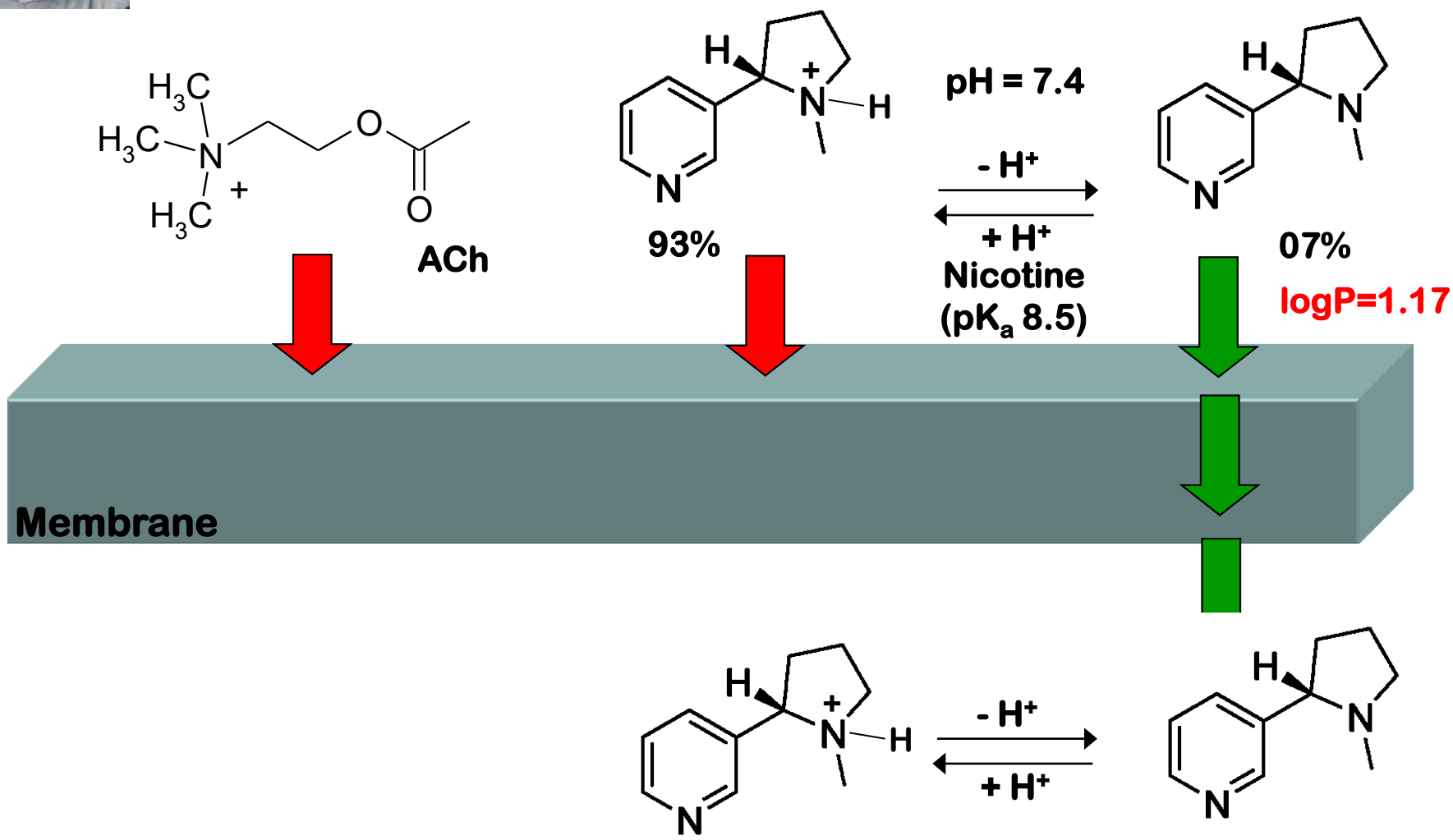
S(-)-Nicotine



(*2S,4R,5S*)-(+)-Muscarine

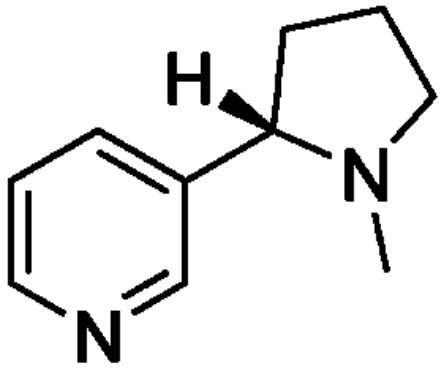
Acetylcholine is natural messenger for both receptor types

Remember?



The first crucial pharmaceutical difference!

thways across the blood–brain barrier



Lipophilicity: ***1.17***

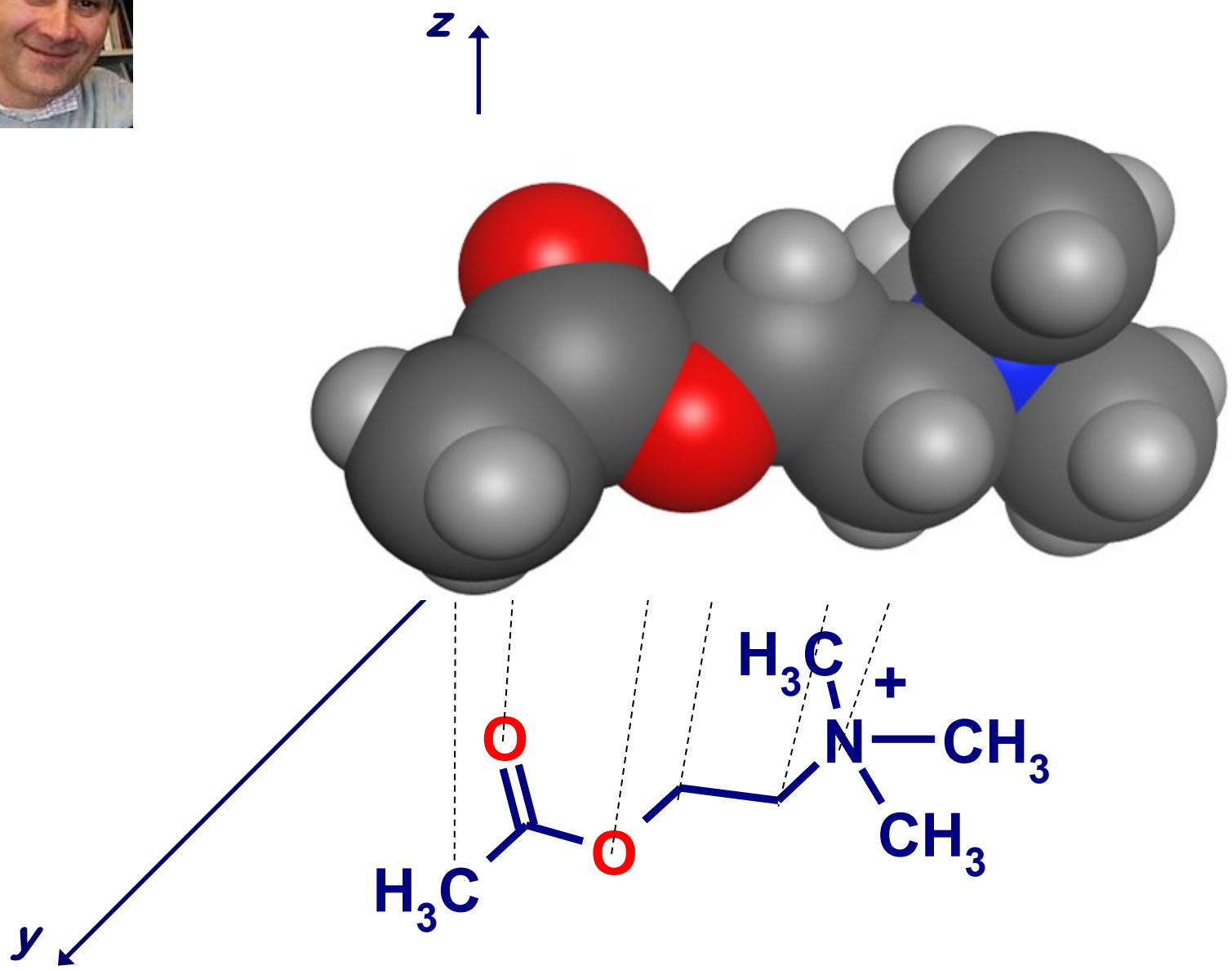
Molecular weight: ***162.24***

Polar surface area (PSA): ***16 Å²***

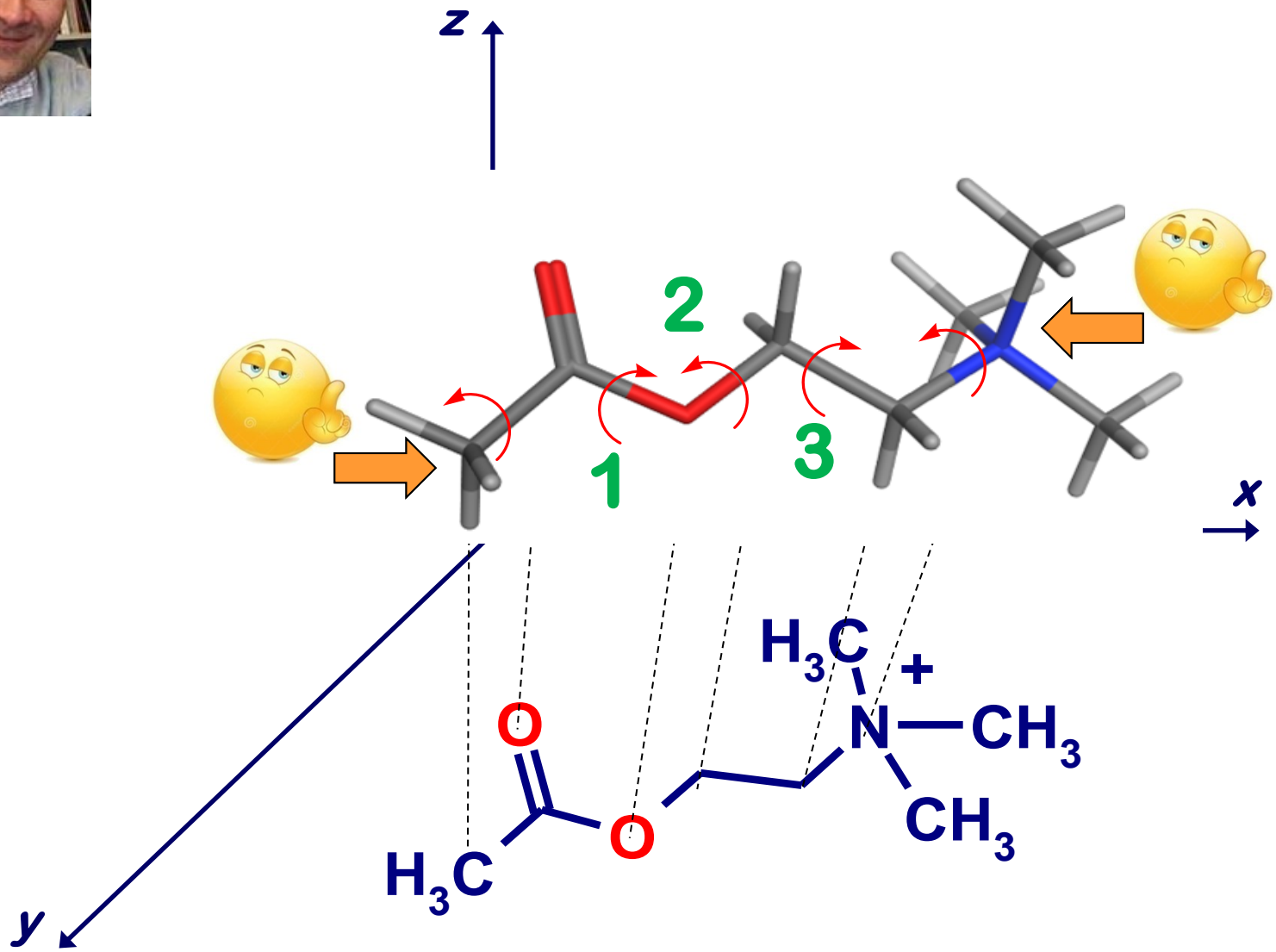
Hydrogen bonding (O + N): ***2***

Charge: ***pKa = 8***

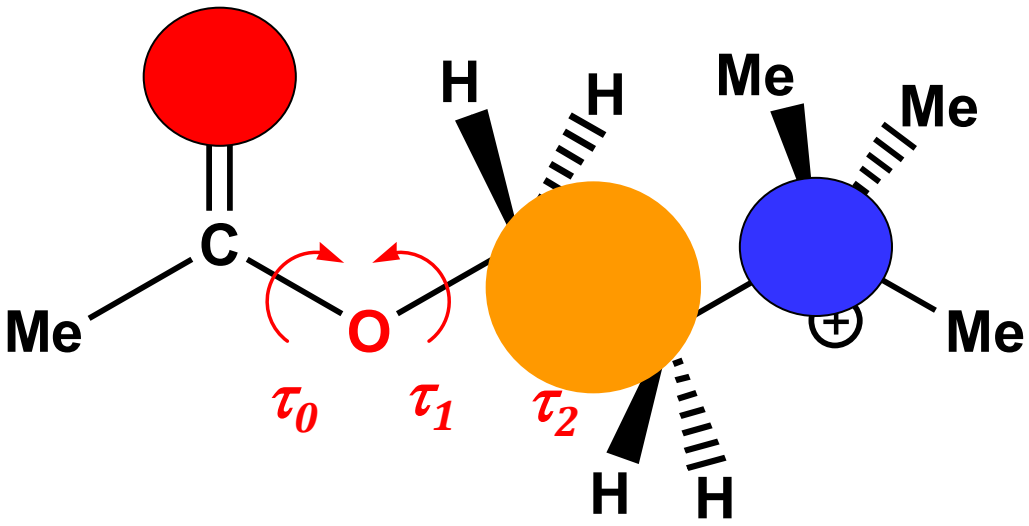
The shadow of reality:



And please not forget this magic behavior:

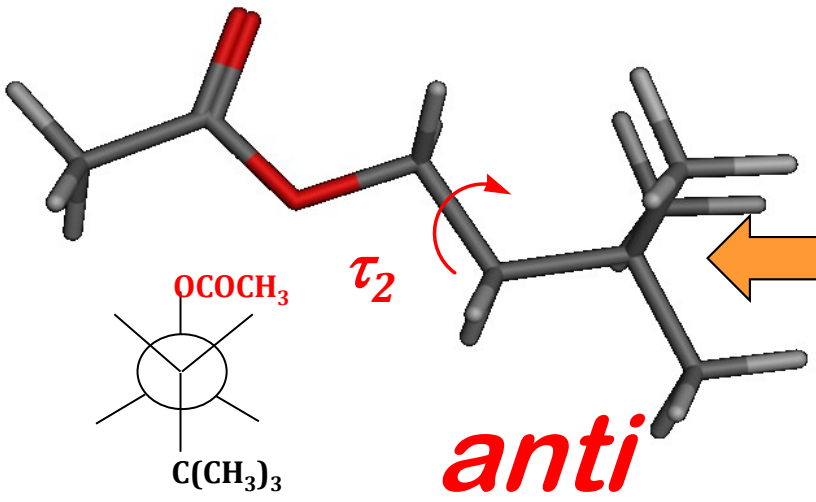


8. Active conformation of acetylcholine



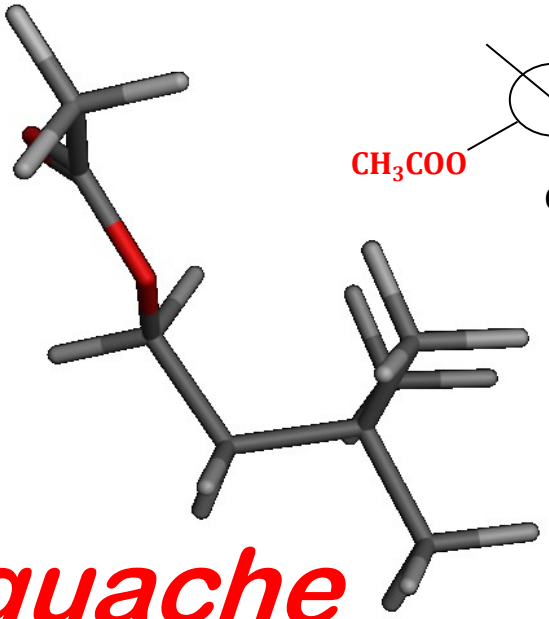
- **Several freely rotatable single bonds**
- **Large number of possible conformations**
- ***Bioactive conformation* does not necessarily equal the most energetically stable conformation!!**

Let's try this exercise together!

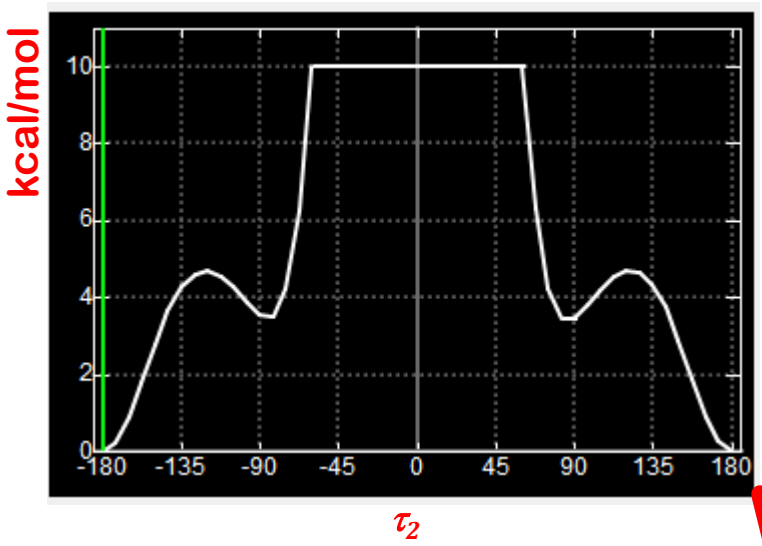


C

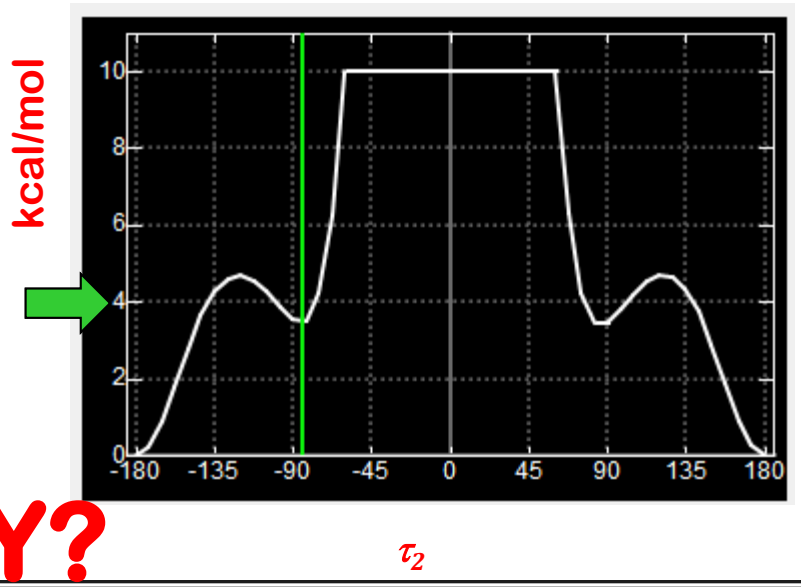
anti



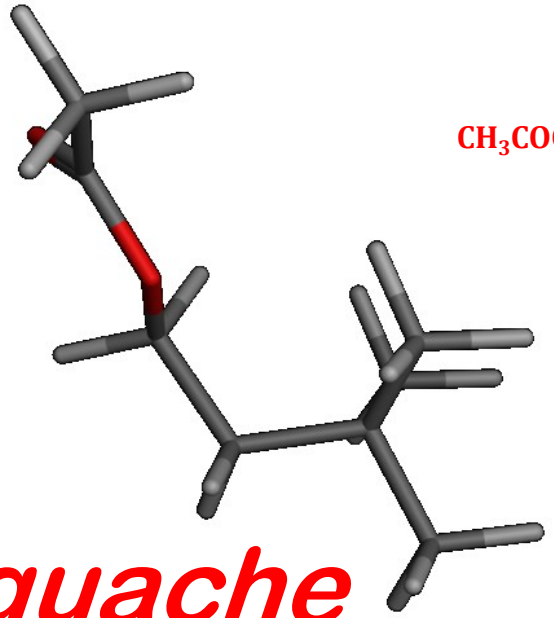
guache

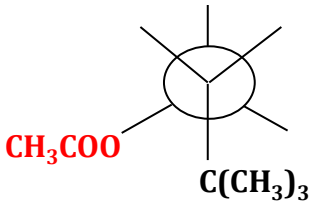


WHY?

