تفريغ ميديسينال

محاضرة: Cholinergic agonist

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لجان الرفعات

Soul Academy

Patrick

An Introduction to Medicinal Chemistry 3/e

Chapter 22

CHOLINERGICS, ANTICHOLINERGICS & ANTICHOLINESTERASES

Part 1: Cholinergic agonists

CHOLINERGIC AGONISTS

Updated by :Dr. Dana Atoum

لما نحكي Cholinergic system رح يخطر ببالنا 2 receptor.

① الـ Nicotinic receptor ← تشتغل على الـ skeltal muscle يعمل relaxation, contraction لـ muscle

② Muscarinic recpt ← تشتغل على smooth muscl و Cardic muscle ويحفزوا الـ Parasympathetic

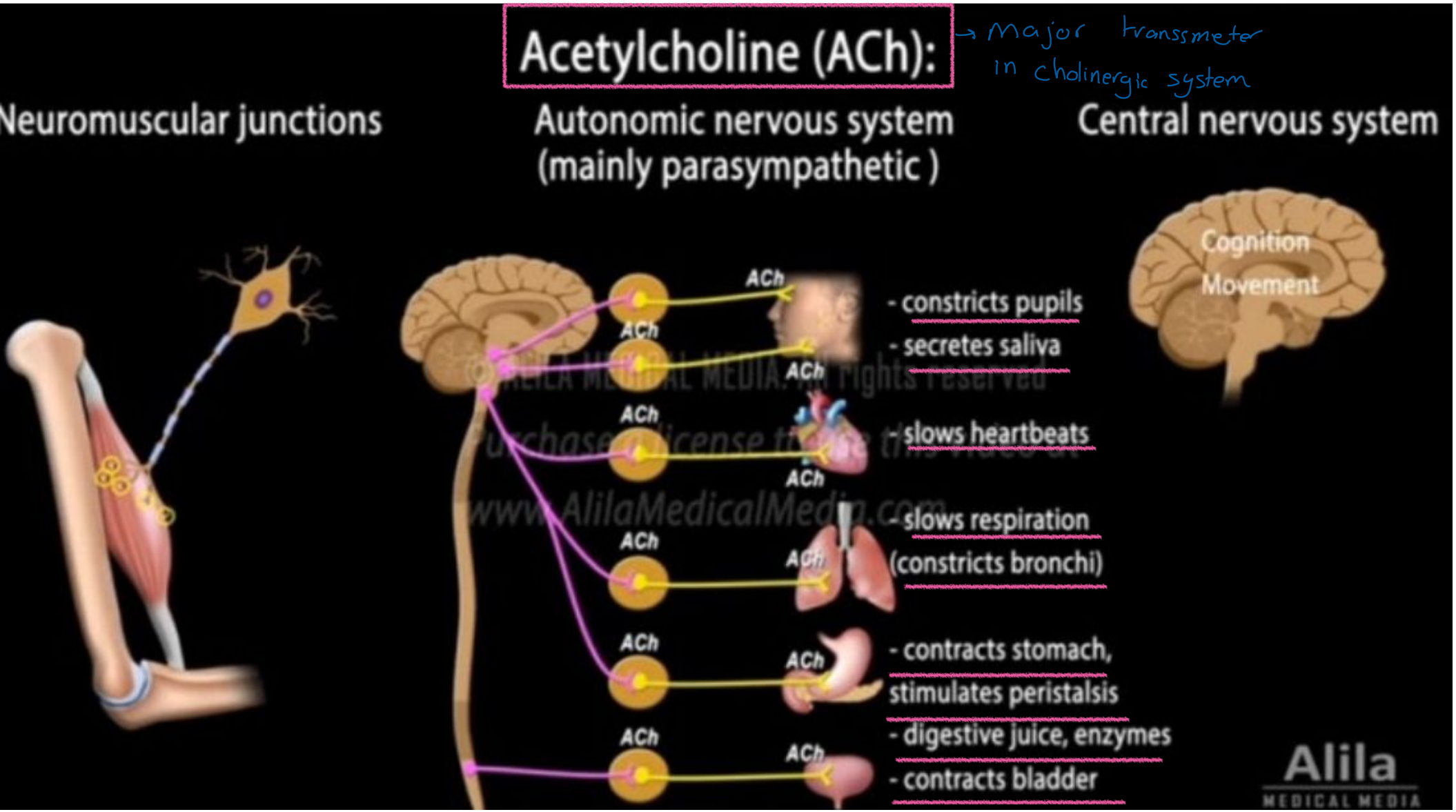
لما نحكي Parasympathetic يعني اكيد بيشتغلوا على different site يعني non-selective

الـ Nicotinic بيشتغل على الـ recptor من α_1 لـ α_{10}

الـ Muscarinic بيشتغل على الـ recptor من M_1 لـ M_5

الـ Nicotine بيشتغل برضه على الـ synaps (central nervous system)

1. Nerve Transmission



1. Nerve Transmission

Peripheral nervous system

The motor nerves of the PNS have been classified into three subsystems: the **somatic motor nervous system**, the **autonomic motor nervous system**, and the **enteric nervous system**.

في عنا 2 type of nerve

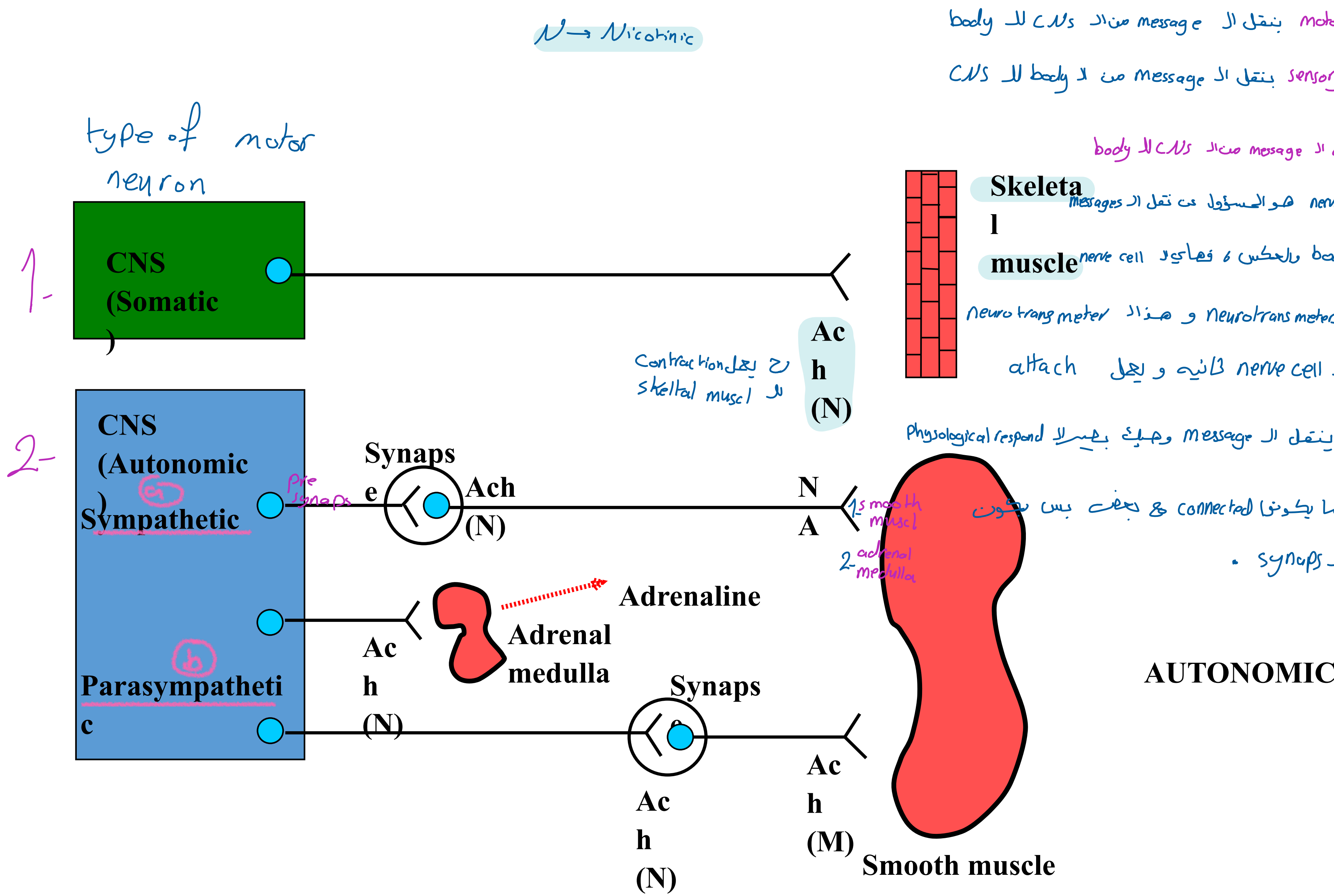
① motor nerve بنقل ال message من ال CNS للـ body

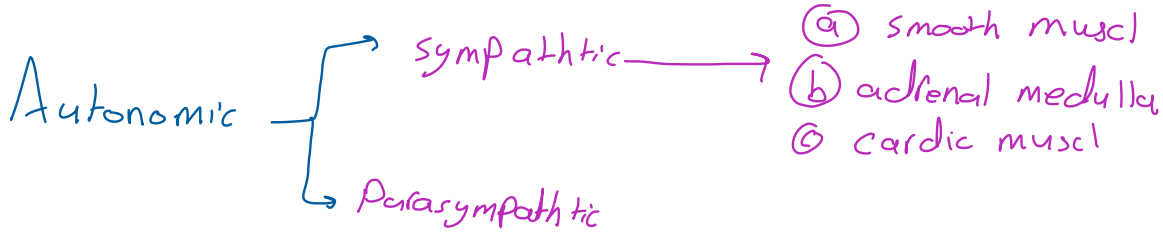
② sensory nerve بنقل ال message من ال body للـ CNS

كيف رح ينتقل ال message من ال CNS لل body

في عنا ال nerve cell هو المسؤول عن نقل ال messages من ال CNS لل body والعكس ، فهاي ال nerve cell بتعمل release للneurotransmeter و هاذ ال neurotransmeter رح يروح لل nerve cell الثانية و يعمل attach عليها لحتى ينتقل ال message وهيك بصير ال Physiological respond

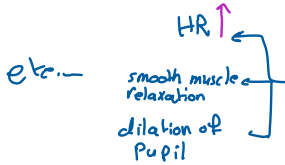
ال neuron لما يكون connected & بعض بس بكون بينهم ال synaps .





كيف يحفز الsympathtic ؟؟

لما يصير releas الAch من الPre-synaps ويرتبط بالmuscrnic receptor الموجود على الPost-synaps رح ينقل massag وهيك



ورح يصير عنا sympathtic الرح يحفز الNor-adrenalin لينتج 2nd neuro رح تحفز الmessag

ومعطى يصير by basr الـ2nd neuron ويروح مباشرة لـadrenal medulla ويعمل إلها Simulation لحتى تفرز الAdrenalin

ويعمل symathtic effect.

طيب كيف رح تحفز الParasympathtic

اذا طلع Ach من الneuron الـ(Pre-synaps) رح يرتبط بـ2nd neuron ويحفزه لينتج الAch كمان وهيك رح يعمل Parasympathtic effect

The peripheral nervous system (PNS) is so called because it is peripheral to the central nervous system (CNS; the brain and spinal column).

- Sensory nerves take messages from the body to the CNS;
- Motor nerves carry messages from the CNS to the rest of the body.

An individual nerve cell is called a neuron, and neurons must communicate with each other in order to relay messages. However, neurons are not physically connected. Instead, there are gaps which are called synapses. If a neuron is to communicate its message to another neuron (or a target organ), it can only do so by releasing a chemical that crosses the synaptic gap and binds to receptors on the target cell.

This interaction between neurotransmitter and receptor can then stimulate other processes, which, in the case of a second neuron, continues the message.
As these chemicals effectively carry a message from a neuron, they are known as chemical messengers or neurotransmitters. There are a large number of neurotransmitters in the body, but the important ones in the peripheral nervous system are acetylcholine and noradrenaline

1- The somatic motor nervous system

The somatic motor nerves carry messages from the CNS to the skeletal muscles. There are no synapses en route, and the neurotransmitter at the neuromuscular junction is **acetylcholine**. Acetylcholine binds to **cholinergic receptors** within the cell membranes of muscle cells, and the final result is contraction of skeletal muscle.

2- The autonomic motor nervous system

The autonomic motor nerves carry messages from the CNS to smooth muscle, cardiac muscle, and the adrenal medulla. It is divided into the **sympathetic** and **parasympathetic** systems.
Sympathetic neurons quickly synapse with a second neuron using **acetylcholine**. This second neuron releases **noradrenaline**, which binds to **adrenergic receptors** in target organs. Noradrenaline increases heart rate, relaxes smooth muscle, slows digestion and urination, reduces salivation, and dilates peripheral blood vessels—supporting the "fight or flight" response.

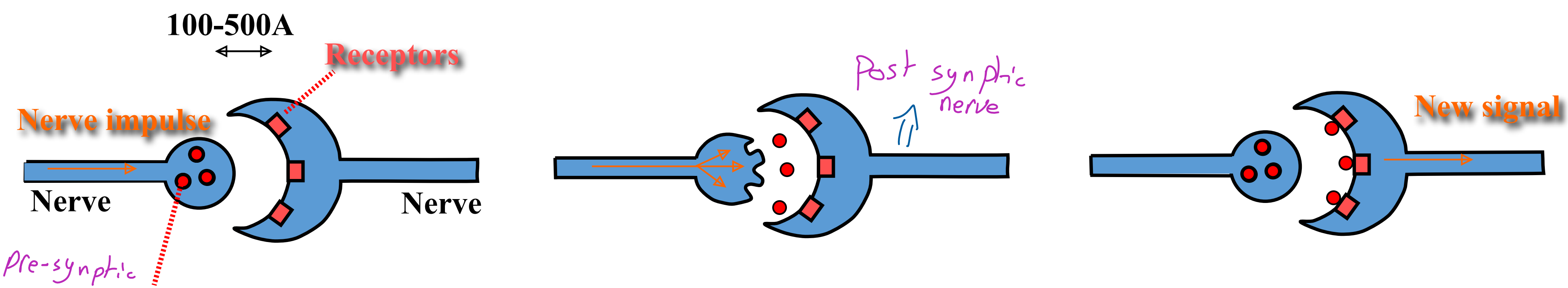
بدء sympathtic effect ال

Some sympathetic neurons bypass a second neuron and directly stimulate the **adrenal medulla**, releasing **adrenaline** into the bloodstream. Adrenaline enhances noradrenaline's effects throughout the body.

Parasympathetic neurons travel farther before synapsing with a second neuron, also using **acetylcholine**. The second neuron targets the same organs as the sympathetic system, but again releases acetylcholine, which binds to **cholinergic receptors** and causes opposite effects—slowing heart rate, promoting digestion, and supporting "rest and digest" functions.

1. Nerve Transmission

Synapses



Vesicles containing neurotransmitters

Release of neurotransmitters

Receptor binding and new signal

بصير عنده biosynthesis لل Ach

Cholin + Acytel CoA = Ach

شو اسم ال enzym الي رح يربط ال cholin مع ال Acytel CoA ⇐ cholin acytel transferas

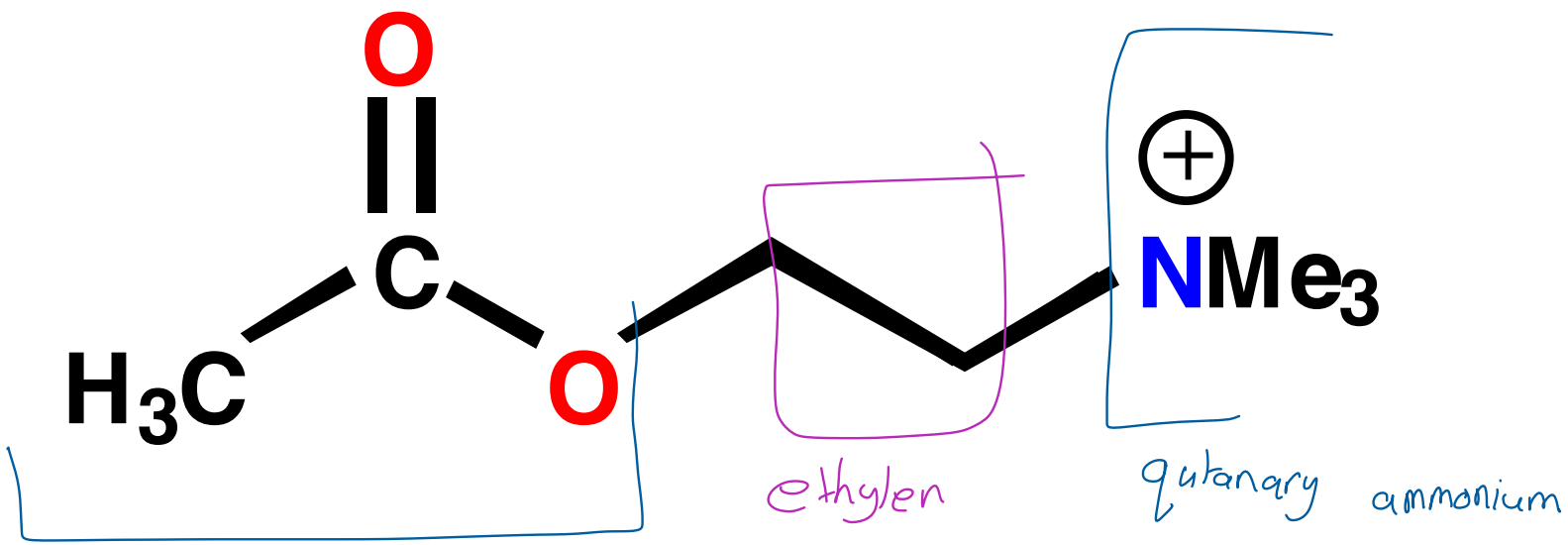
ال Ach رح يطلع إله release من ال Pre synptic nerve

ورح يروح لل post synptic nerve

هون ارتبط ال Ach بال Post synptic nerve

2. Neurotransmitter

Acetylcholine (Ach)



Acetyl **Choline**

The Cholinergic Signaling System

At synapses using **acetylcholine (ACh)** as the neurotransmitter, such as between two neurons or a neuron and muscle cell, the following steps occur:

1. **Biosynthesis**: ACh is synthesized from **choline** and **acetyl coenzyme A** by the enzyme **choline acetyltransferase** at the end of the presynaptic neuron.