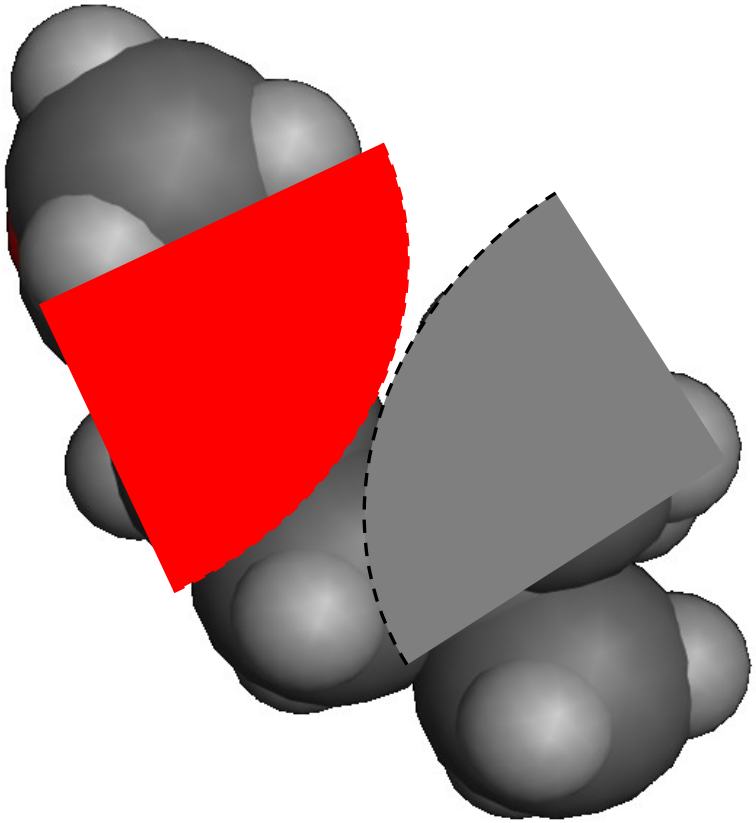


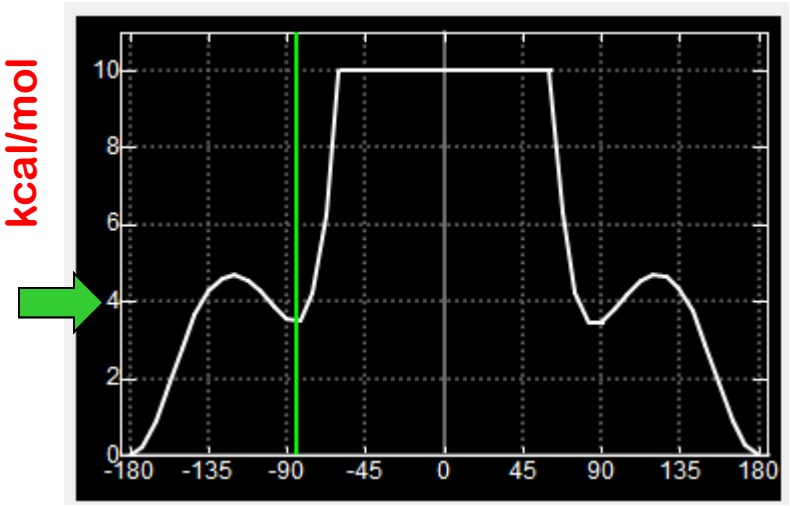
BRAVI!!!!





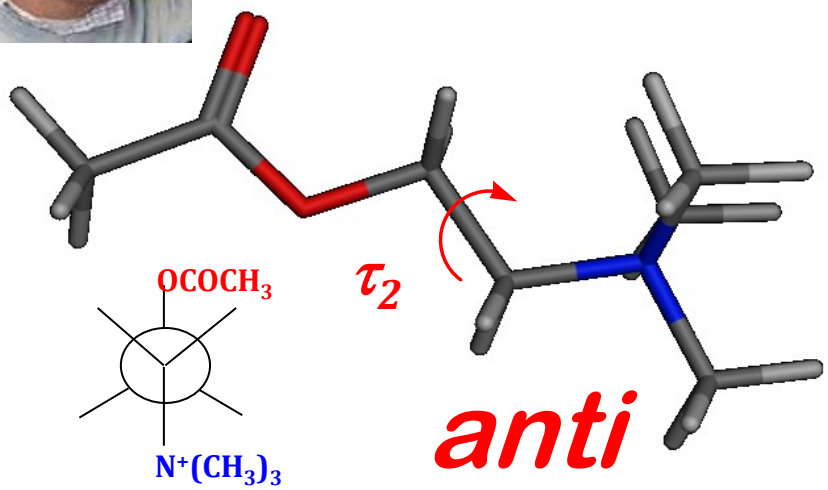
guache



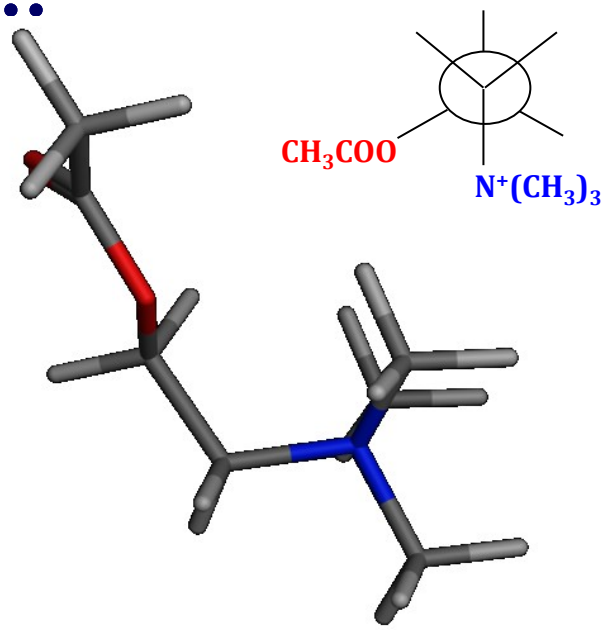


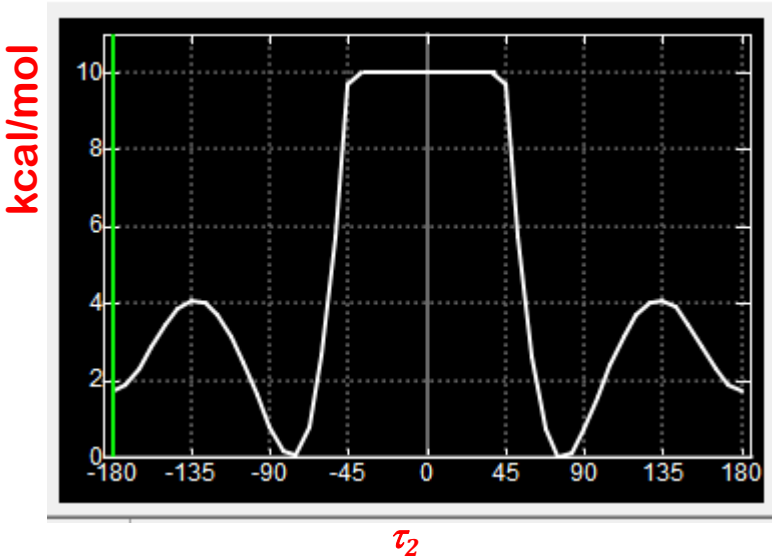
Steric hindrance: *means coulombic electrons-electrons repulsion!!!*

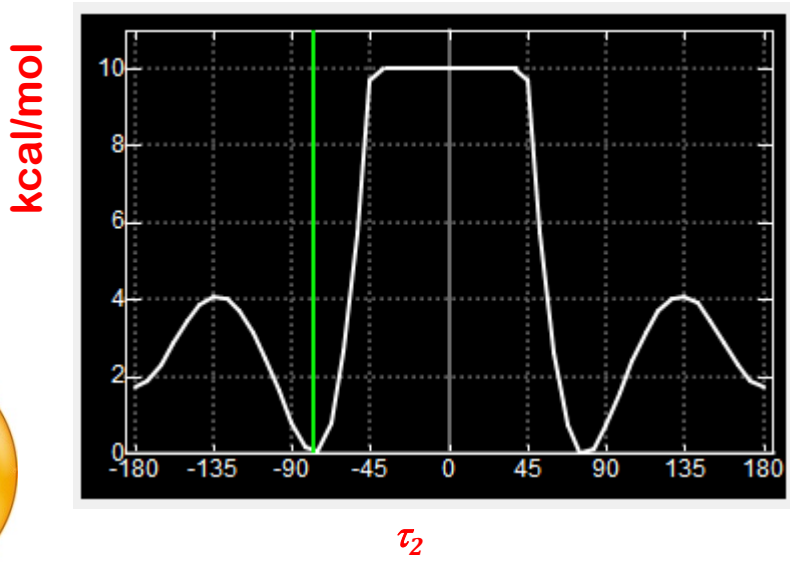
… and now, our little Ach!!!



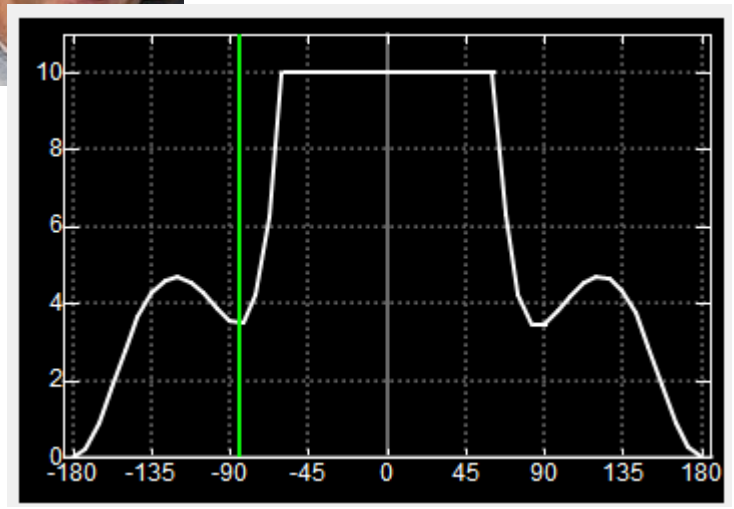
anti

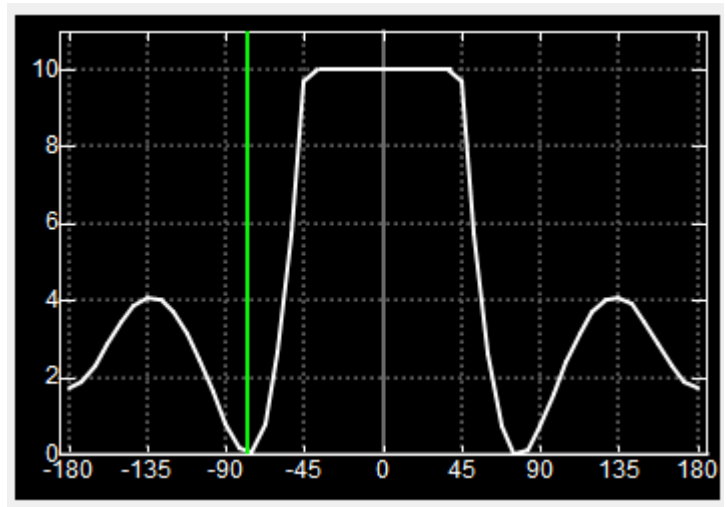




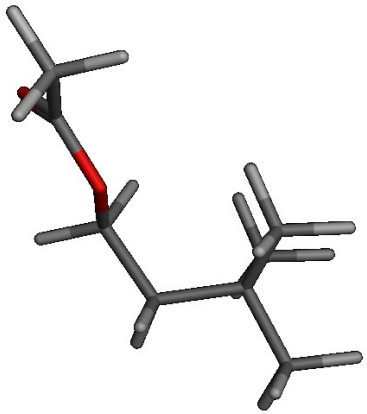


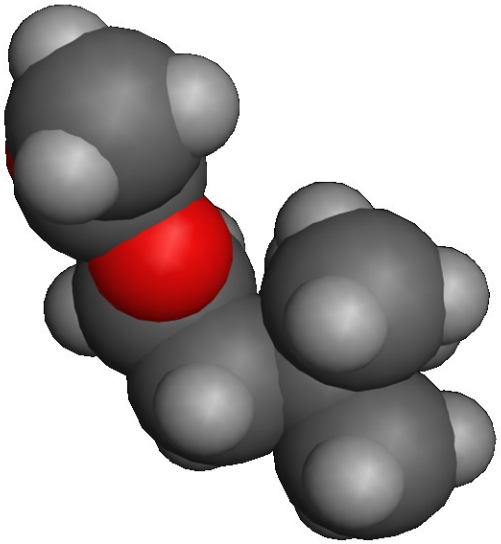
… and now, our little Ach!!!

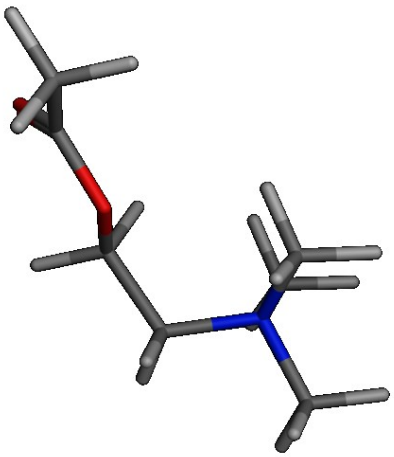


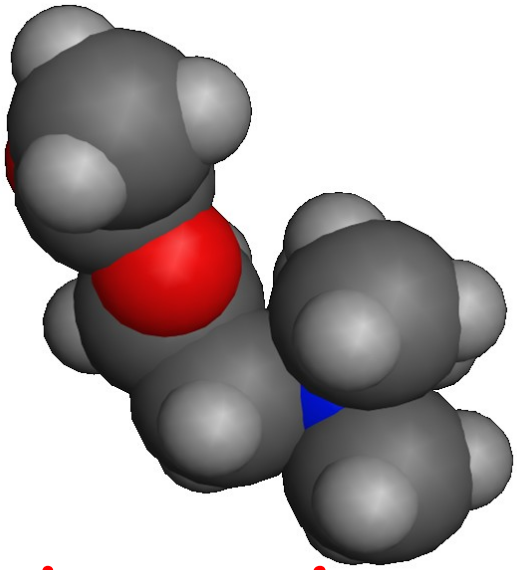


τ_2



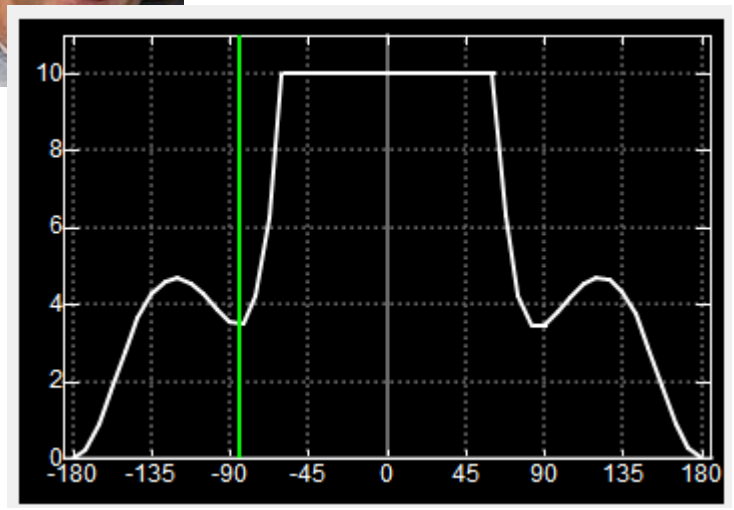


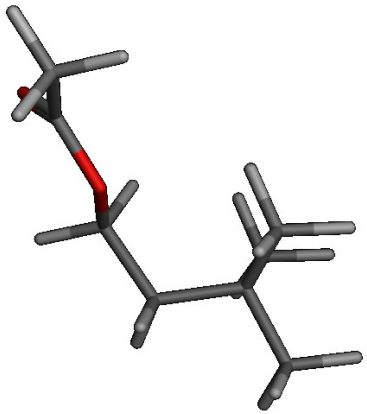


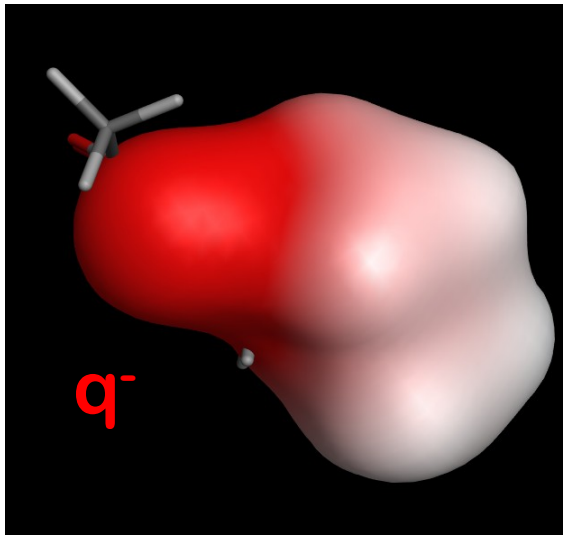


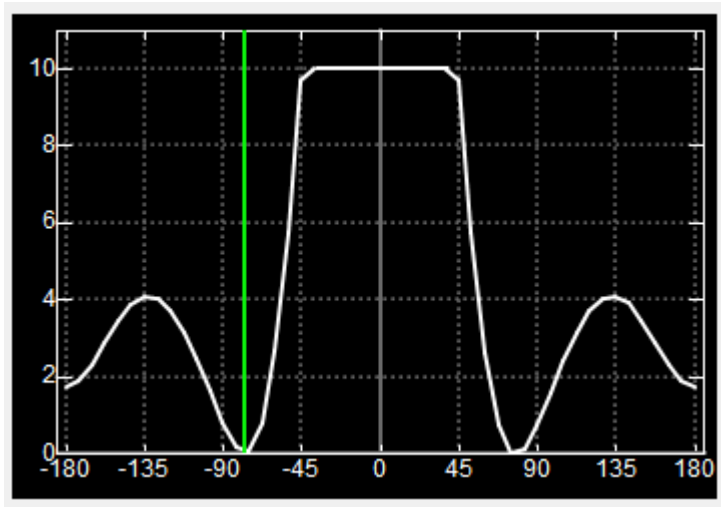
Same steric hindrances!