2. **Vesicle packaging**: ACh is stored in membrane-bound vesicles via a specific transport protein

3. **Release**: A nerve signal opens **calcium channels**, increasing intracellular calcium, which triggers vesicle fusion with the membrane and ACh release into the synaptic gap.

4. **Receptor binding**: ACh crosses the gap and binds to **cholinergic receptors**, stimulating the postsynaptic cell.

5. **Breakdown**: ACh is broken down by **acetylcholinesterase** on the postsynaptic membrane into **choline** and **acetic acid**.

6. **Reuptake**: Choline is reabsorbed into the presynaptic neuron to restart the cycle.

Presynaptic Control Systems

Cholinergic synapses contain **autoreceptors** on the presynaptic neuron. When activated by ACh, they **inhibit further ACh release** for local feedback control.

Additionally, **noradrenaline receptors** on the presynaptic neuron provide another layer of regulation. When the sympathetic nervous system is active, noradrenaline binds to these receptors, further **suppressing ACh release**. This enhances **sympathetic effects** by reducing cholinergic activity. The chemical messenger **nitric oxide (NO)** can also influence acetylcholine (ACh) release—**promoting** its release. Many other messengers, including **co-transmitters**, are also involved in presynaptic control.

① بال Presynaptic nerve رح تصير عمليه ال biosynthesis لل Ach

② رح تصير عمليه store بال vesicel
وبعدين ال vesicel رح ترتبط بال membran
عن طريق transporter موجود ع
ال nerve membran

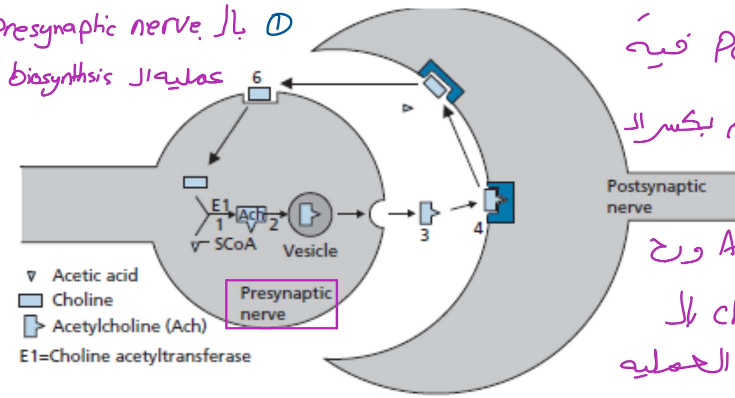


FIGURE 22.4 Synapse with acetylcholine acting as the neurotransmitter.

بال Post synaptic nerve فيه Ach-esteras ، وهو الإنزيم بكسر ال Ach بعد ما يعطي ال respond لـ cholin و Acetic acid ورح يصير reaptake لل cholin بال Presynaptic nerve وترجع العمليه تتكرر من الاول

③ رح يصير ال release لل Ach

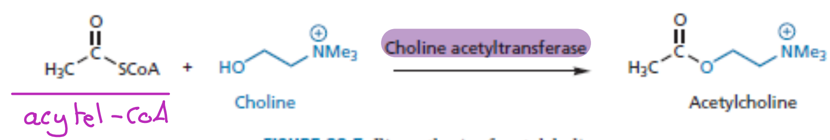


FIGURE 22.5 Biosynthesis of acetylcholine.

كل ال Post synaptic nerve في cholanergic recptor

وال Ach بده يرتبط فيه فشو بصير؟؟ لما يصير ال Fusion لل vescel بال membran رح يزيد ال intracellular Ca+ ولما يزيد ال Ca+ رح يصير ال release لل Ach بال synptic gap وال Ach رح يرتبط بال Post synptic nerve وهيك رح ينقل ال 2nd messenger او بعمل releas لـ other neurotransmitter

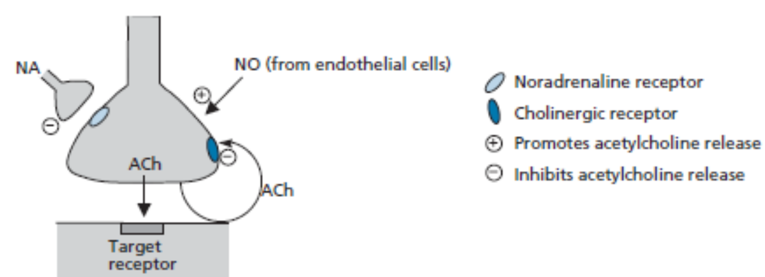
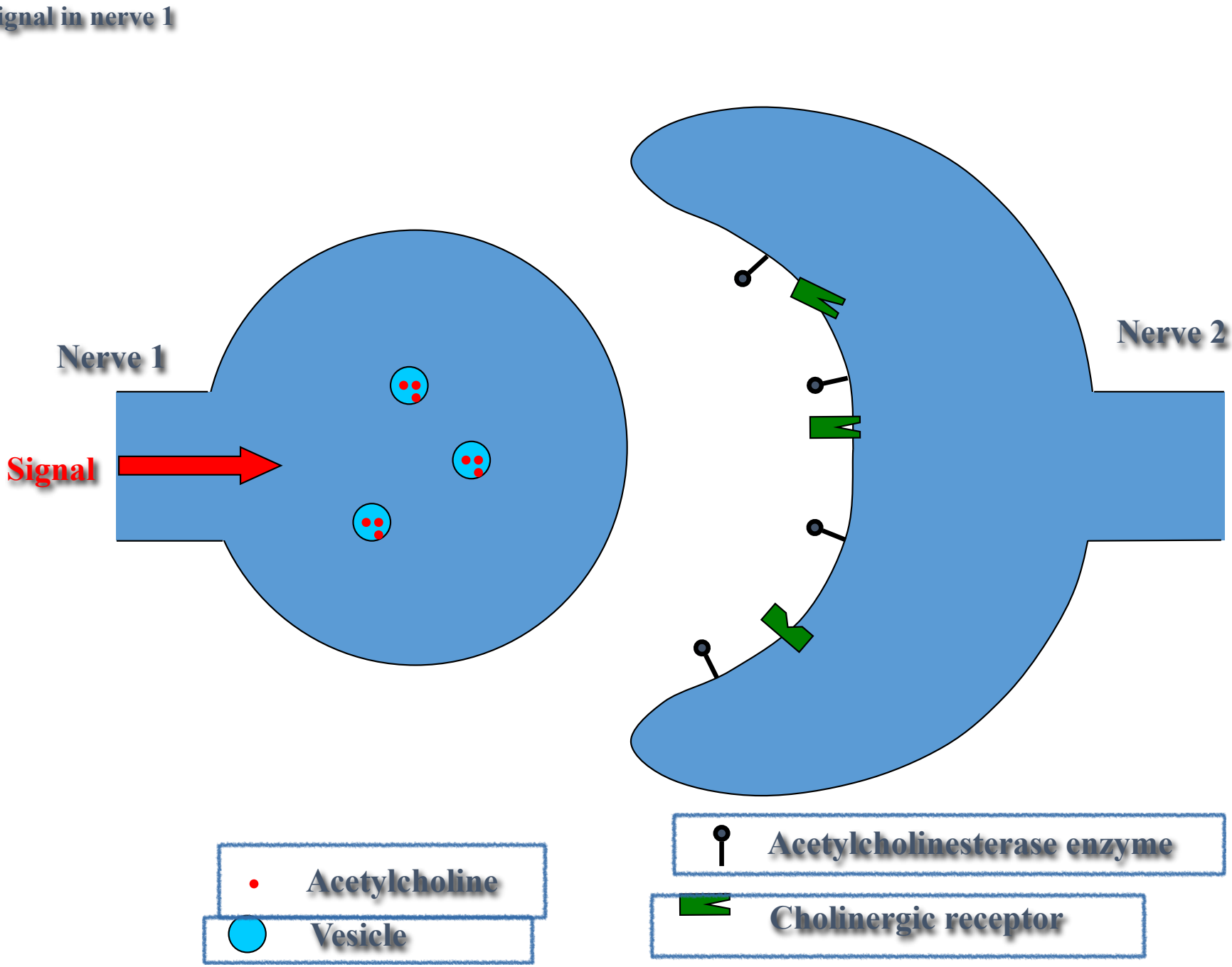


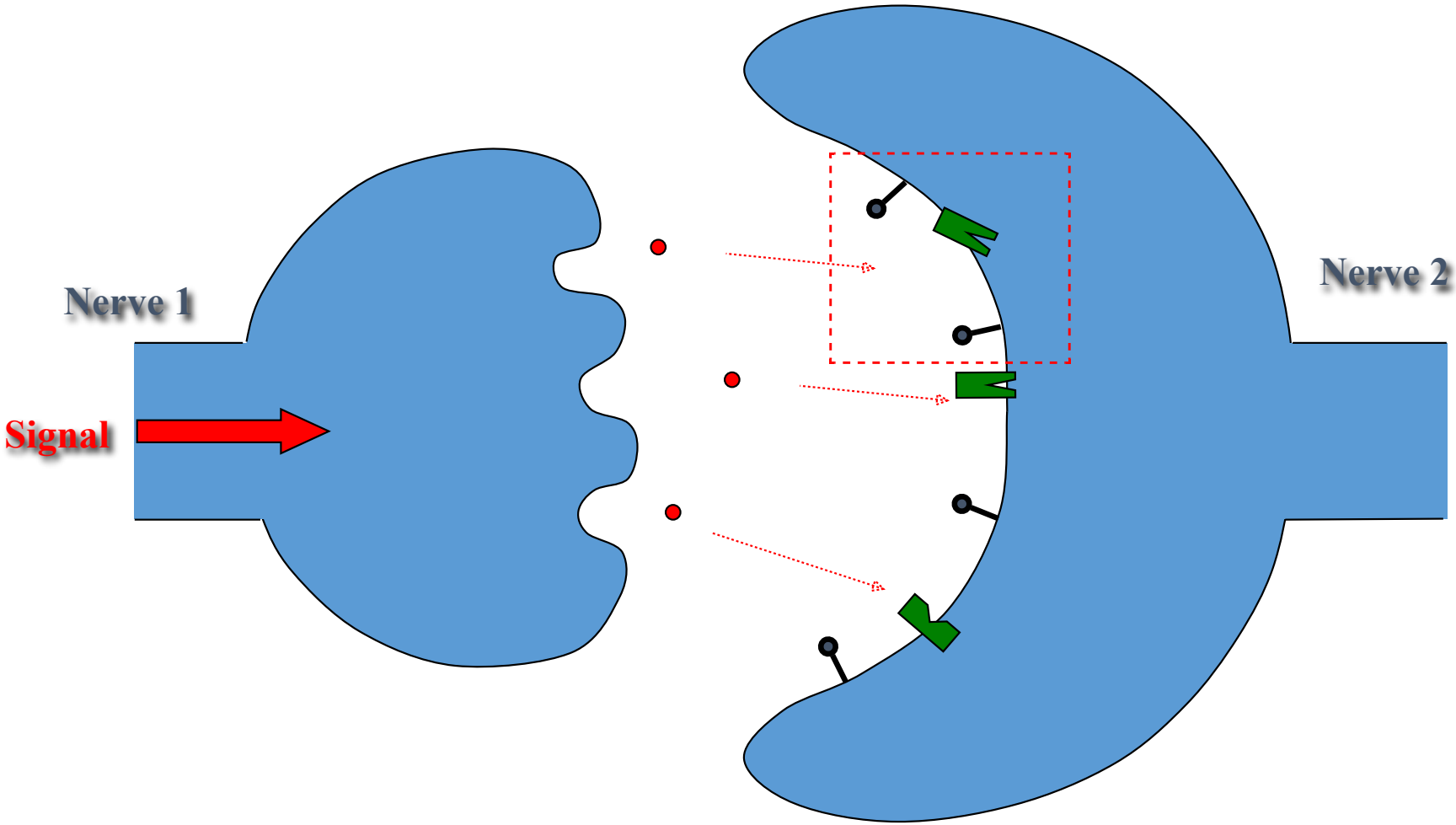
FIGURE 22.6 Presynaptic control systems.