… and now, our little Ach!!!

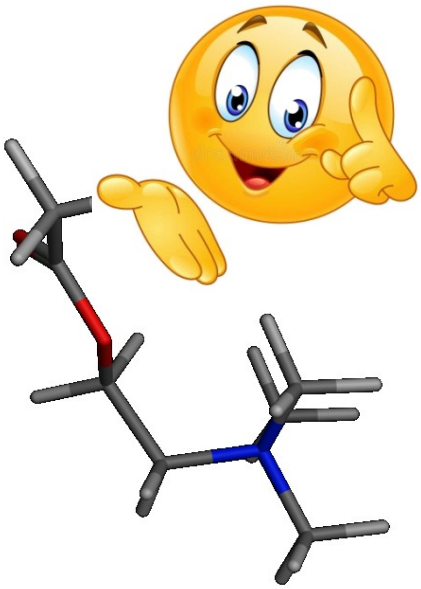


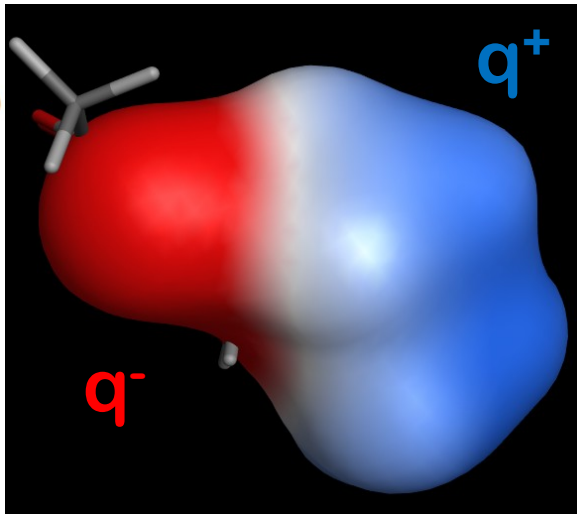






τ_2



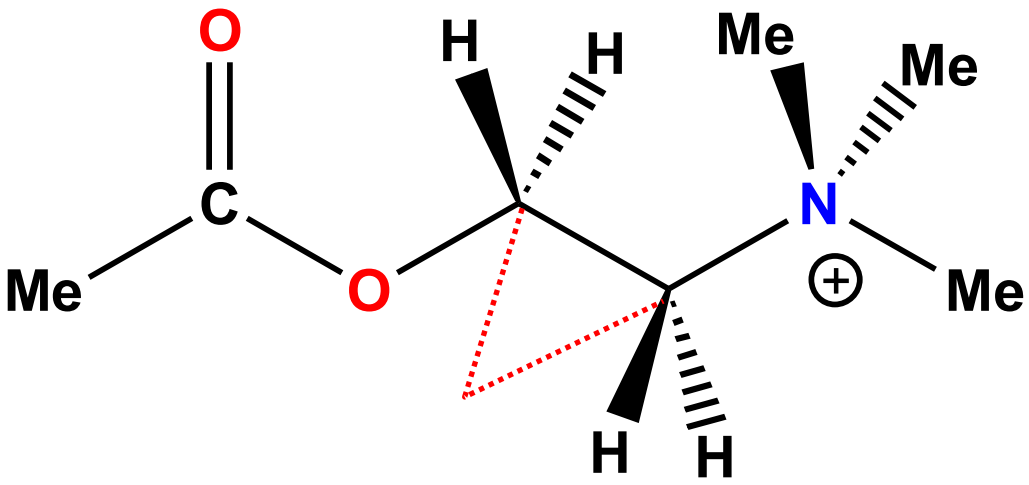


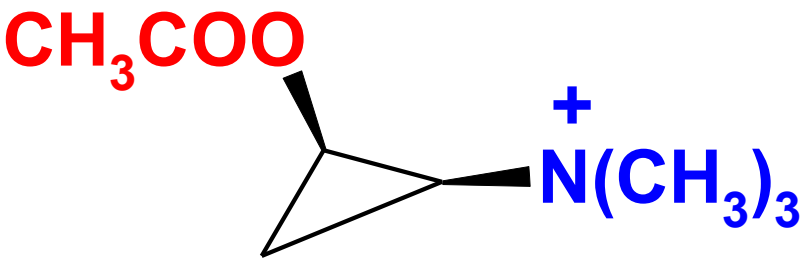
Coulomb!!!

Any correlation between *gauche/anti* and *nicotinic/muscarinic* binomio?

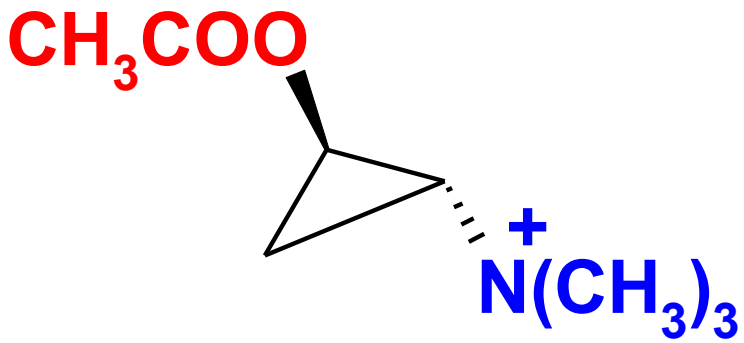
8. Active conformation of acetylcholine

Rigid Analogues of acetylcholine





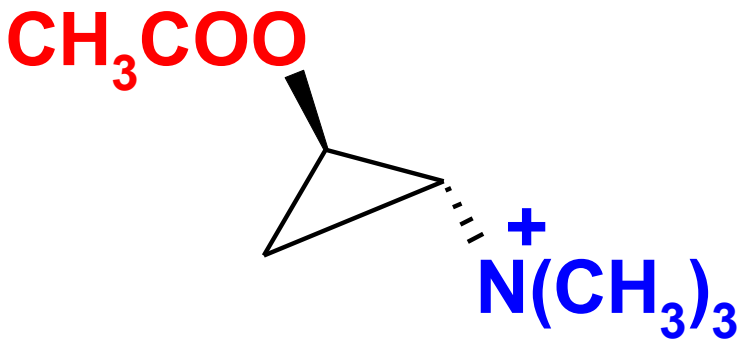
cis



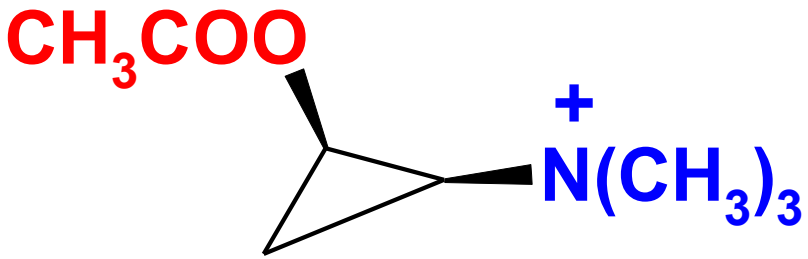
trans

trans **is 100 fold more active than** ***cis*****, and selective again muscarinic receptors**

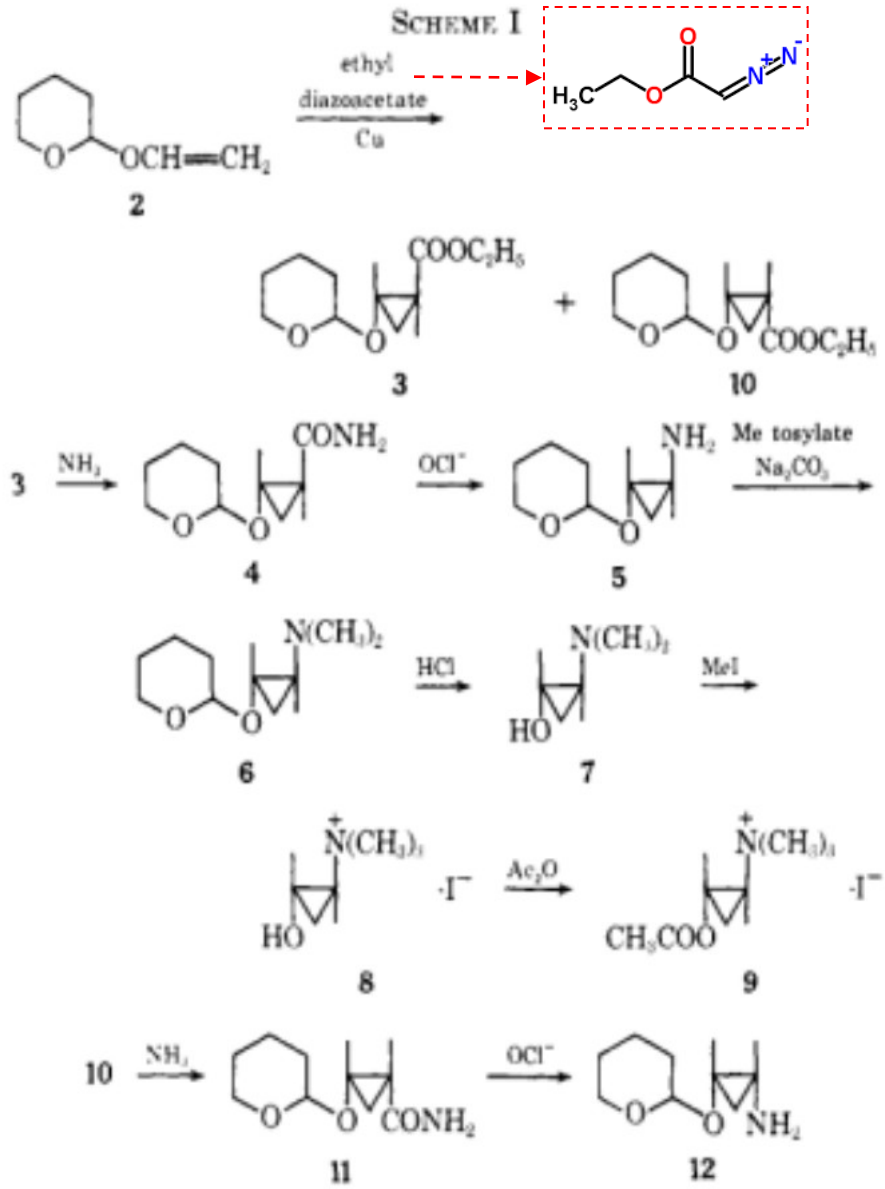
Only for fans of organic pharmaceutical chemistry!!!



trans



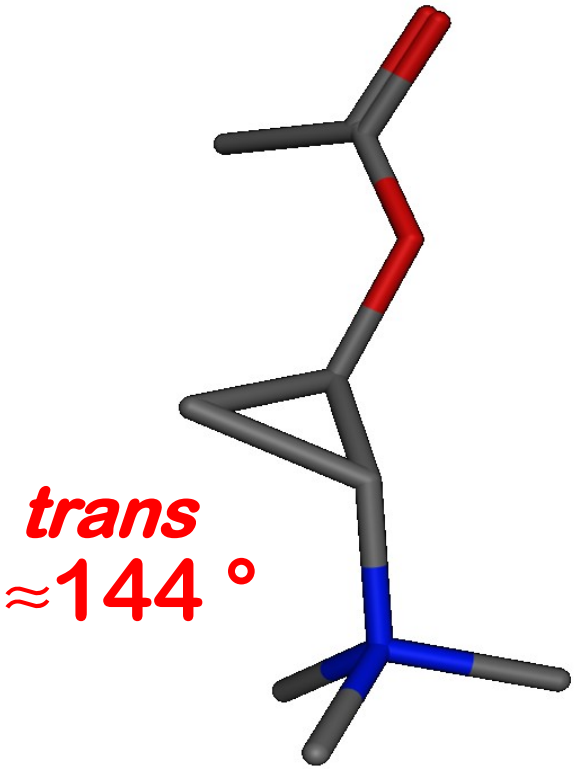
cis



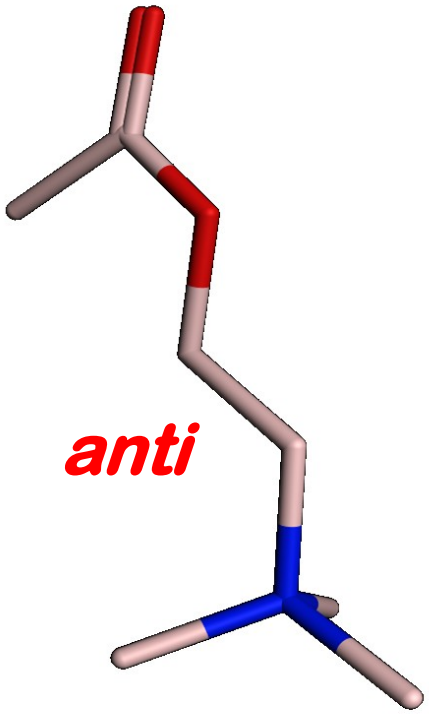
credits: https://pubs.acs.org/doi/pdf/10.1021/jm00300a003#

8. Active conformation of acetylcholine

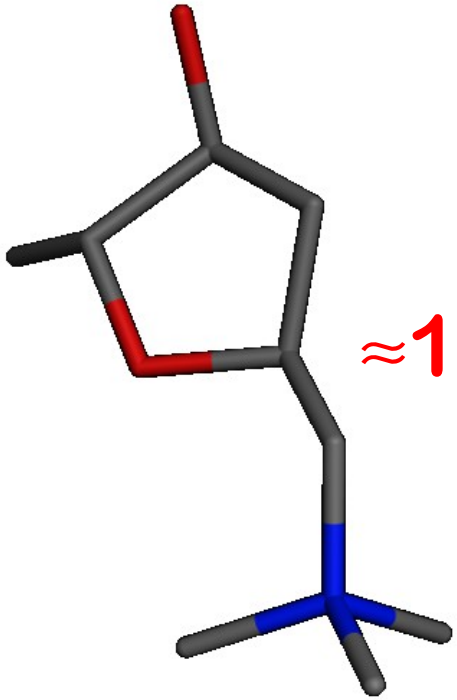
Rigid Analogues of acetylcholine



trans
≈144 °

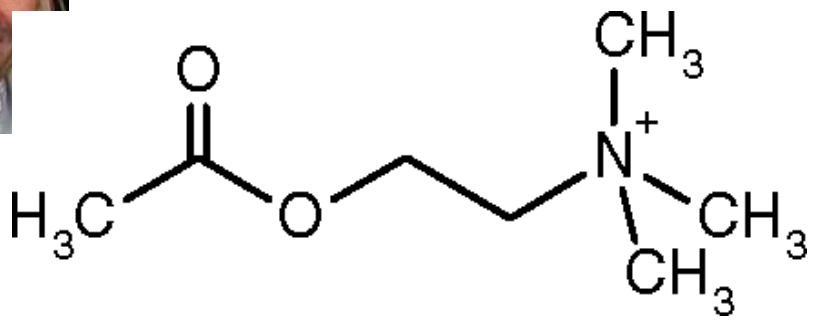


anti

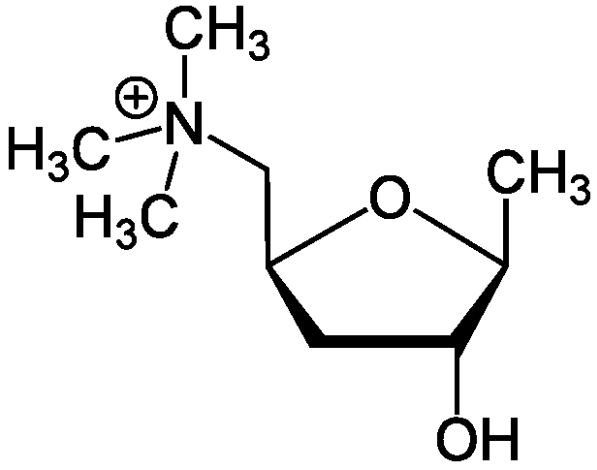


≈170 °

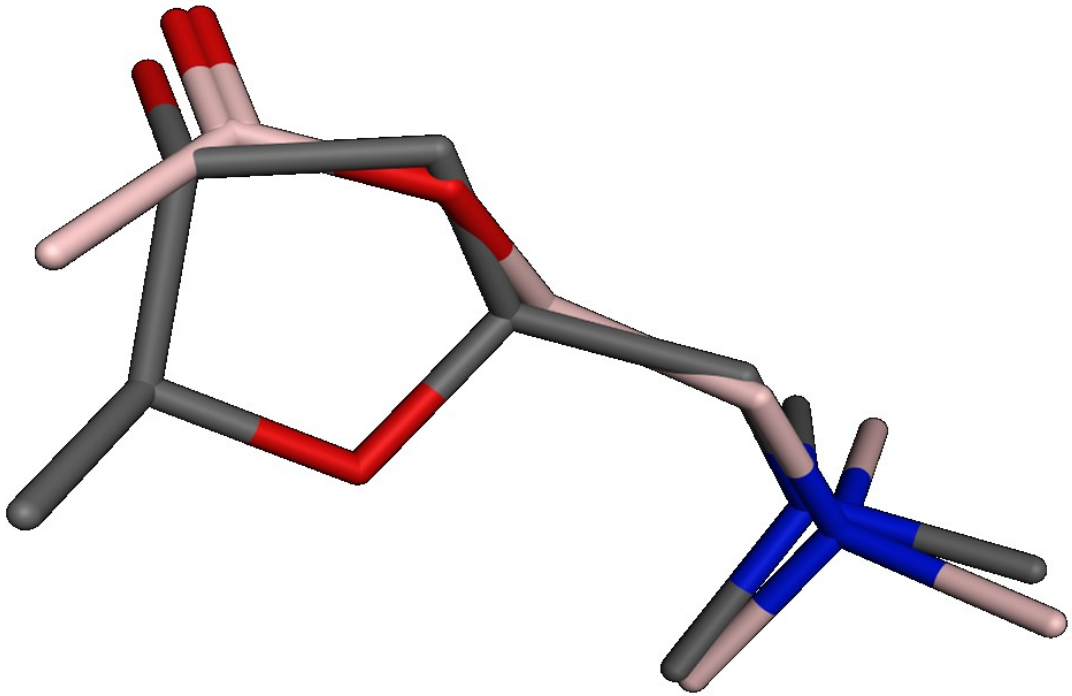
Now it is more clear?



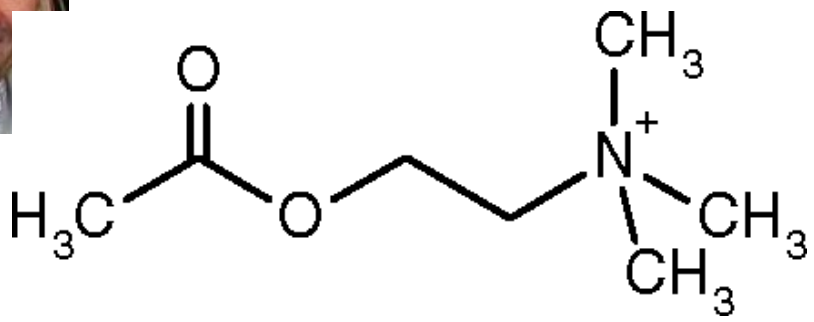
Acetylcholine (Ach)



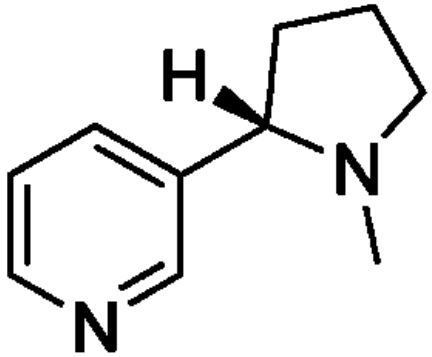
(*2S,4R,5S*)-(+)-Muscarine



And for the little Nicotine? Same approach…



Acetylcholine (Ach)



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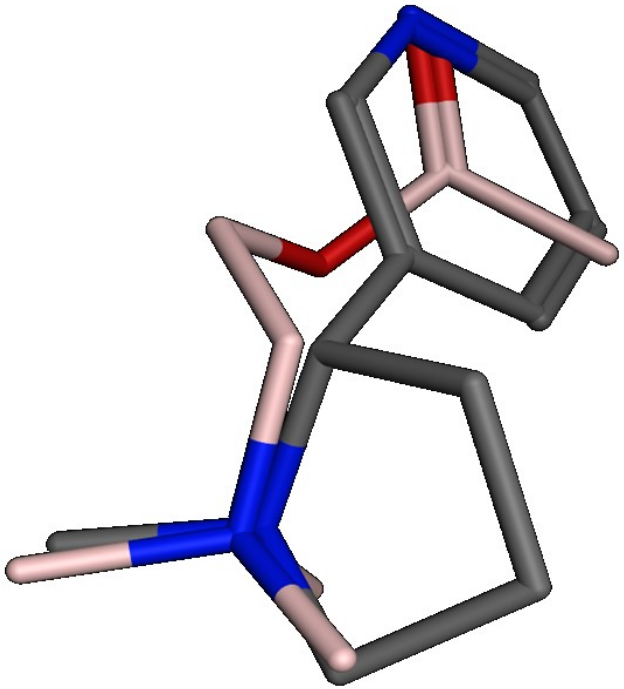
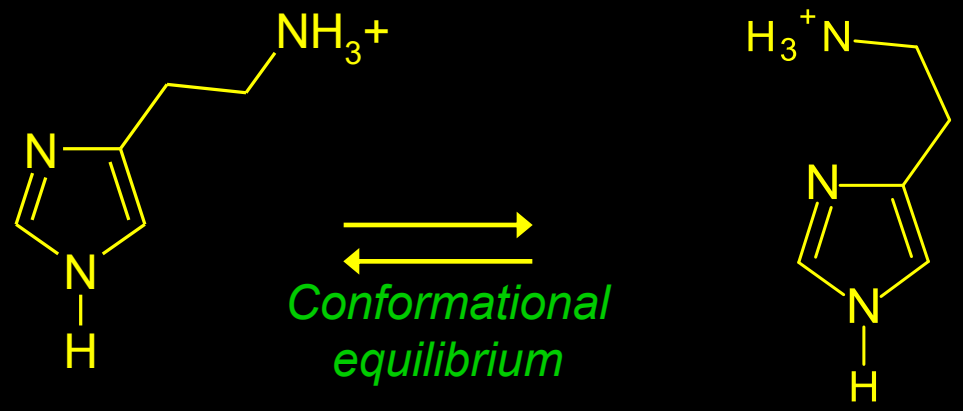
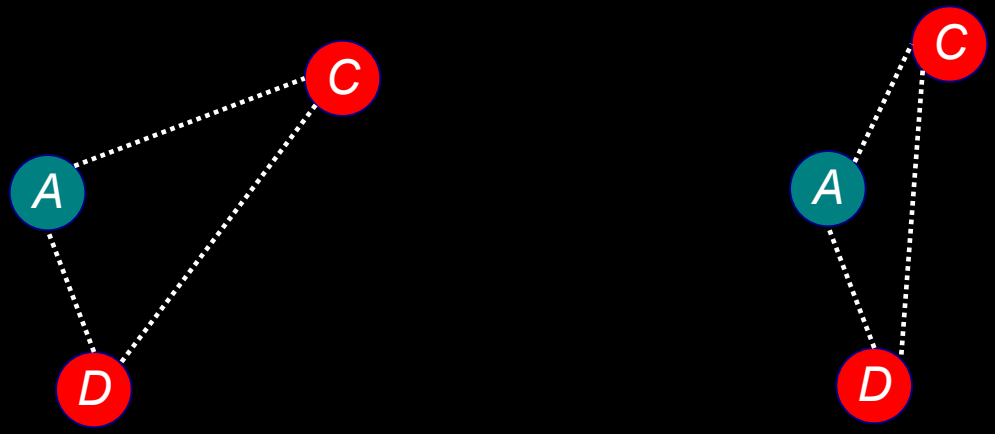
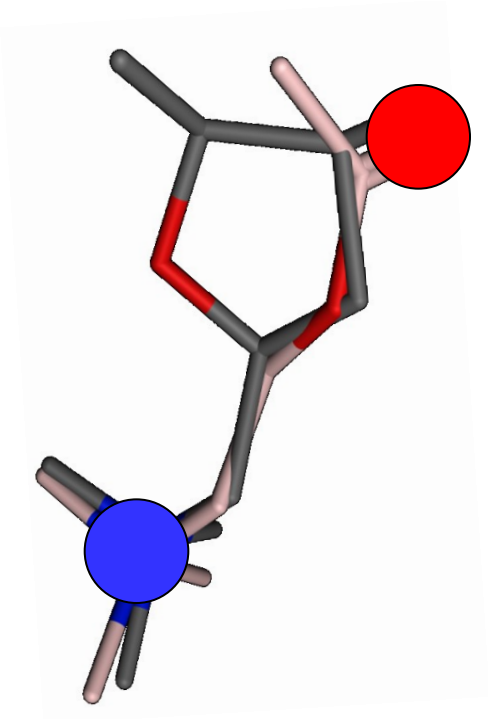


Do you remember?

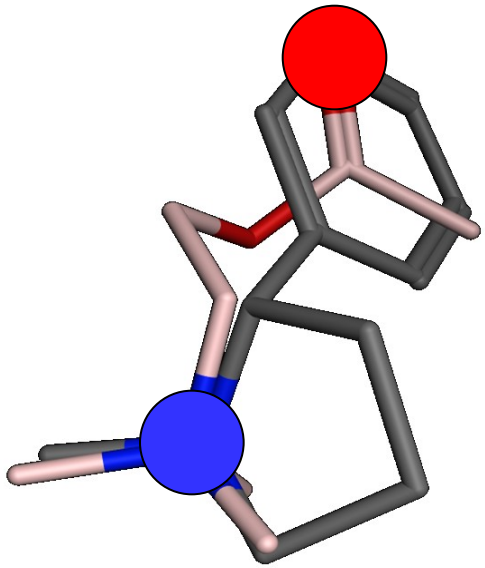




Now it is more clear… two different interaction schemes… two different pharmacophore hypothesis!

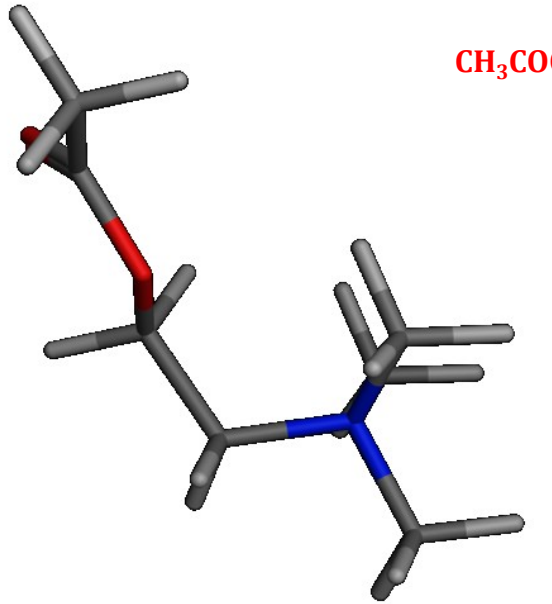


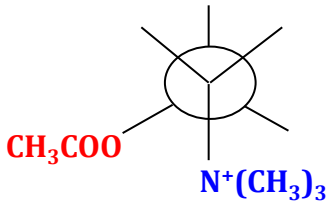
Muscarinic

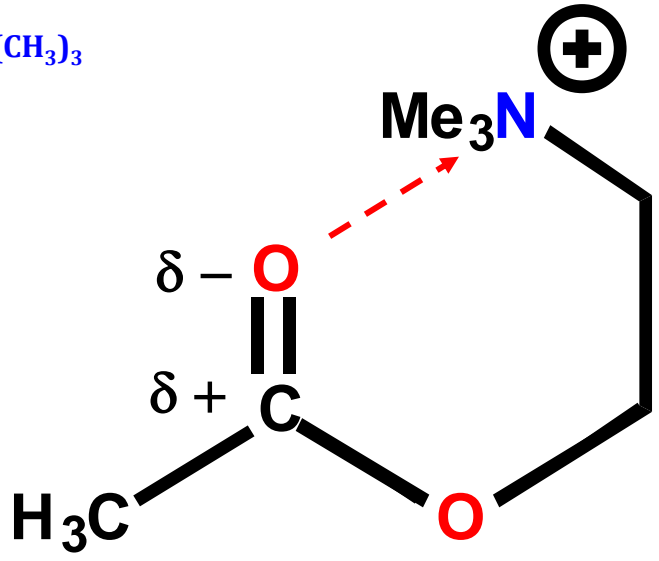


Nicotinic

...and now back to our simple 2D chemistry:

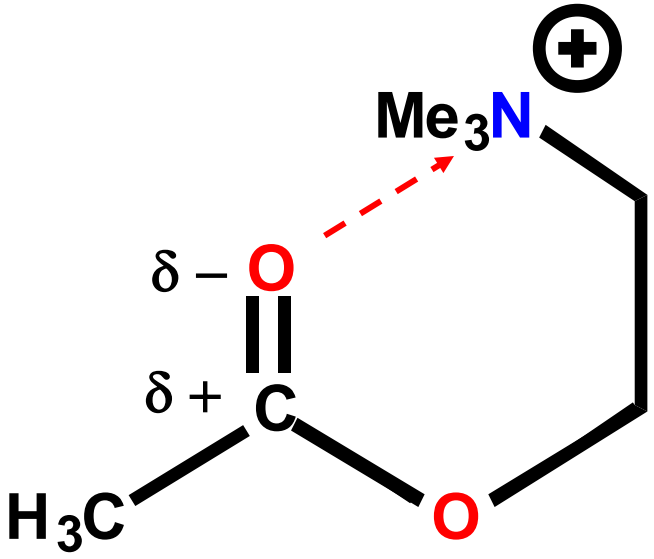






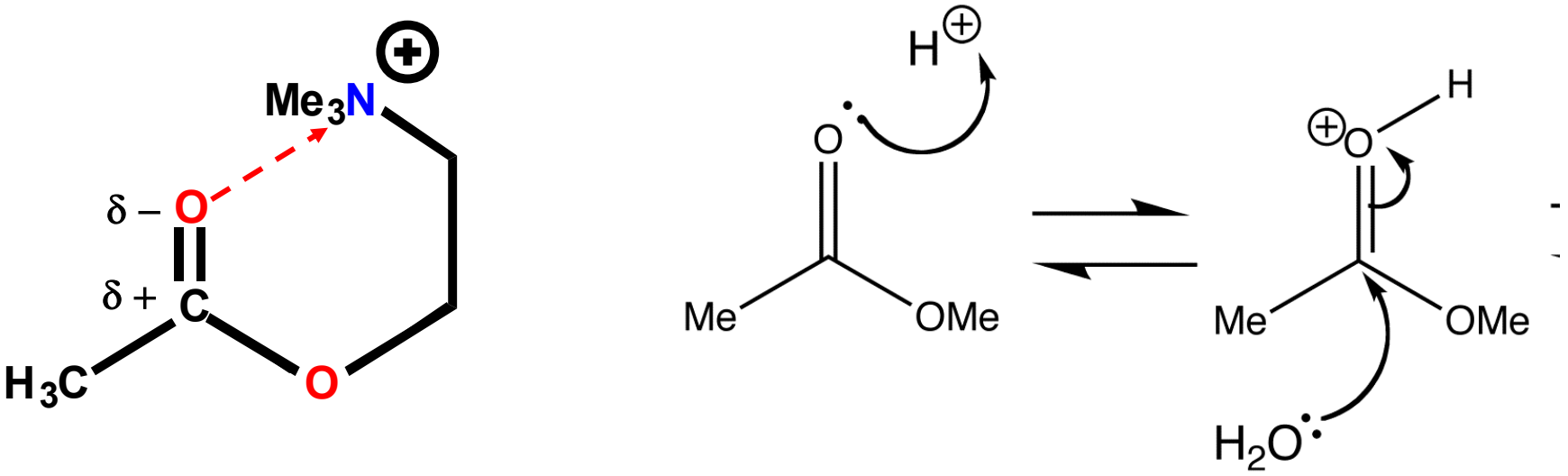
BRAVI... the gauche conformation is stabilized by a charge-dipole interamolecular interaction through the formation of a 6 membered ring!!!

And now it is also very clear why Ach it's so *chemically fragile*... and it is not a drug!



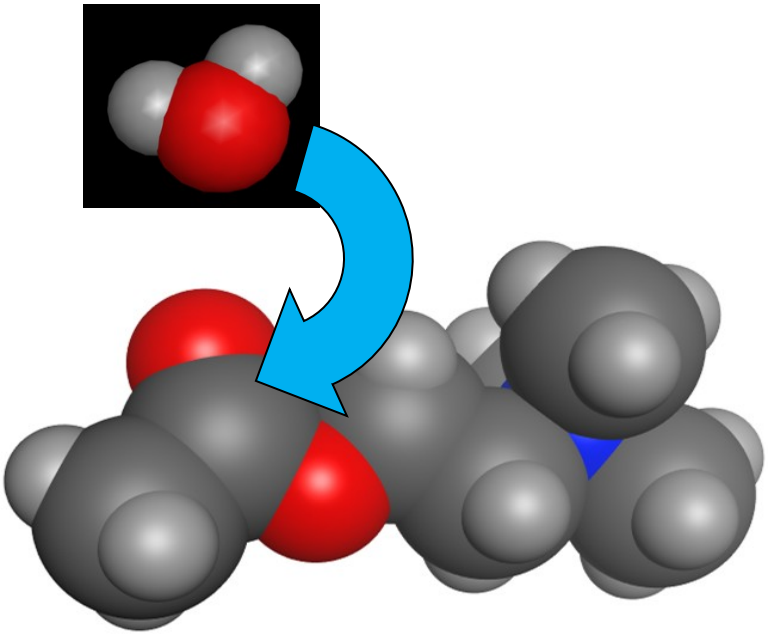
- Neighbouring group participation
- Increases electrophilicity of carbonyl group
- Increases sensitivity to nucleophiles

9. Instability of acetylcholine



Do you see the analogy… Ach in its gauche conformation is permanently under acid catalysis!

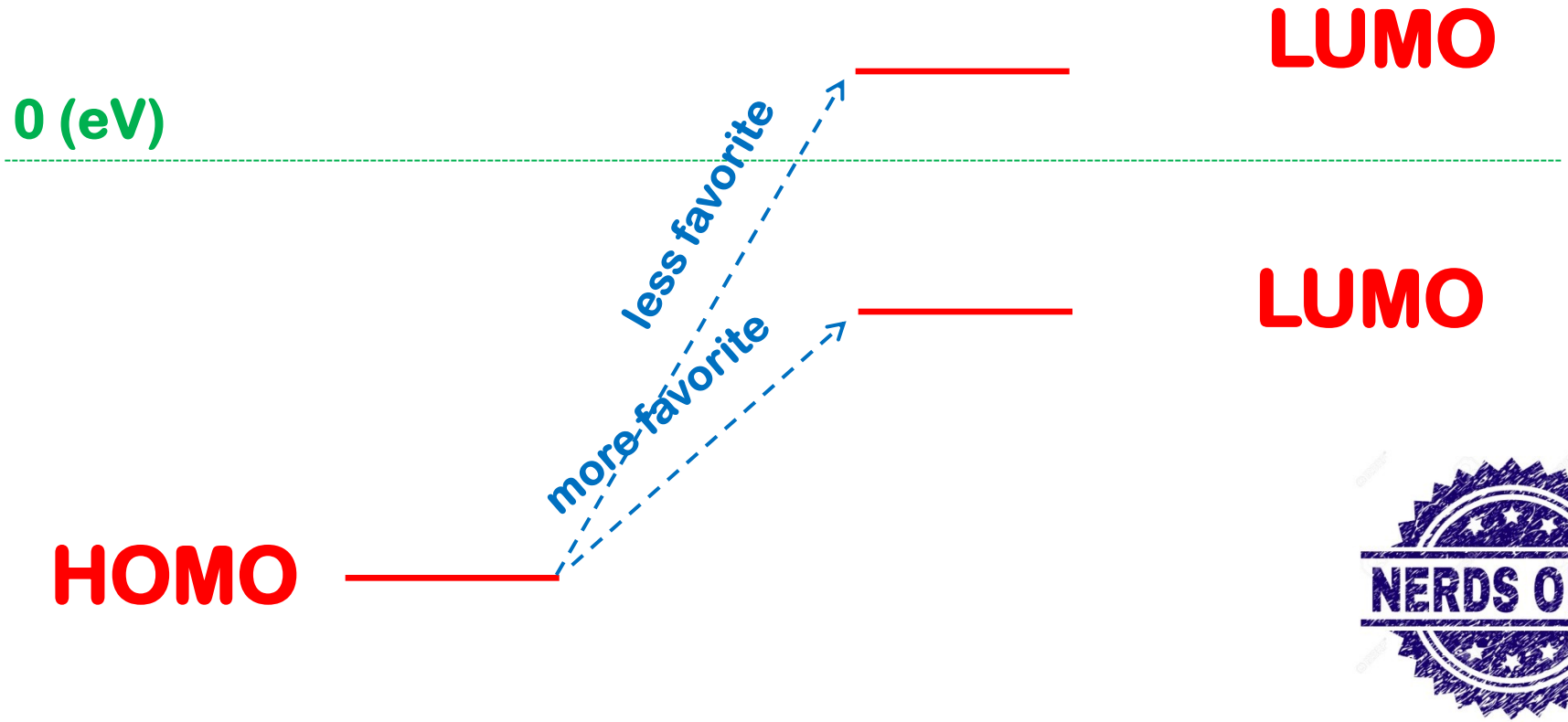
… do you remember HOMO-LUMO in reagents interaction?