3. Transmission process

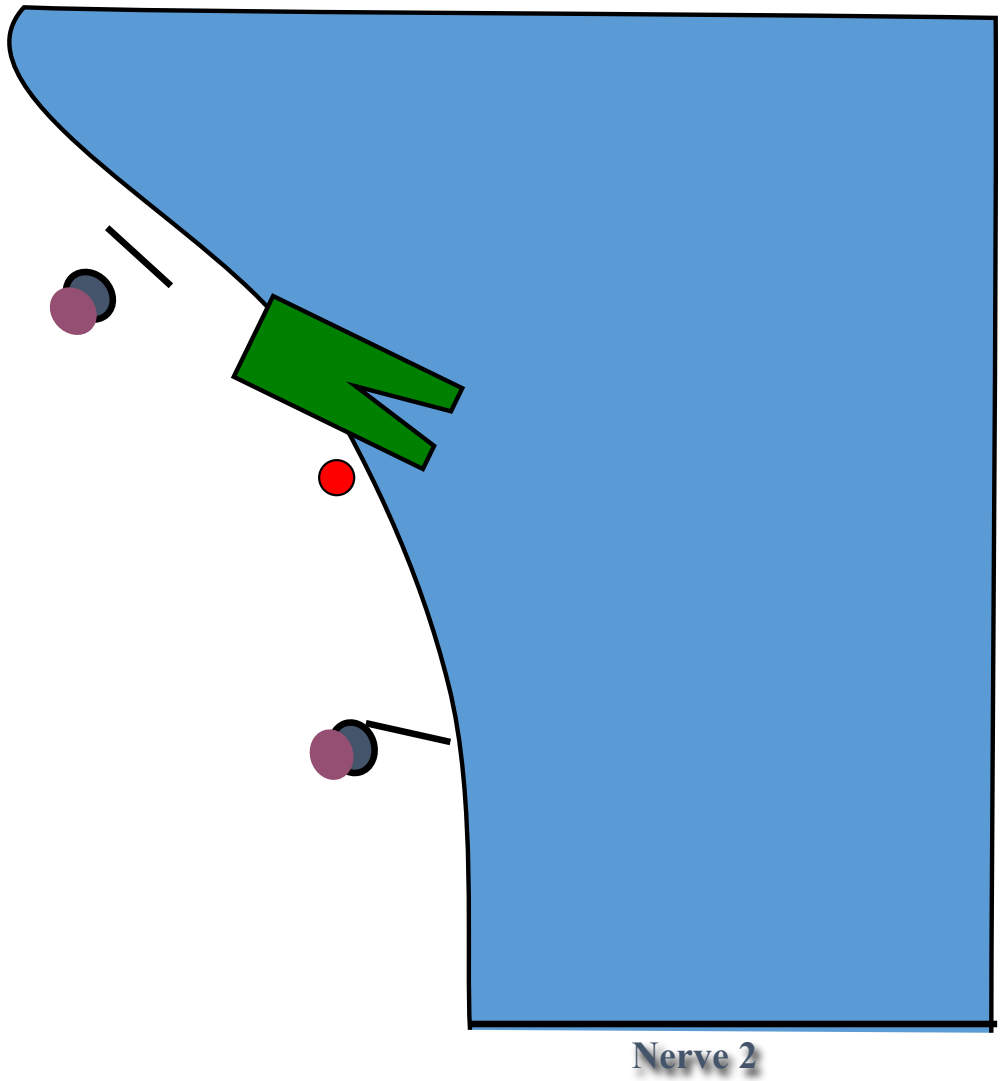


3. Transmission process

Vesicles fuse with membrane and release Ach

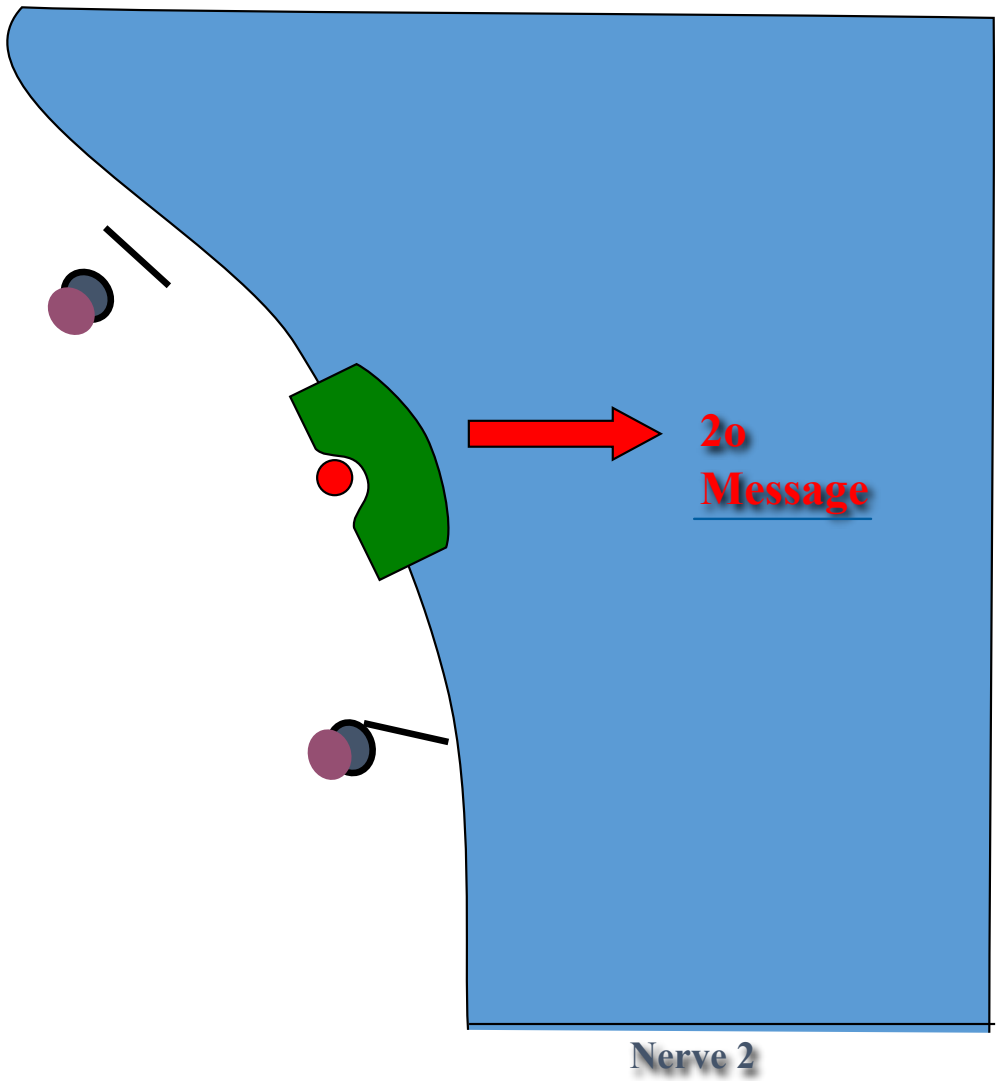


3. Transmission process



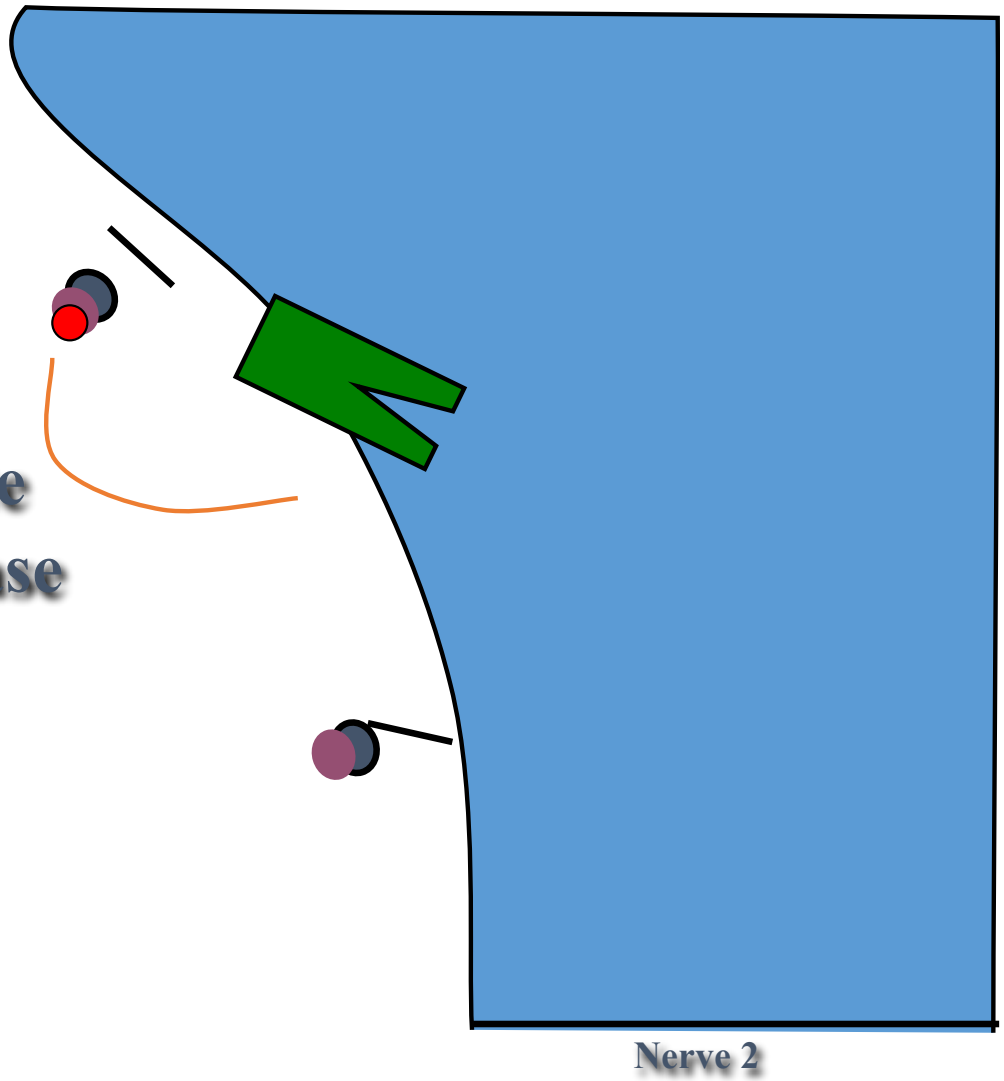
3. Transmission process

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



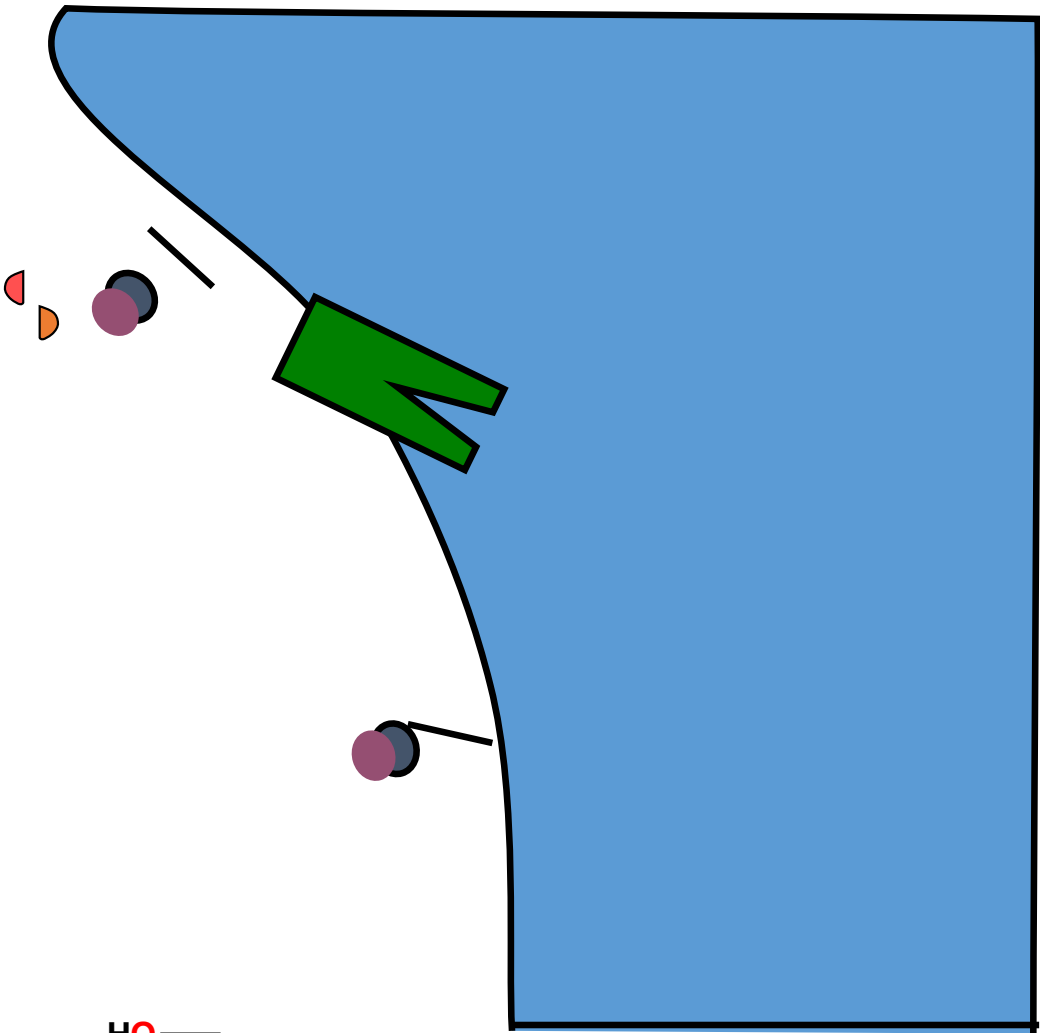
3. Transmission process

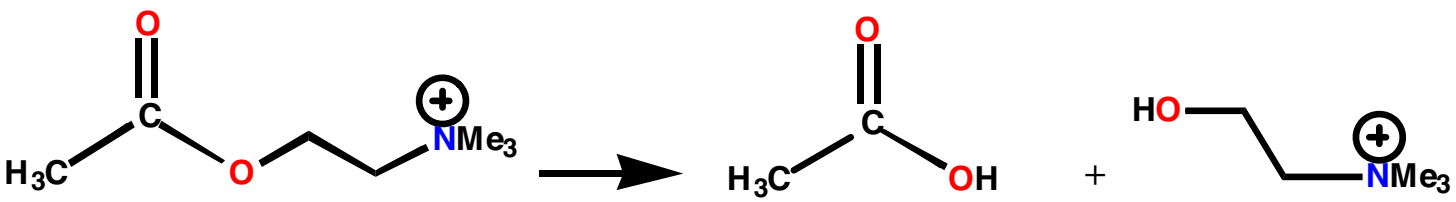
Ach departs receptor
Receptor reverts to resting state
Ach binds to acetylcholinesterase