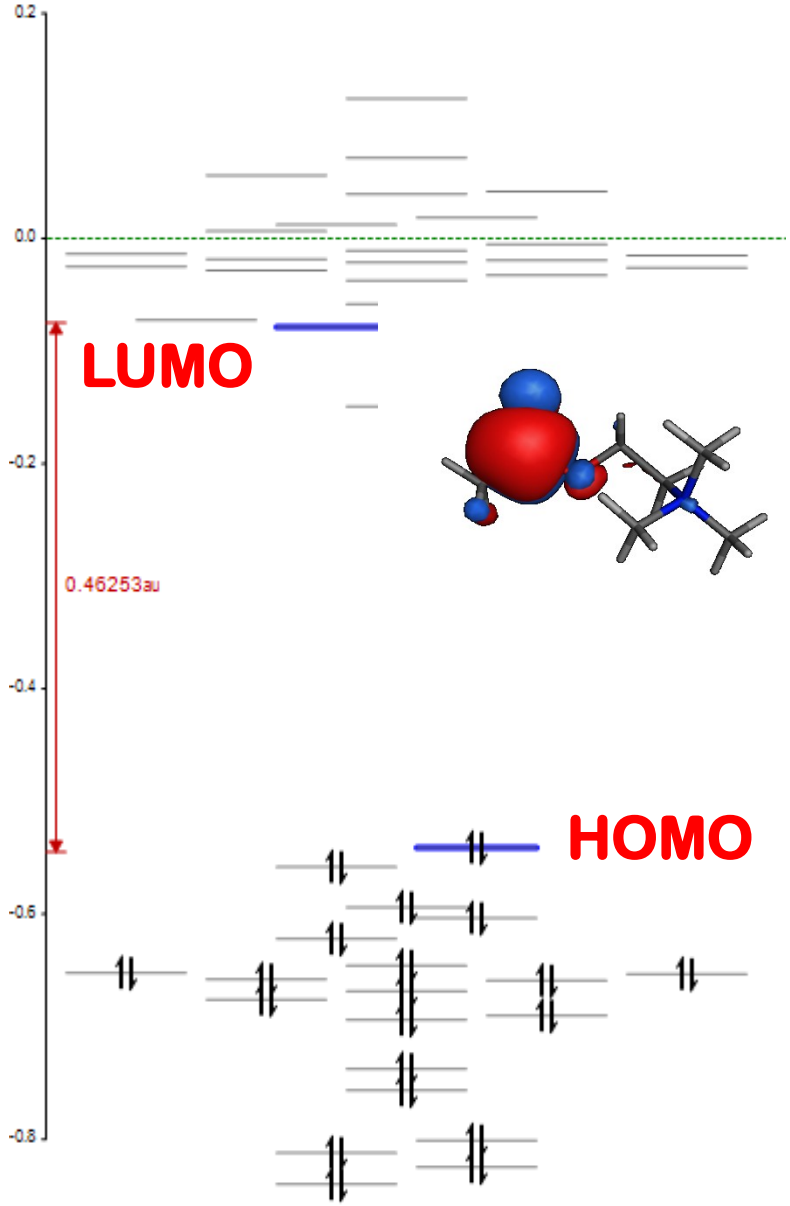
Nucleophile ⇒ HOMO

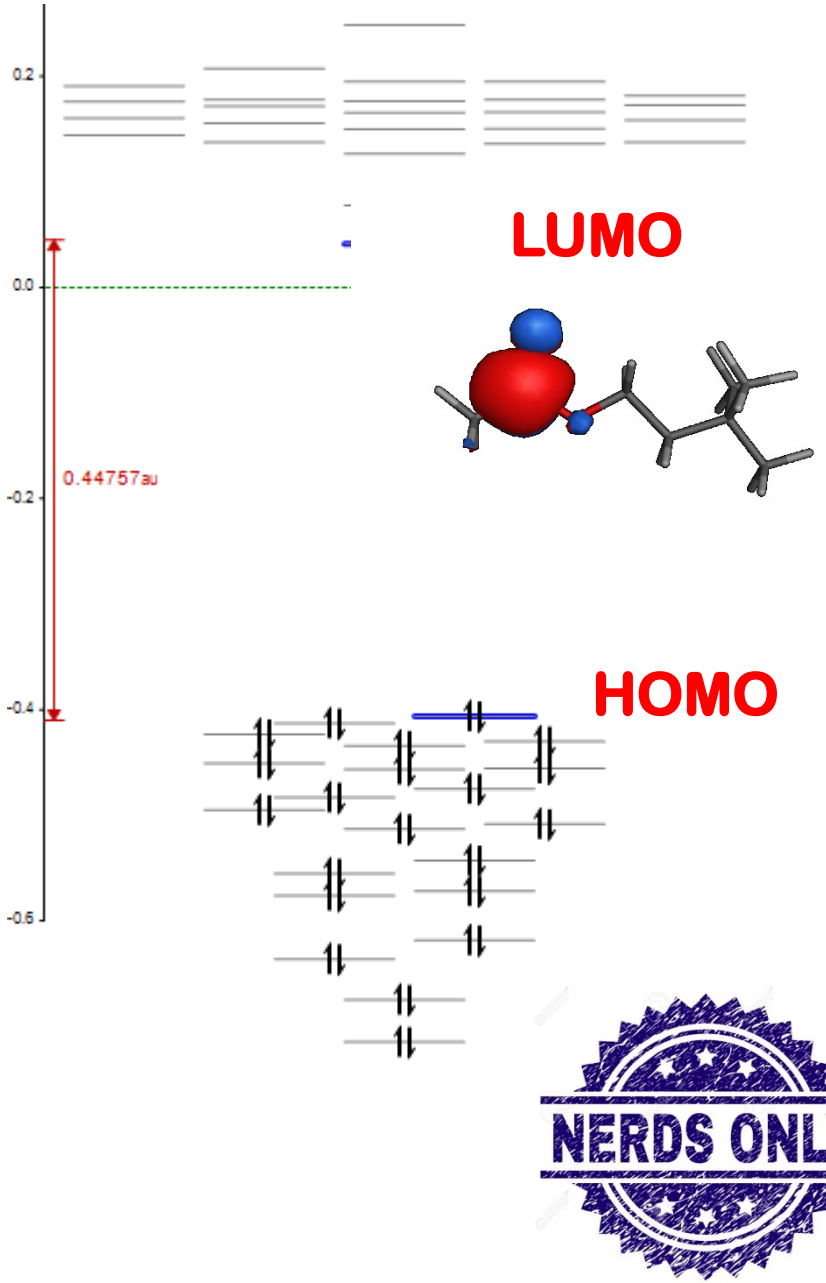
Electrophile ⇒ LUMO

… do you remember HOMO-LUMO in reagents interaction?

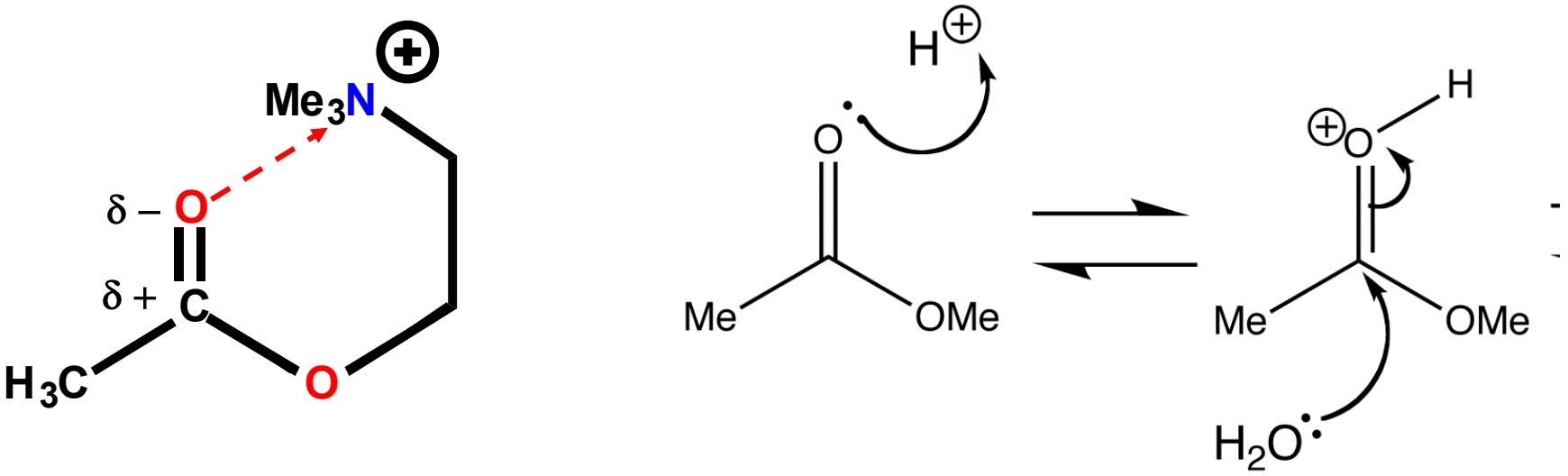


HOMO-LUMO energy gap difference affects the evolution of a chemical reaction: the smaller this difference, the more facilitated the reaction will be.



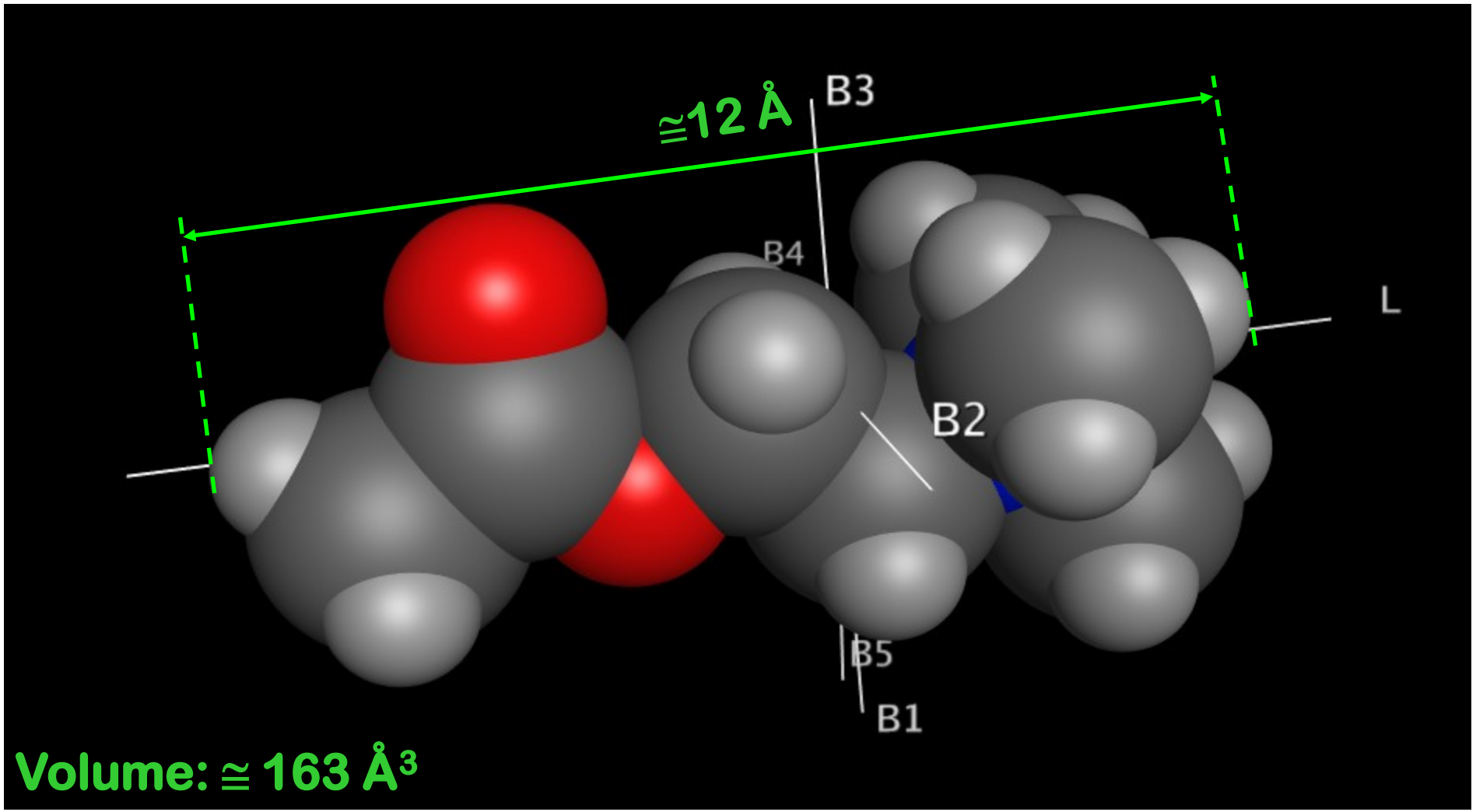


9. Instability of acetylcholine

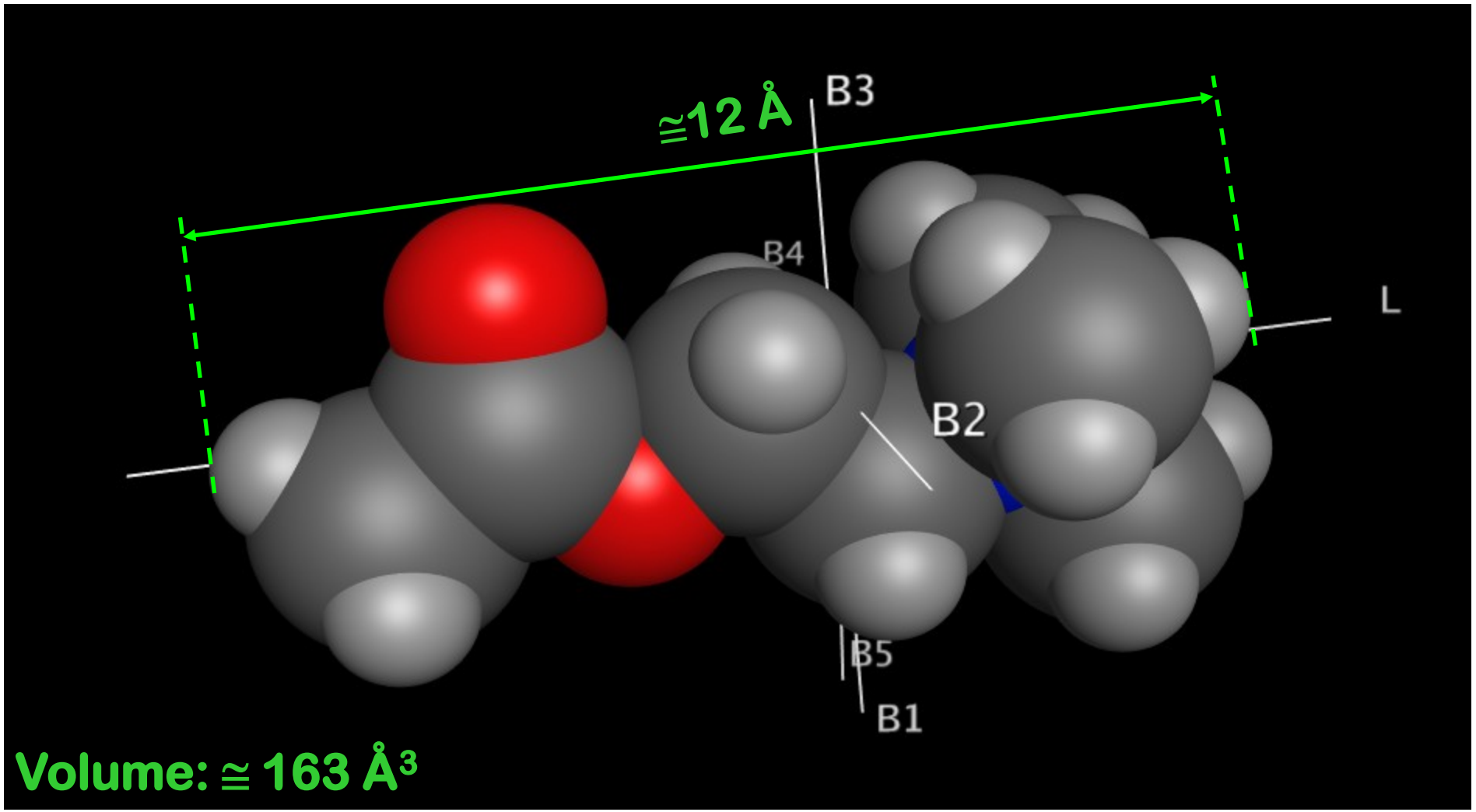


Do you see the analogy… Ach in its gauche conformation is permanently under acid catalysis!

3D… where it is possible to measure geometrical properties:

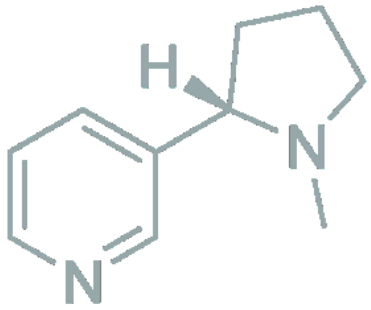


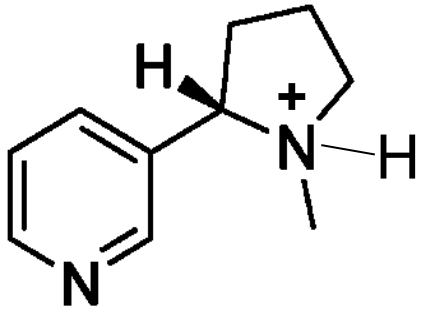
3D… where it is possible to measure geometrical properties: I am an agonist!!!

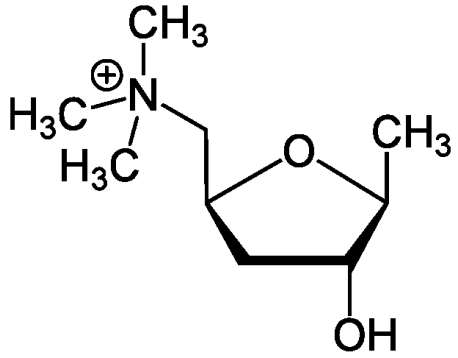


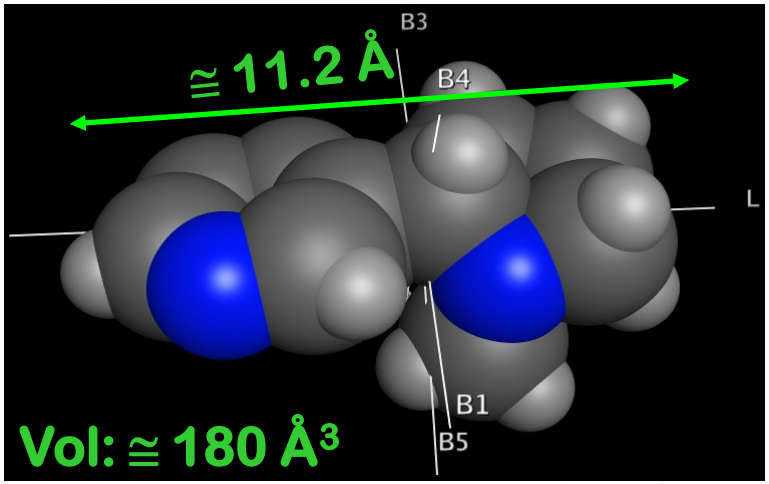
5. Cholinergic agonists

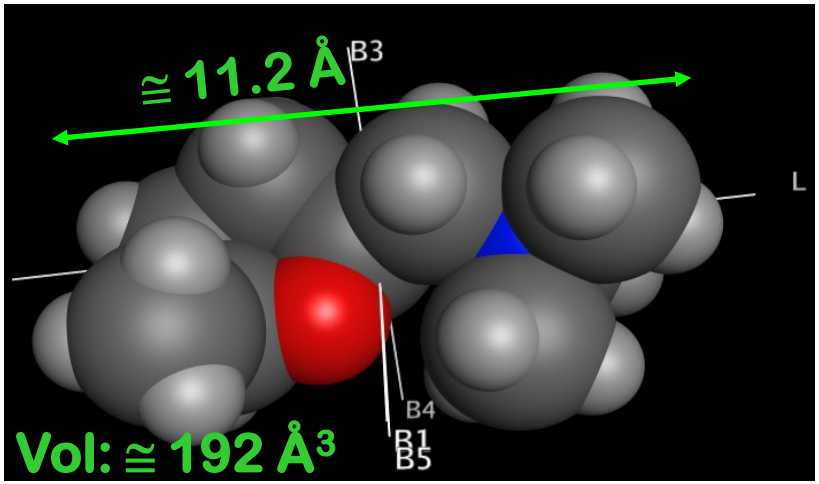
5.2 Nicotine and muscarine as cholinergic agonists



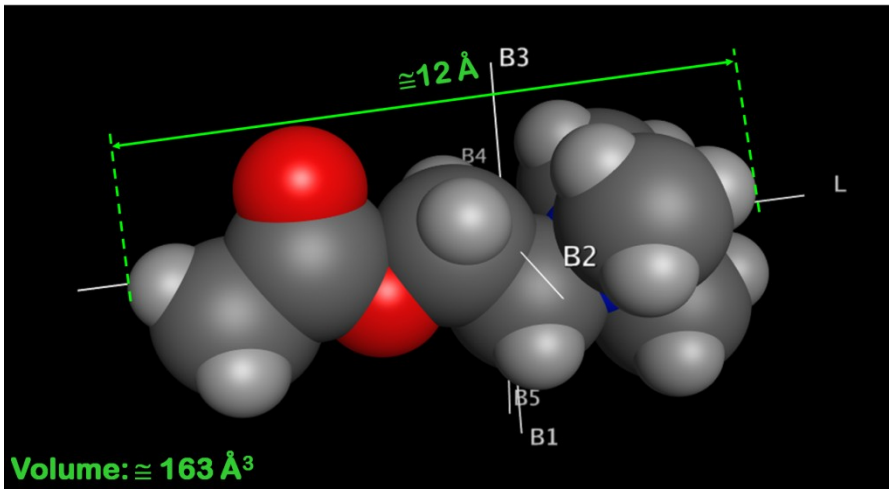


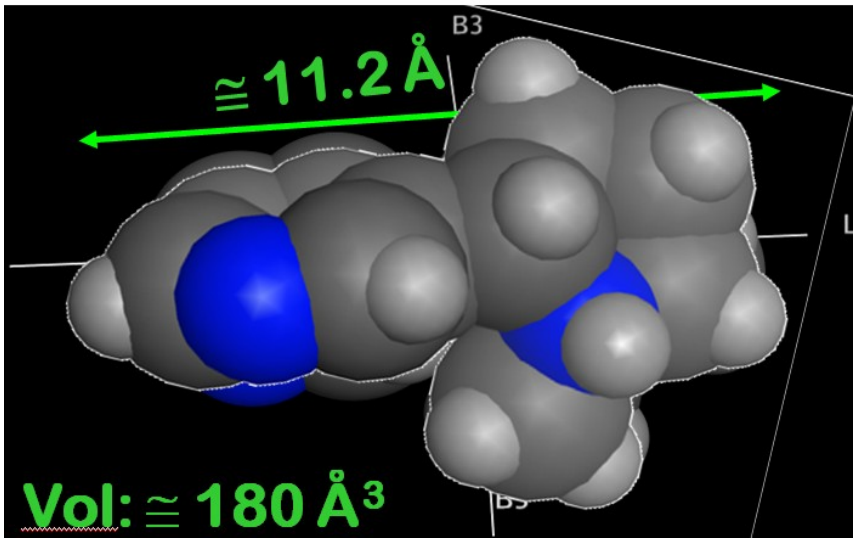


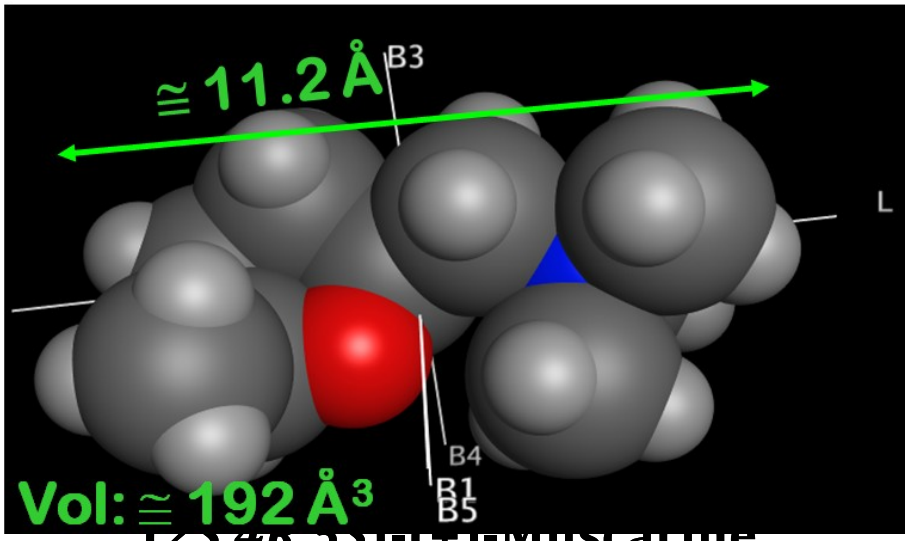




As agonists, we share the *similar* topological properties!







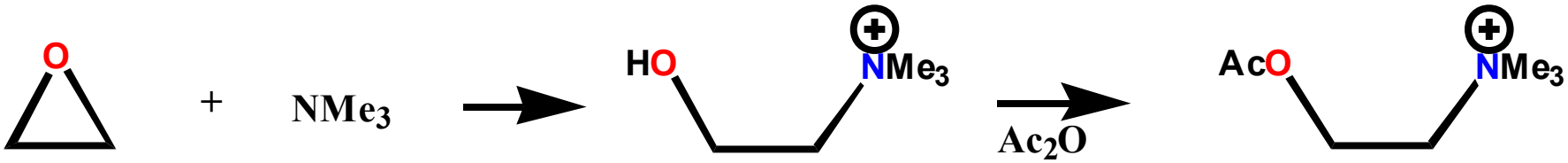
(2S,4R,5S)-(+)-Muscarine

5. Cholinergic agonists

5.1 Acetylcholine as an agonist but not a good drug!

Advantages

- **Easily synthesised**



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

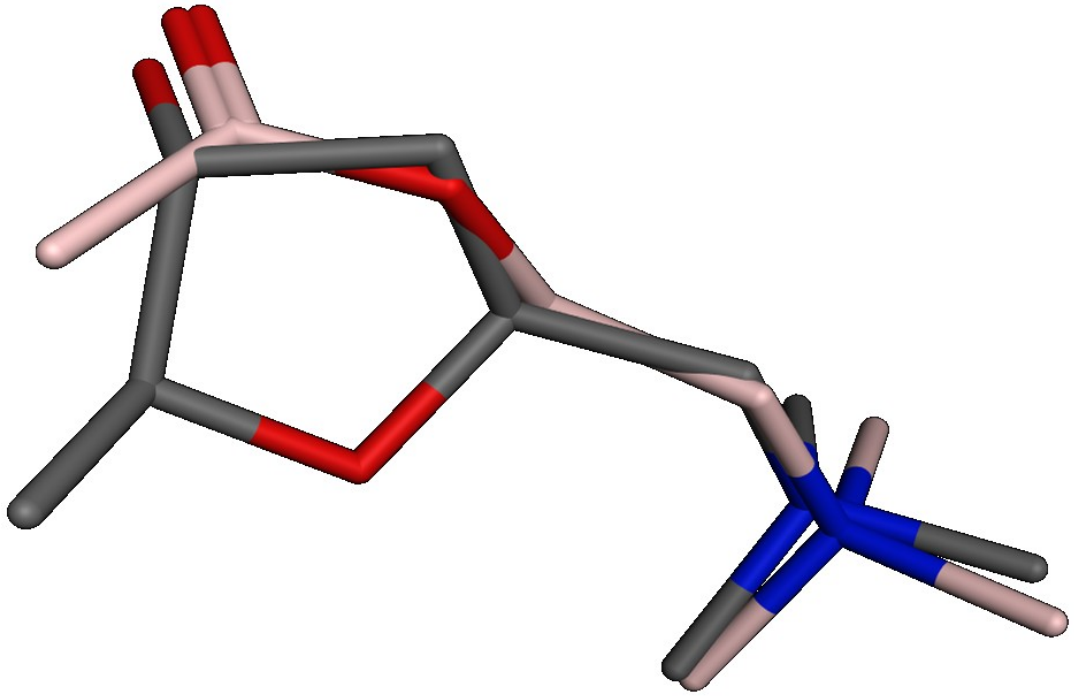
5. Cholinergic agonists

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**

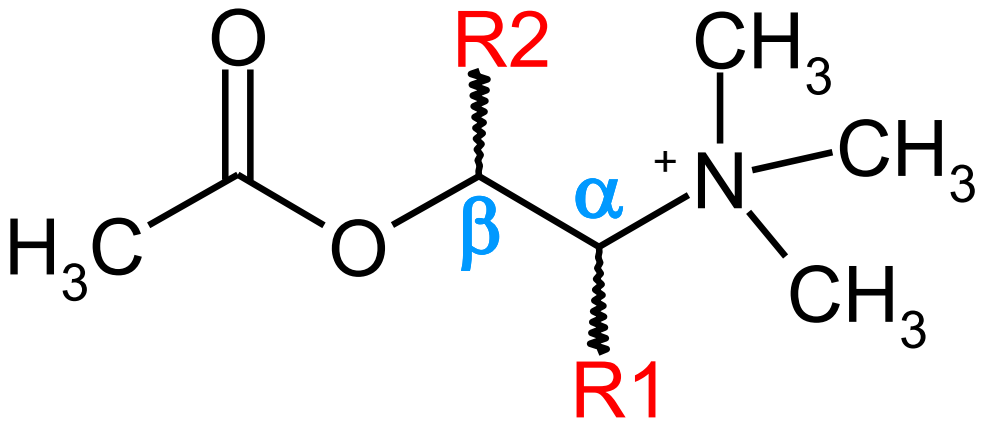
10. Design of cholinergic agonists

Another bit of SAR: we can start from here...



10. Design of cholinergic agonists

Another bit of SAR:

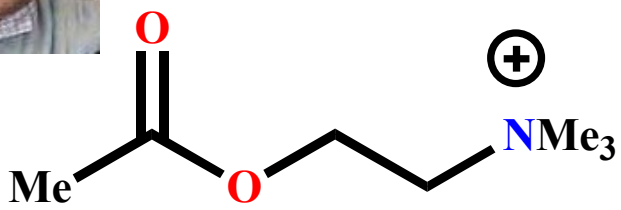


R2 = CH_3 (β position): ↑ muscarinic activity and ↓ nicotinic activity *compare to Ach*

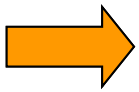
S >> R (on M3 muscarinic receptors)

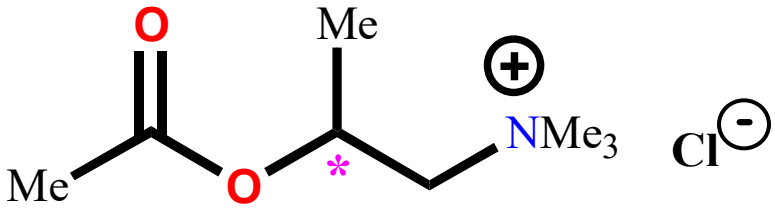
R1 = CH_3 (α position): ↓ muscarinic activity and ≅ nicotinic activity *compare to Ach*

Welcome to methacholine!



Ach





Methacholine

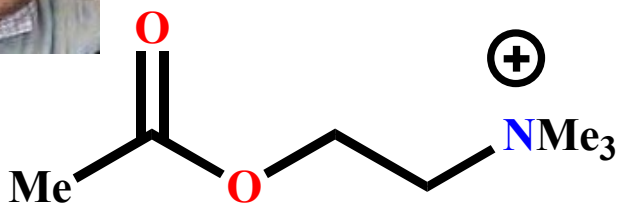
Advantages

- More stable than Ach
- It is highly active at all of the muscarinic receptors, but has little effect on the nicotinic receptors.

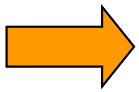
Disadvantages

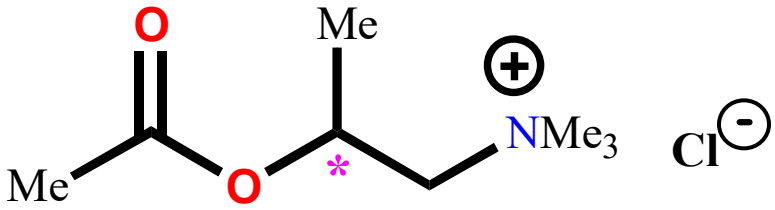
- As Ach, it has a charged quaternary amine structure, rendering it insoluble to cell membranes. Clinically, this means that it will not cross the blood–brain barrier and has poor absorption from the gastrointestinal tract.
- It is broken down at a relatively slow rate within the body, due to its relative resistance to acetylcholinesterases.

Why methacholine is more stable than Ach?



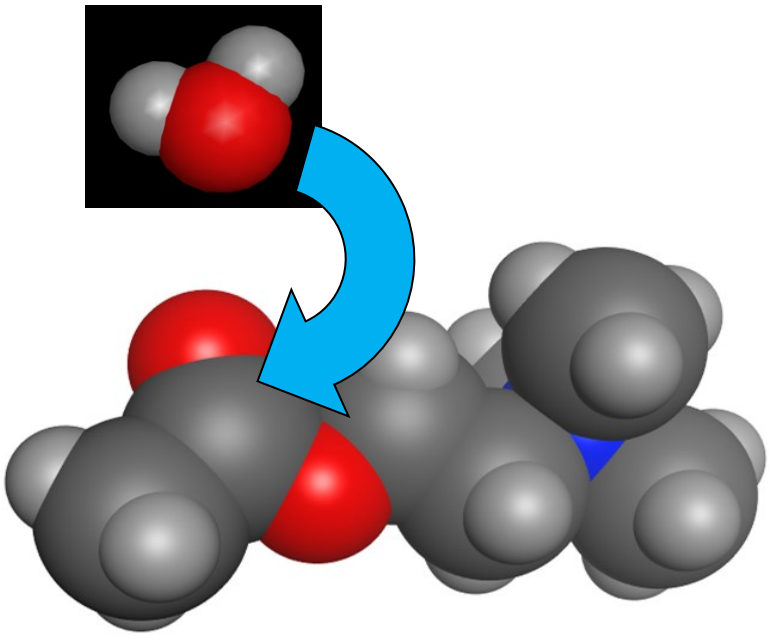
Ach

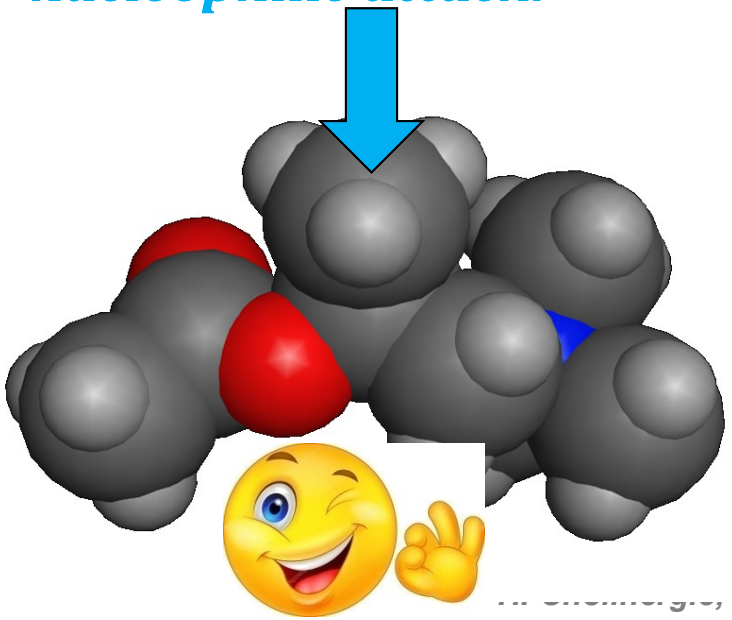




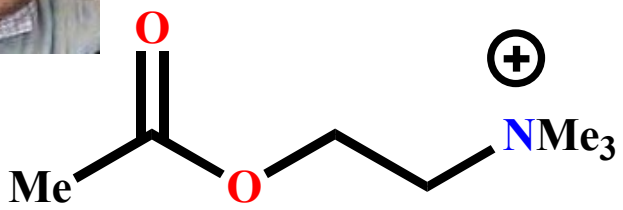
Methacholine

hinders binding to esterase and provides a shield to nucleophilic attack!

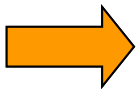


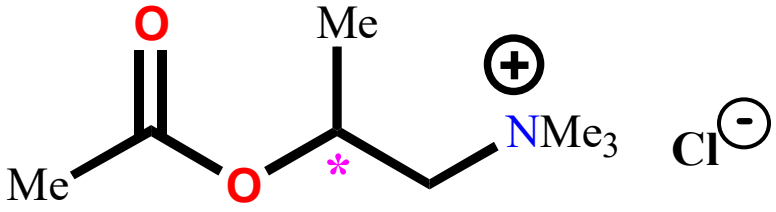


Why methacholine is selective against muscarinic receptors?