3. Transmission process

Ach hydrolysed
by acetylcholinesterase





Acetylcholine

Acetic acid

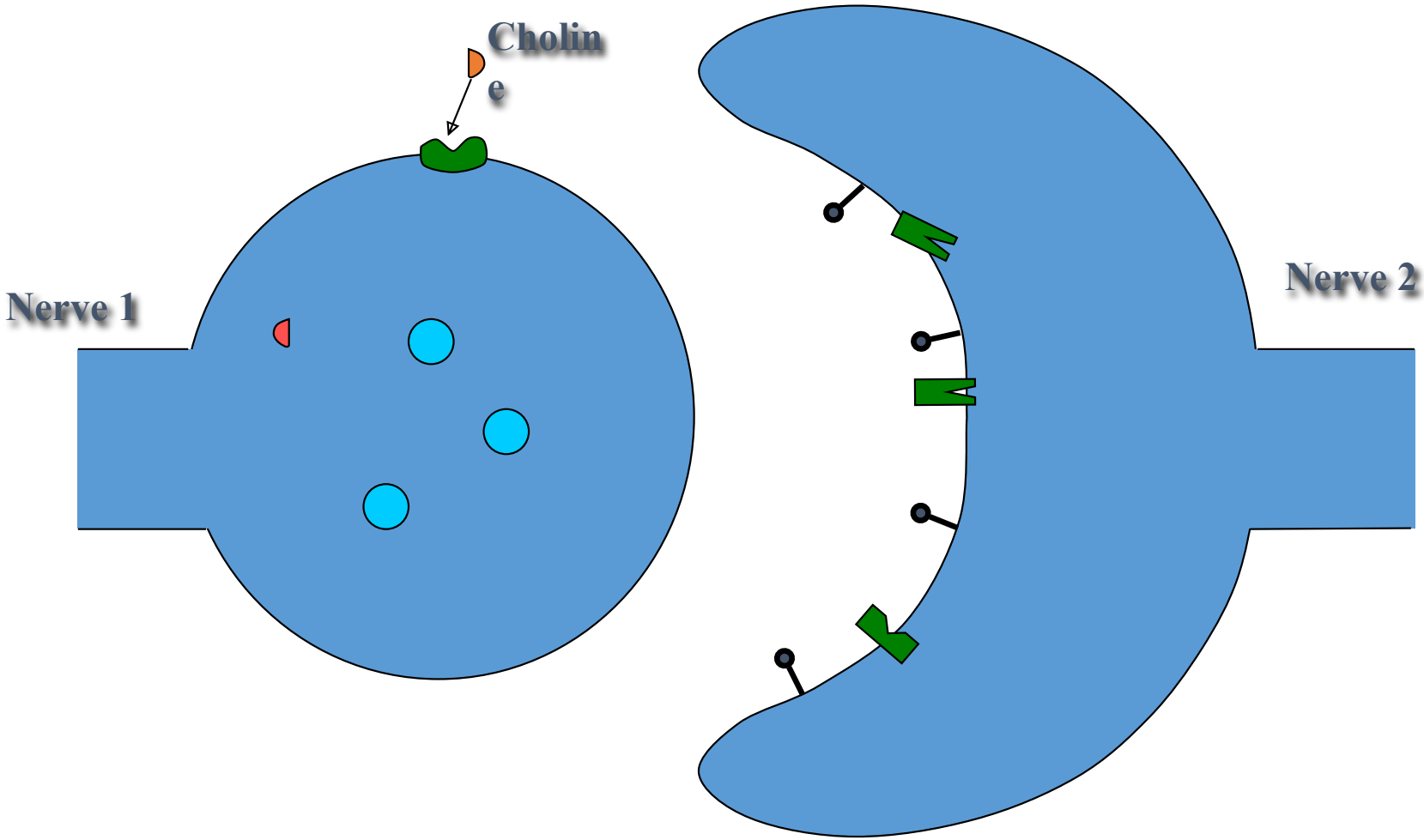
+

Choline

3. Transmission process

Choline binds to carrier protein

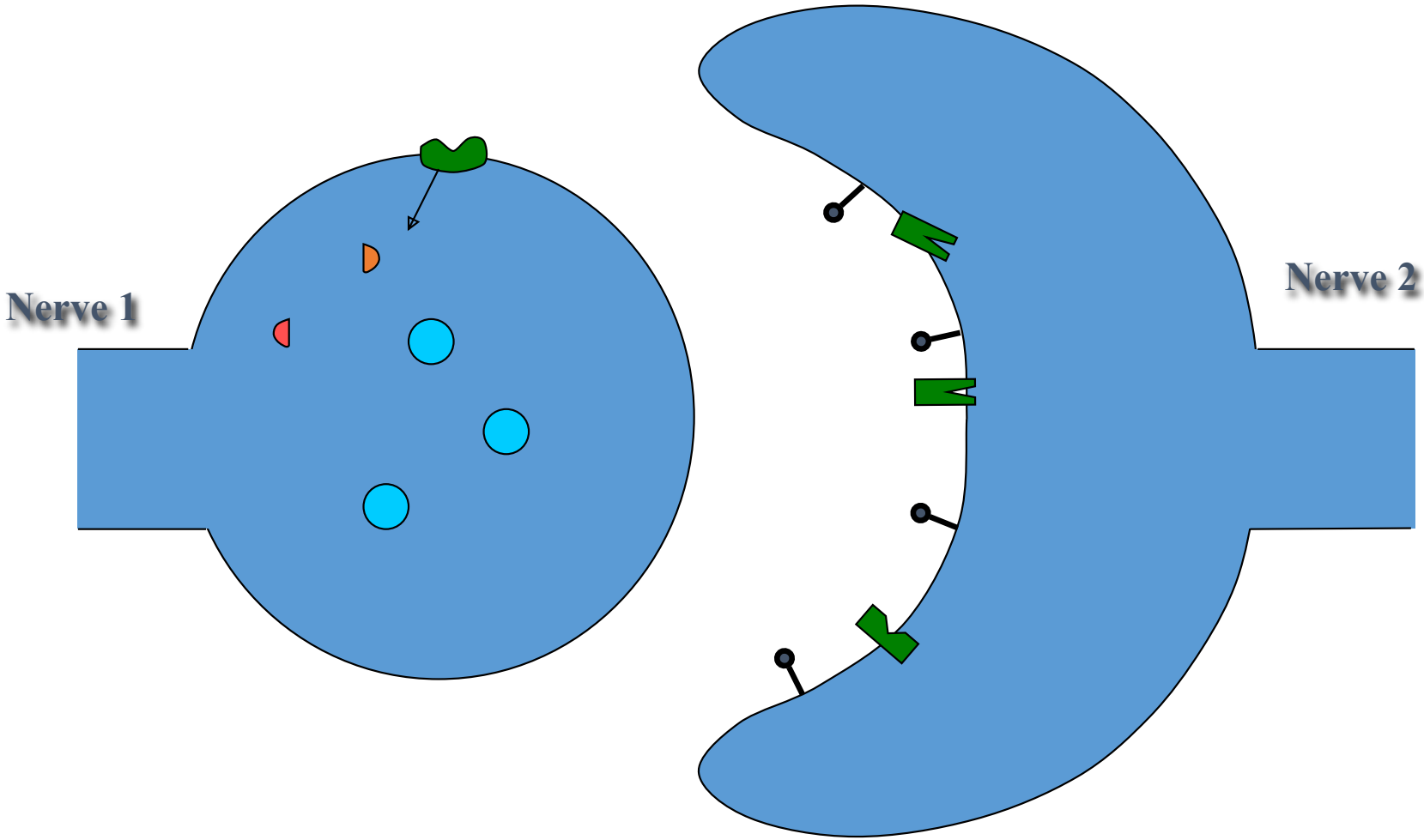
reaptake



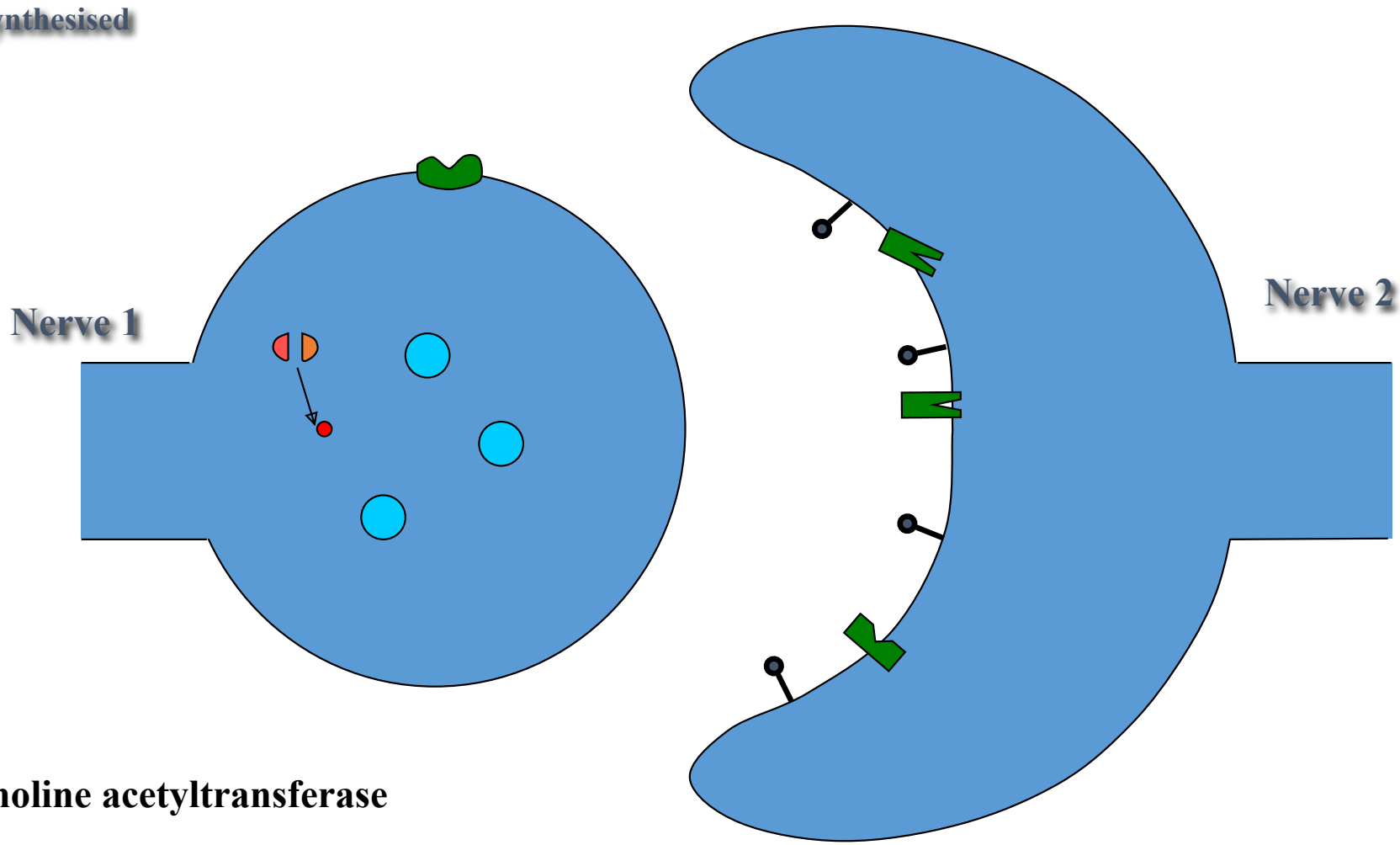
Carrier protein for choline

3. Transmission process

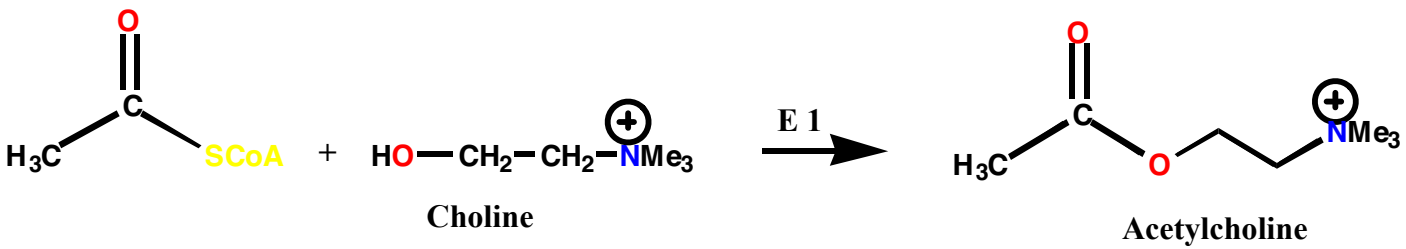
Choline transported into nerve



3. Transmission process

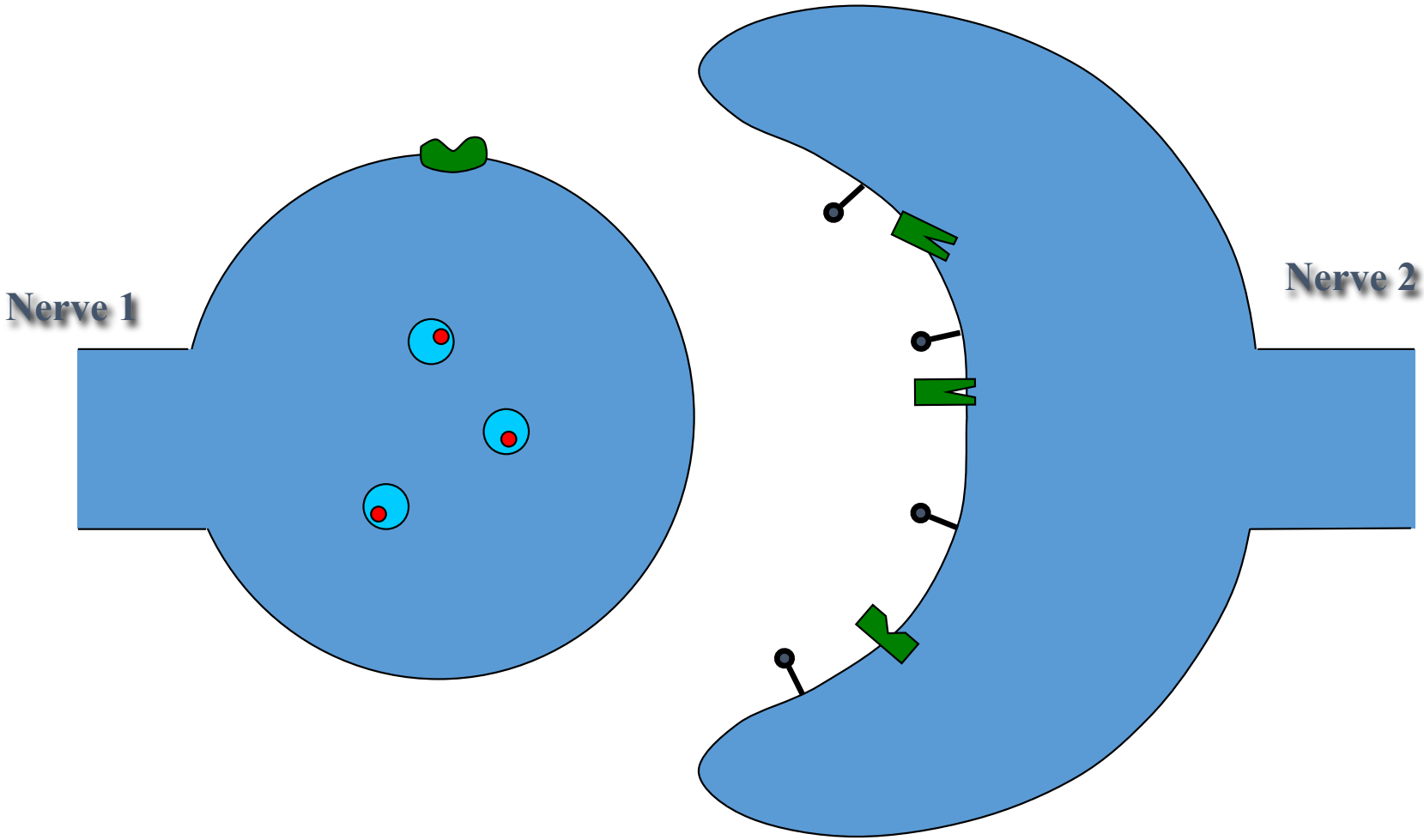


E 1 = Choline acetyltransferase



3. Transmission process

Ach repackaged in vesicles



Why Not Just Use Acetylcholine as a Drug?

Although acetylcholine (ACh) can be easily synthesized, it's not practical to use as a drug for three main reasons:

1. •It's **rapidly broken down in the stomach** by acid and cannot be taken orally.
2. •It's **quickly hydrolyzed in the blood** by esterase enzymes.
3. •It **lacks selectivity**, activating all cholinergic receptors throughout the body.

To overcome this, we need **ACh analogues** that are more stable and **selective** in their action.

بيشتغل على ال Nicotinic و Muscrinic فممكن
يعطي effect على ال smooth muscel و ال skeltal muscel إلى
several side effect

اذا بدي استخدم ال Ach لازم اخليه selectiv

Achieving Selectivity

While nicotine and muscarine showed the principle of receptor selectivity, they are unsuitable as medicines due to **side effects** from acting on multiple receptors.

Effective drug design aims for:

هون بحكي على اي اساس
بصنع ال drug

1. •**Receptor class selectivity** (e.g. cholinergic vs. adrenergic).
2. •**Receptor type selectivity** (e.g. muscarinic vs. nicotinic).
3. •**Receptor subtype selectivity** (e.g. M1–M5 for muscarinic, α1–α10 for nicotinic).

The discovery of receptor subtypes has driven the development of more **targeted and safer** drugs.