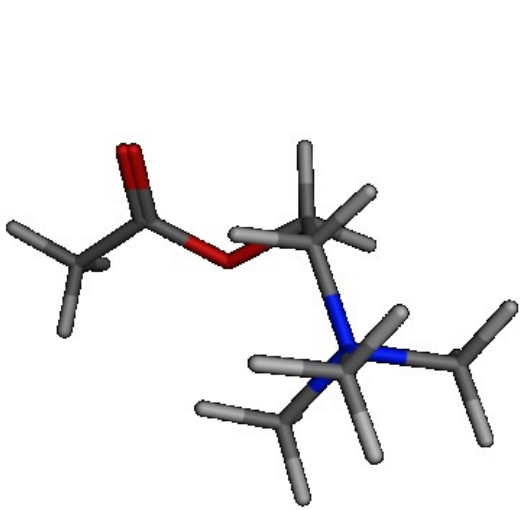


Ach

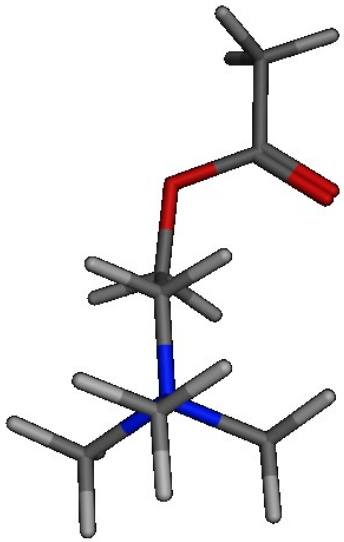




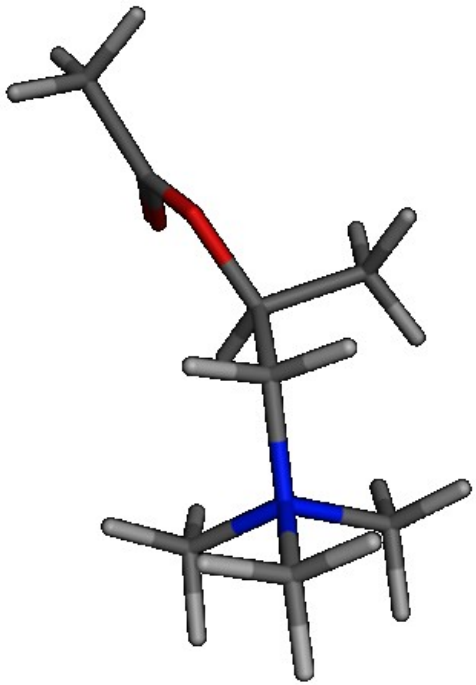
Methacholine



gauche



anti



quasi-anti

10. Design of cholinergic agonists

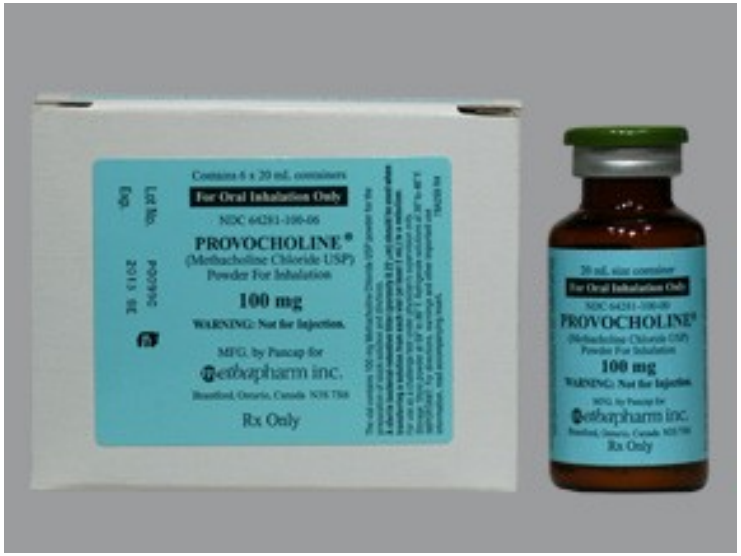
Properties

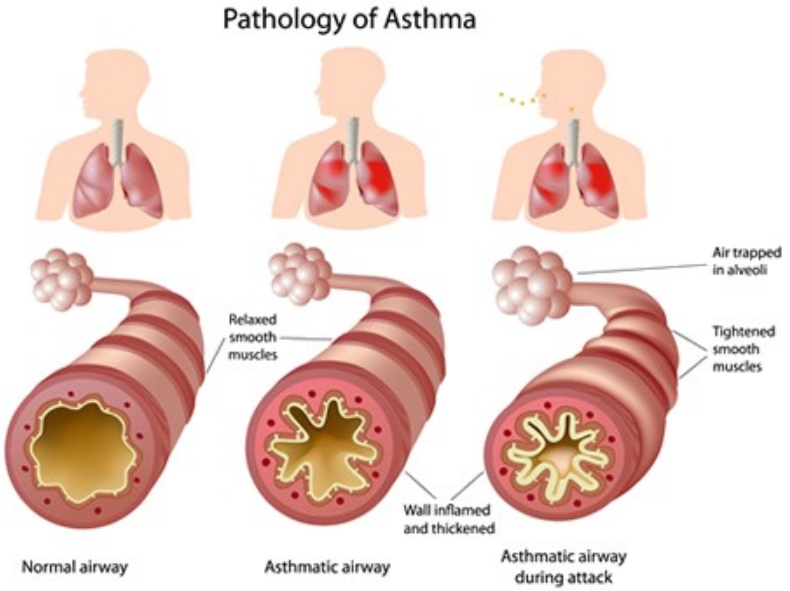
- ***Three times*** **more stable than acetylcholine**
- **Increasing the shield size increases stability but decreases activity**
- **Selective for muscarinic receptors over nicotinic receptors**
- ***S*-enantiomer is more active than the *R*-enantiomer**
- **Stereochemistry matches muscarine**
- **Methacholine is primarily used to *diagnose bronchial hyper-reactivity*, which is the hallmark of asthma and also occurs in chronic obstructive pulmonary disease. This is accomplished through the bronchial challenge test, or methacholine challenge, in which a subject inhales aerosolized methacholine, leading to bronchoconstriction. *Other therapeutic uses are limited by its adverse cardiovascular effects, such as bradycardia and hypotension, which arise from its function as a cholinomimetic.***

10. Design of cholinergic agonists

Bronchial challenge test

A **bronchial challenge test** is a medical test used to assist in the diagnosis of asthma. The patient breathes in nebulized methacholine or histamine. Thus the test may also be called a **methacholine challenge test** or **histamine challenge test** respectively. Both drugs provoke bronchoconstriction, or narrowing of the airways. Whereas histamine causes nasal and bronchial mucus secretion and bronchoconstriction via the **H1 receptor**, methacholine utilizes the **M3 receptor** for bronchoconstriction.



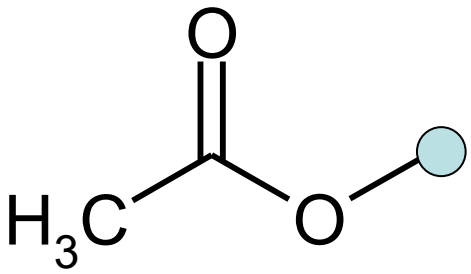


10. Design of cholinergic agonists

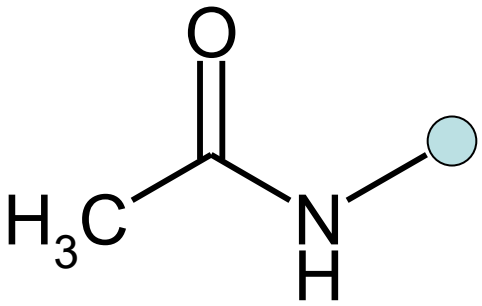
Bronchial challenge test

credits: https://www.youtube.com/watch?reload=9&v=OlXoNKDPtVU

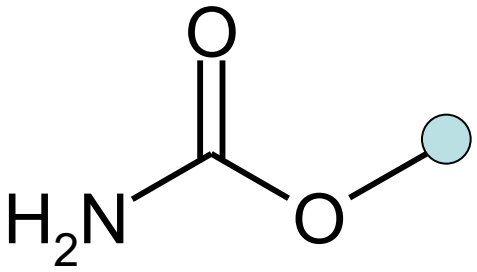
Really wonderful… .. from a small memory of organic chemistry to a great pharmaceutical intuition!!!



Ester

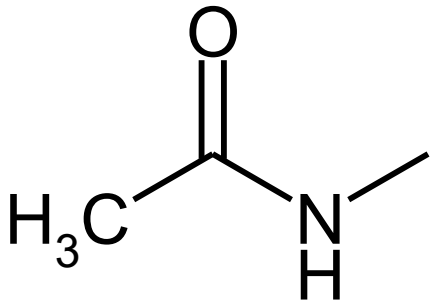


Amide



Urethane or Carbamate

Really wonderful… .. from a small memory of organic chemistry to a great pharmaceutical intuition!!!



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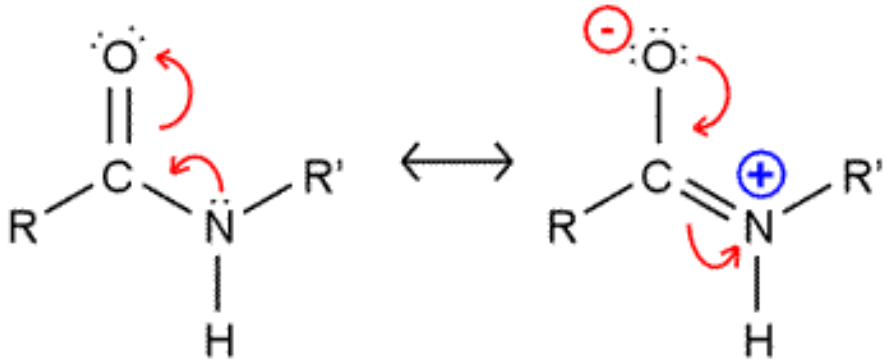
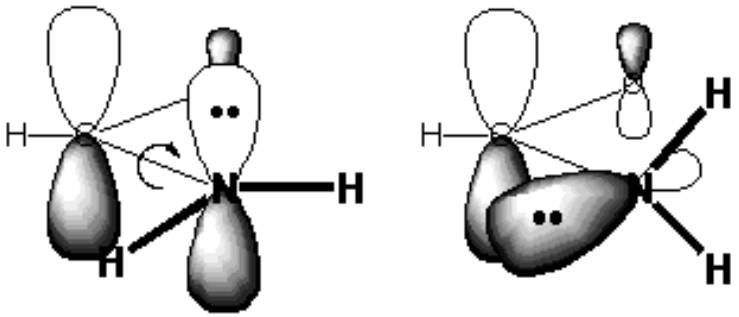
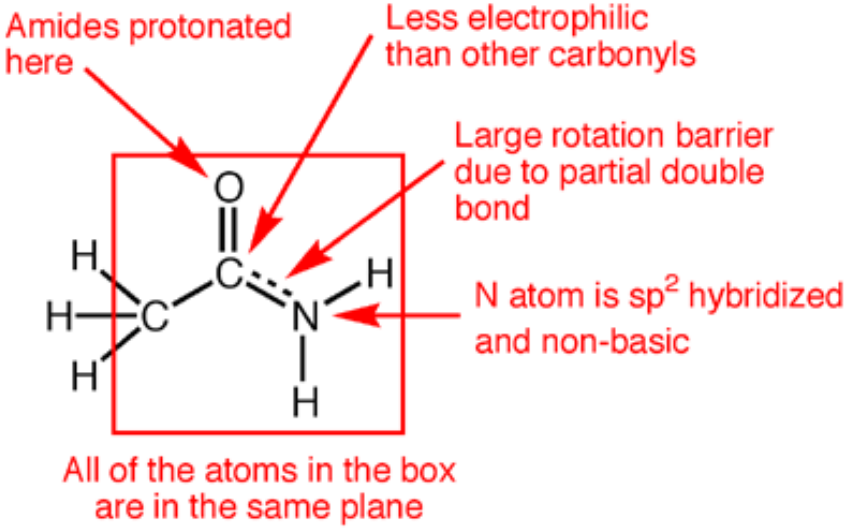


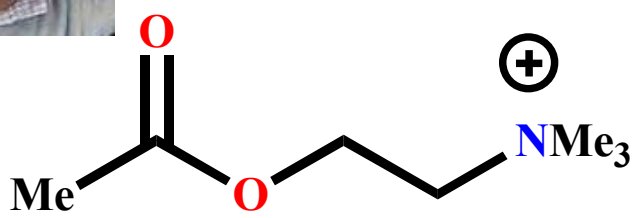


good overlap

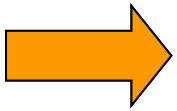
poor overlap

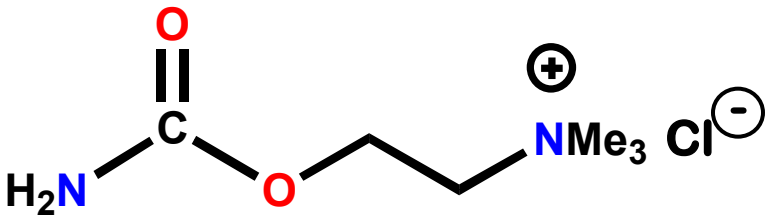


And here the drug is served…



Ach





Carbachol

Properties

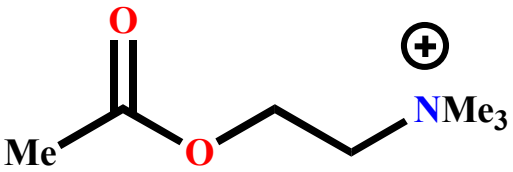
- Resistant to hydrolysis
- Long lasting
- NH_2 and CH_3 are equal sizes. Both fit the hydrophobic pocket
- NH_2 is considered bio-isostere of CH_3 in case!
- Muscarinic activity ≅ nicotinic activity (side effects!!)
- Used topically for glaucoma

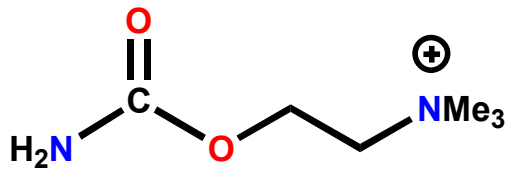
Disadvantages

- Copy&Paste from Methacholine

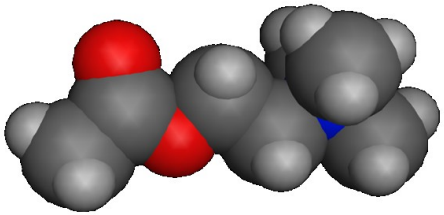
A smart use of electronic factors…

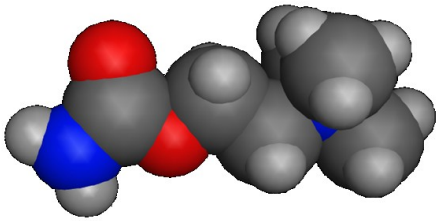
- Replace *ester* with *urethane*
- Stabilizes the carbonyl group



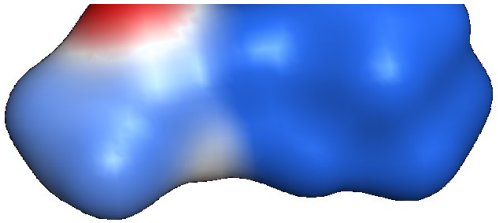


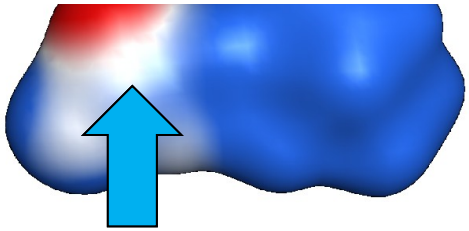
L ≅ 12 Å
Volume ≅ 163 Å^3





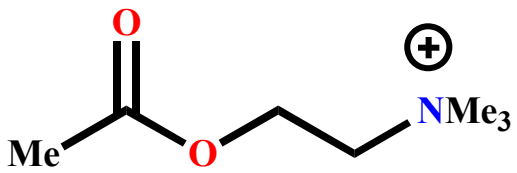
L ≅ 12 Å
Volume ≅ 157 Å^3

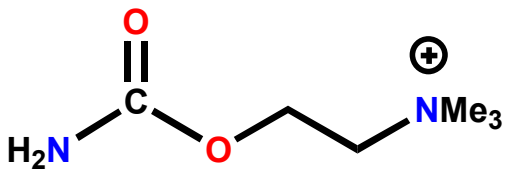




This carbon is less electrophilic than in Ach!!!

Selective or non selective?





L ≅ 12 Å
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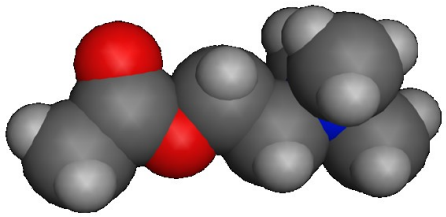
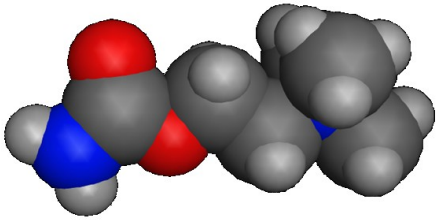
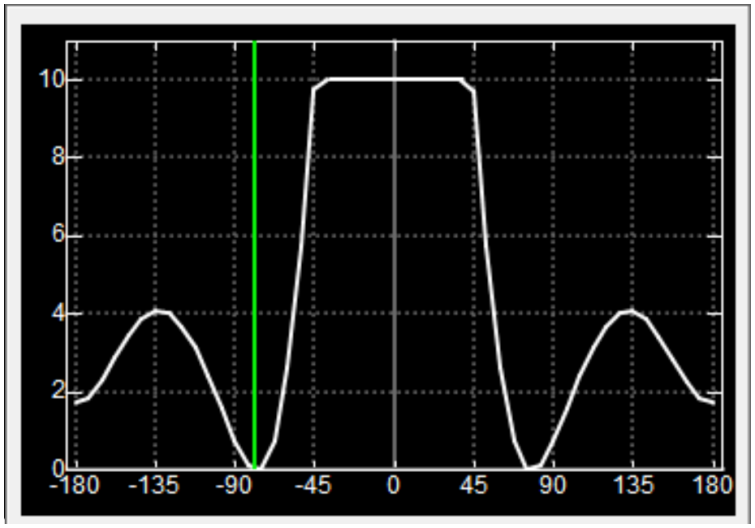
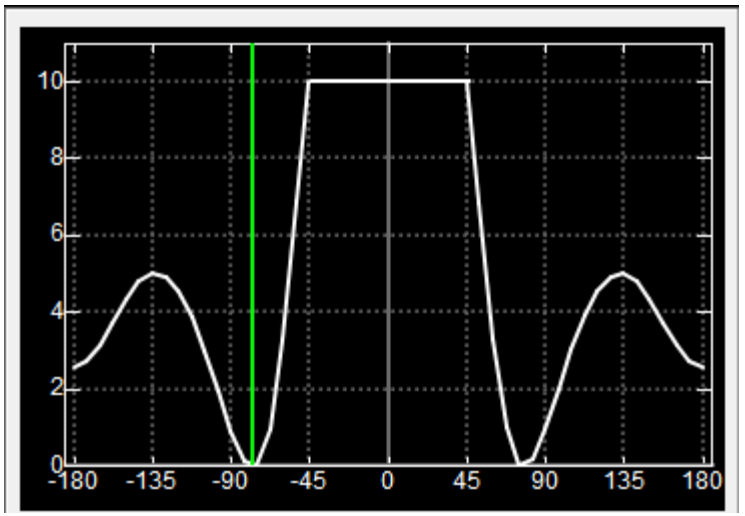




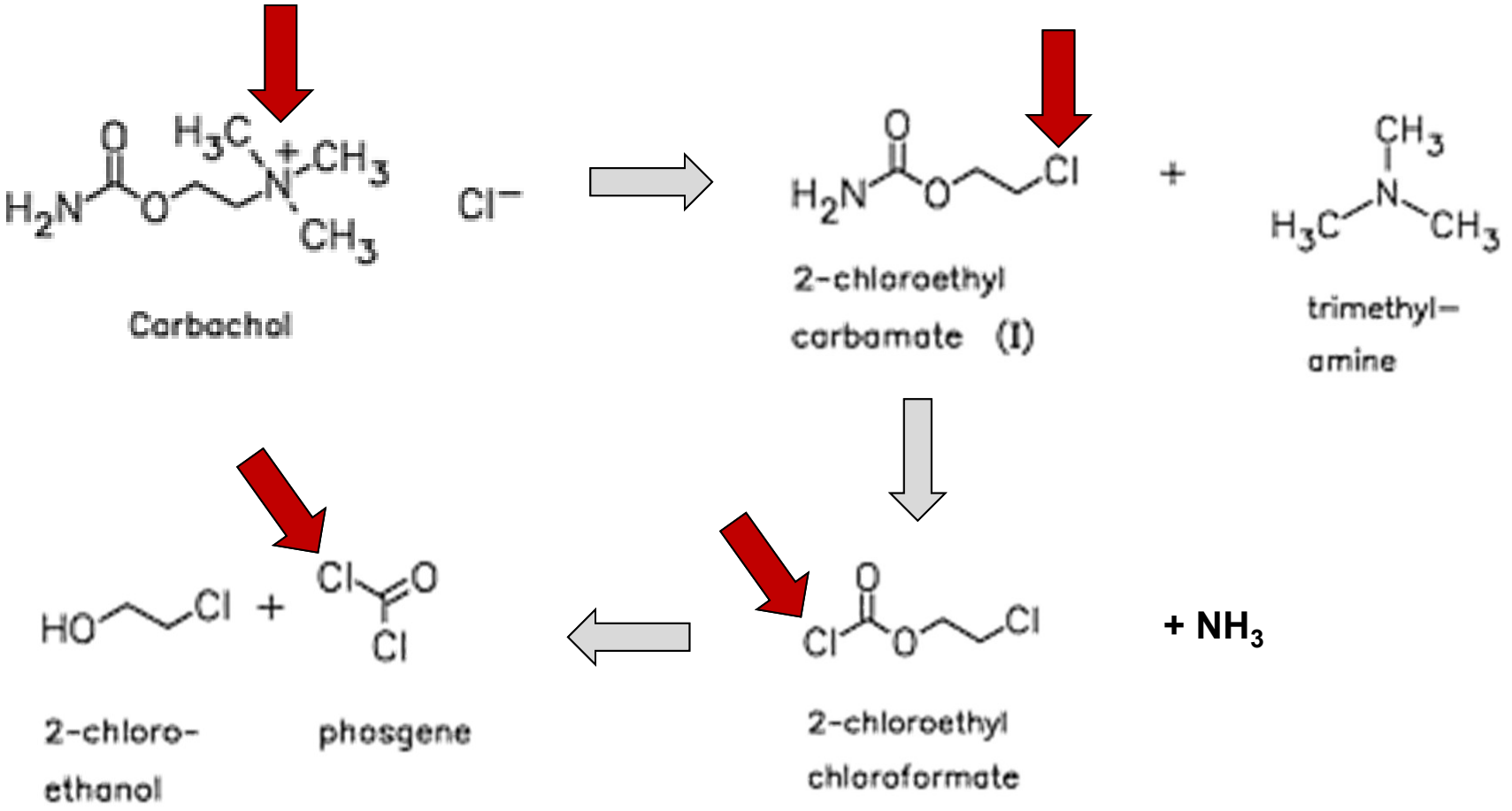
L ≅ 12 Å
Volume ≅ 157 Å^3



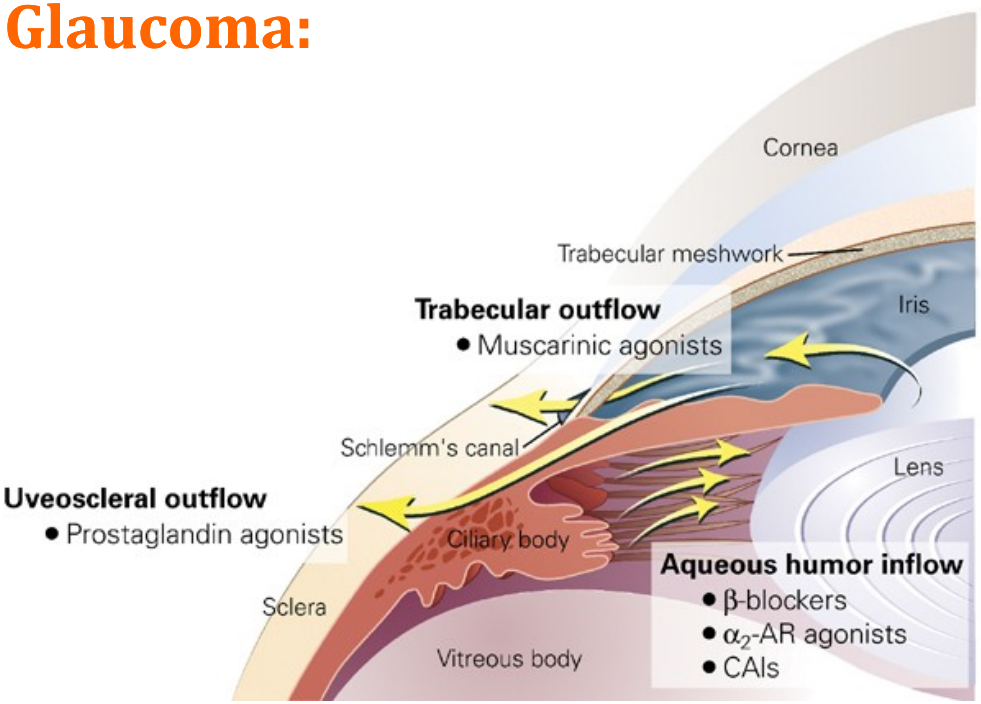


Back to chemistry…

A possible retro synthesis path:



Glaucoma:



Schematic of anterior portion of the human eye highlighting anatomy relevant to glaucoma therapeutics. The clear intraocular fluid called aqueous humor is produced by the ciliary body and secreted by the ciliary body epithelial bilayer into the posterior chamber (three yellow arrows indicate the 'aqueous humor inflow' pathway). The aqueous humor baths and nourishes the crystalline lens (Lens), and then circulates into the anterior chamber (enclosed by the Cornea) through the pupil (indicated by the single yellow arrow going across the iris). The aqueous humor leaves the eye through the trabecular meshwork and into ***Schlemm's canal*** ('trabecular outflow') and through the peripheral base of the iris, into the ciliary body, and through the sclera ('uveoscleral outflow').

Current glaucoma medical therapy modulates intraocular pressure by decreasing 'aqueous humor inflow' [β2-blockers, α2-adrenergic receptor (AR) agonists, and carbonic anhydrase inhibitors (CAIs)], by enhancing 'trabecular outflow' (**M3 muscarinic agonists**), or by enhancing 'uveoscleral outflow' (prostaglandin agonists).

Effect of Glaucoma:

NORMAL VISION

EARLY GLAUCOMA

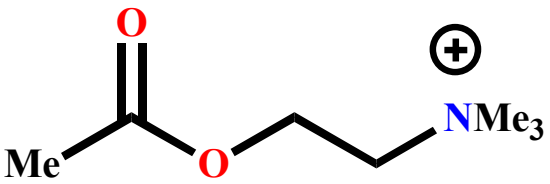
ADVANCED GLAUCOMA

Normal Vision

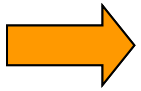
Vision With Glaucoma*

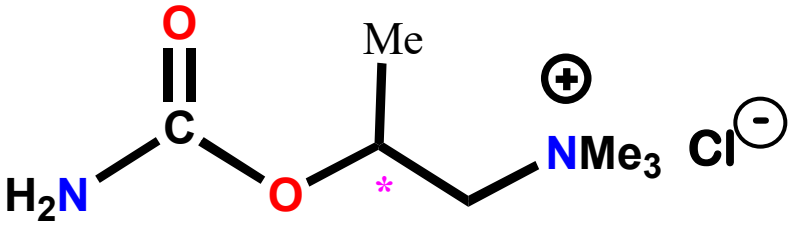
credits: http://www.goyaleye.com/glaucoma.html#

Give my the third…



Ach



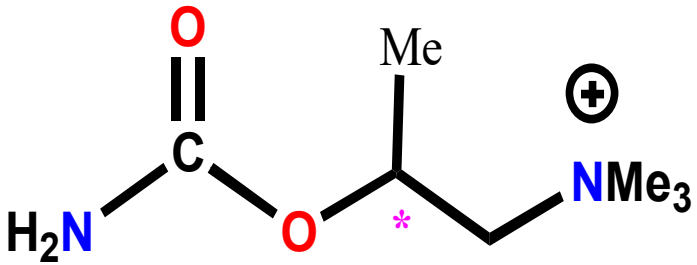


Bethanechol

BRAVI!!!

10. Design of cholinergic agonists

A super-smart use of Steric + Electronic factors



Bethanechol

2-(carbamoyloxy)- N,N,N-trimethylpropan- 1-aminium

Properties

- **Very stable**
- **Orally active**
- **Selective for the muscarinic receptor (with further selectivity for M3 receptors)**
- **Used to stimulate GI tract (*oral*) and urinary bladder (*subcutaneous*) after surgery, and glaucoma (*ophthalmic solution*).**

Disadvantages

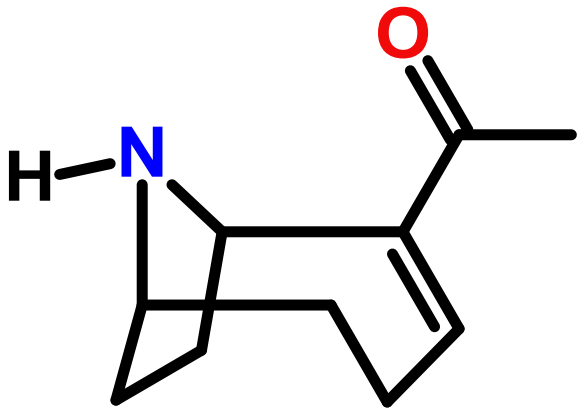
- **Copy&Paste from Methacholine**

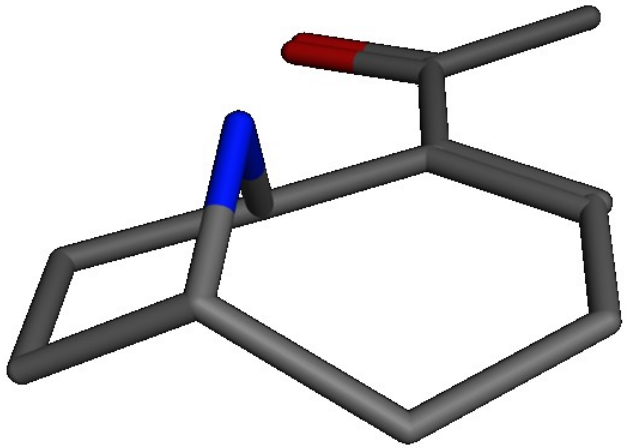
Honestly, we cannot really consider ourselves satisfied from a pharmaceutical point of view:

We still miss:

- Selective nicotinic agonists
- Orally avaiable and BBB permeable cholinergic drugs
- Wider therapeutic window

Just a prototype of nicotinic agonist… again from mother nature: Anatoxin-A, a cyanotoxin produced by multiple genera of cyanobacteria

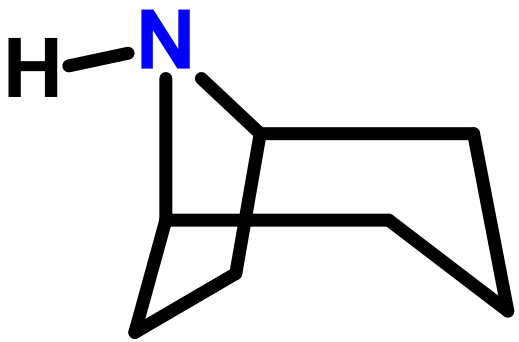




(+) Anatoxin-A

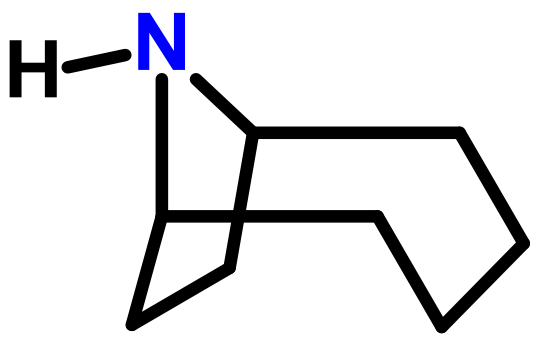
1-(9-azabicyclo[4.2.1]non-2-en-2-yl)ethan-1-one

Just a prototype of nicotinic agonist… again from mother nature: Anatoxin-A, a cyanotoxin produced by multiple genera of cyanobacteria



Tropane

8-azabiciclo[3.2.1]ottano

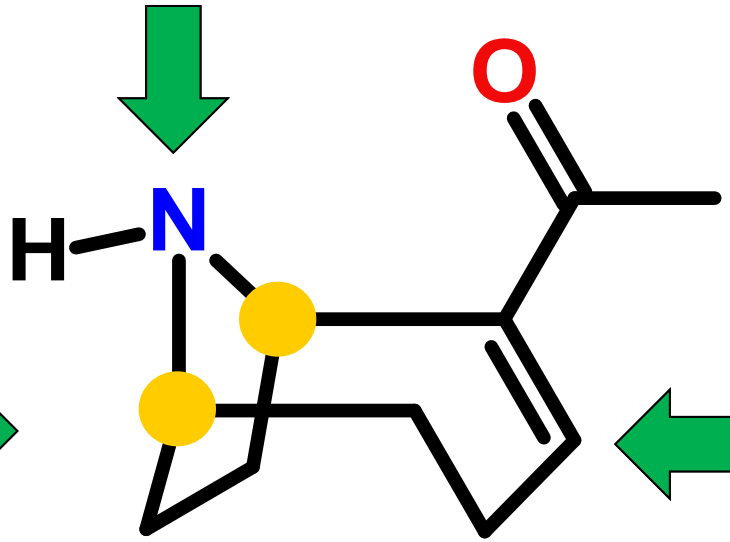


Homotropane

9-azabiciclo[4.2.1]nonane

Just a prototype of nicotinic agonist… again from mother nature: Anatoxin-A, a cyanotoxin produced by multiple genera of cyanobacteria

pKa = 9.4



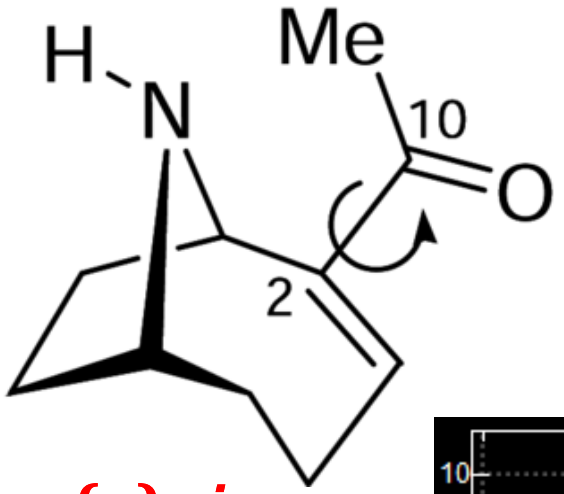
logP = 0.9

Michael addition

(+) Anatoxin-A

1-(9-azabicyclo[4.2.1]non-2-en-2-yl)ethan-1-one

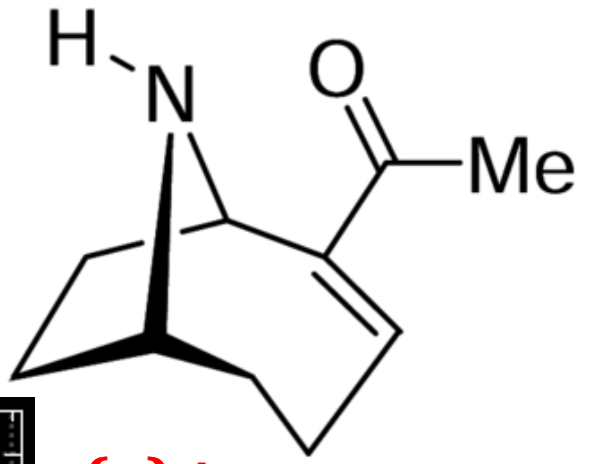
Just a prototype of nicotinic agonist… again from mother nature: Anatoxin-A, a cyanotoxin produced by multiple genera of cyanobacteria



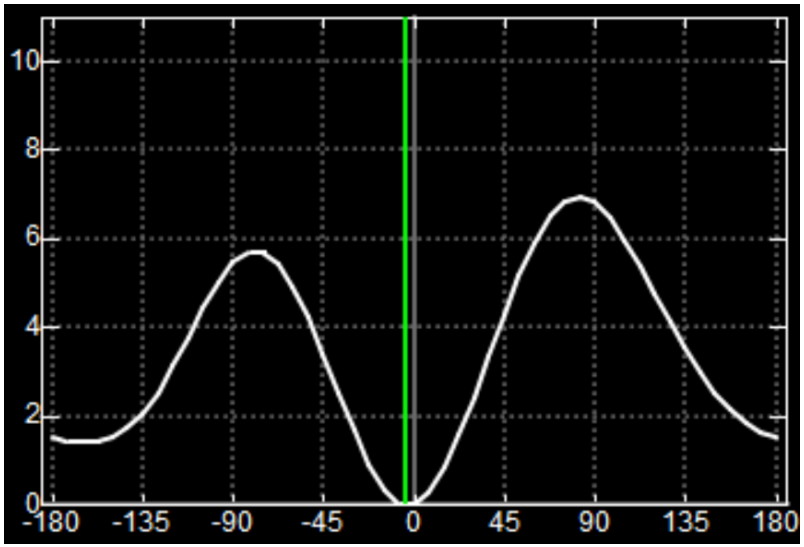
(+) *cis*

rotation

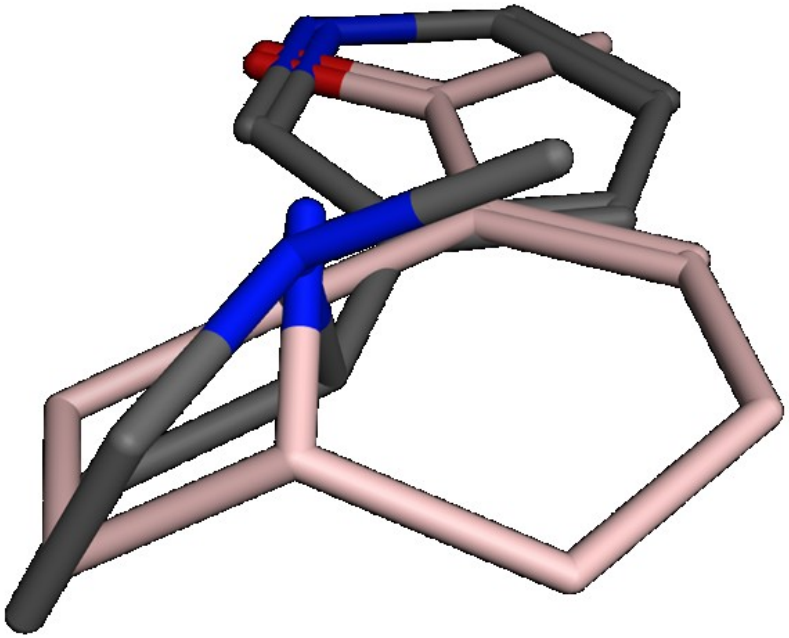
about *C(2)-C(10)*



(+) *trans*



Just a prototype of nicotinic agonist… again from mother nature: Anatoxin-A, a cyanotoxin produced by multiple genera of cyanobacteria



Nicotinic activity!!!