كيف احصل ال selectivity ؟؟

في بالجسم نوعين cholinergic effect وهما muscrin و nicotin وعن طريقهم عرفوا

انه ال Ach بيرتبط بال nicotinic و muscrinic (همة سبب تسميتهم هيك) فبصنع ال drug بناءً على وين
بدي اياه يروح وعلى اي receptor يشتغل

The **cholinergic nervous system** uses **acetylcholine (ACh)** as a neurotransmitter. It includes motor nerves to **skeletal muscle**, **neuron-to-neuron synapses** in the PNS, and **parasympathetic nerves** to smooth and cardiac muscle.

•**Two receptor types**:

Muscarinic – in smooth and cardiac muscle

Nicotinic – in skeletal muscle and nerve synapses

Nicotinic vs. Muscarinic Receptors

The existence of receptor subtypes was first suggested by the differing actions of two natural compounds:

•**Nicotine**, from tobacco, activates receptors in **skeletal muscle and neuron synapses**.

•**Muscarine**, from poisonous mushrooms, acts on **smooth and cardiac muscle**.

These led to the identification of two main types of cholinergic receptors:

•**Nicotinic receptors** – found in skeletal muscle and synapses.

•**Muscarinic receptors** – found in smooth and cardiac muscle.

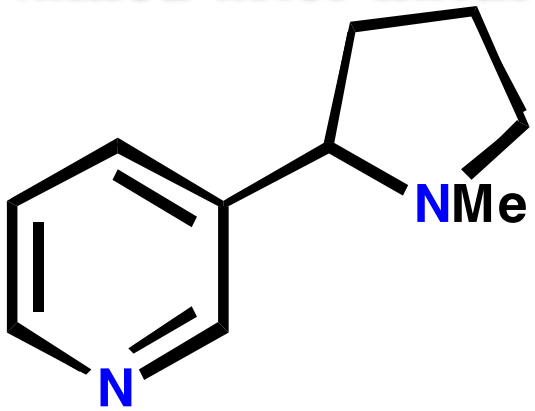
4. Cholinergic receptors

شكل ال cholinergic receptors ما بشبهوا بعض

Receptor types

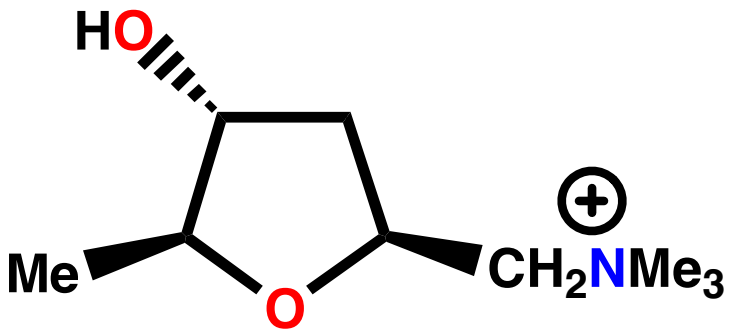
ال structure حفظ !

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



Nicotine

Activates cholinergic receptors at nerve synapses and on skeletal muscle



L-(+)-Muscarine

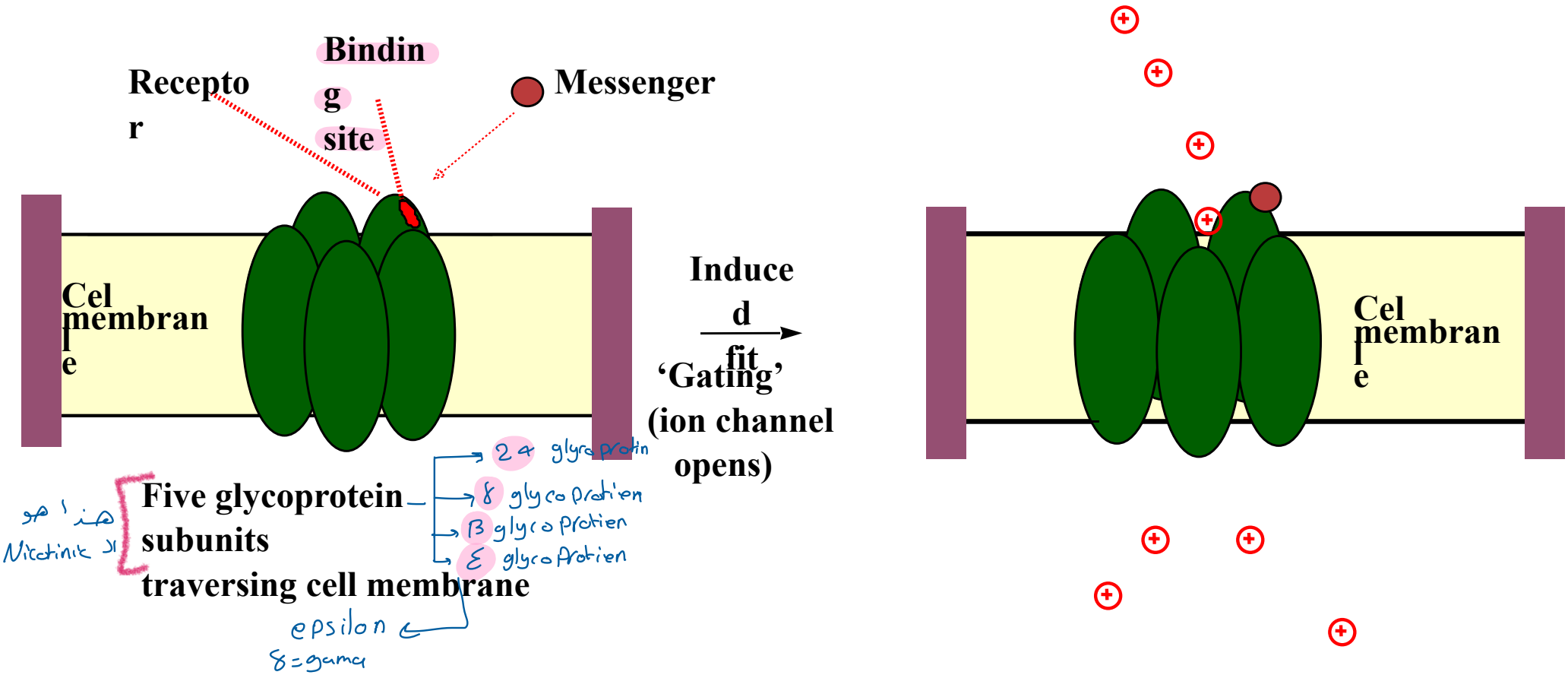
Activates cholinergic receptors on smooth muscle and cardiac muscle

Acetylcholine is natural messenger for both receptor types

4.1 Nicotinic receptor → ion channel receptor

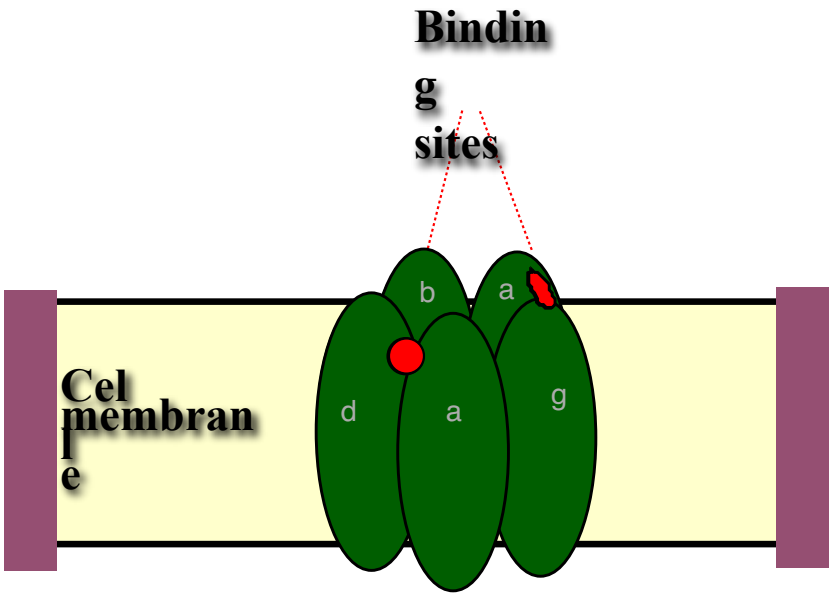
Control of Cationic Ion Channel:

لما الـ messenger يرتبط بالـ binding site ع ر يغير
ion channel الـ من ion الـ releas

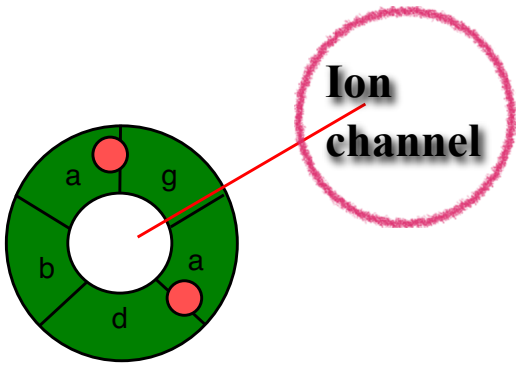


4.1 Nicotinic receptor

The binding sites



2xa, b, g, d subunits



Two ligand binding sites mainly on a-subunits

a-subunit ال كل يعني binding ال

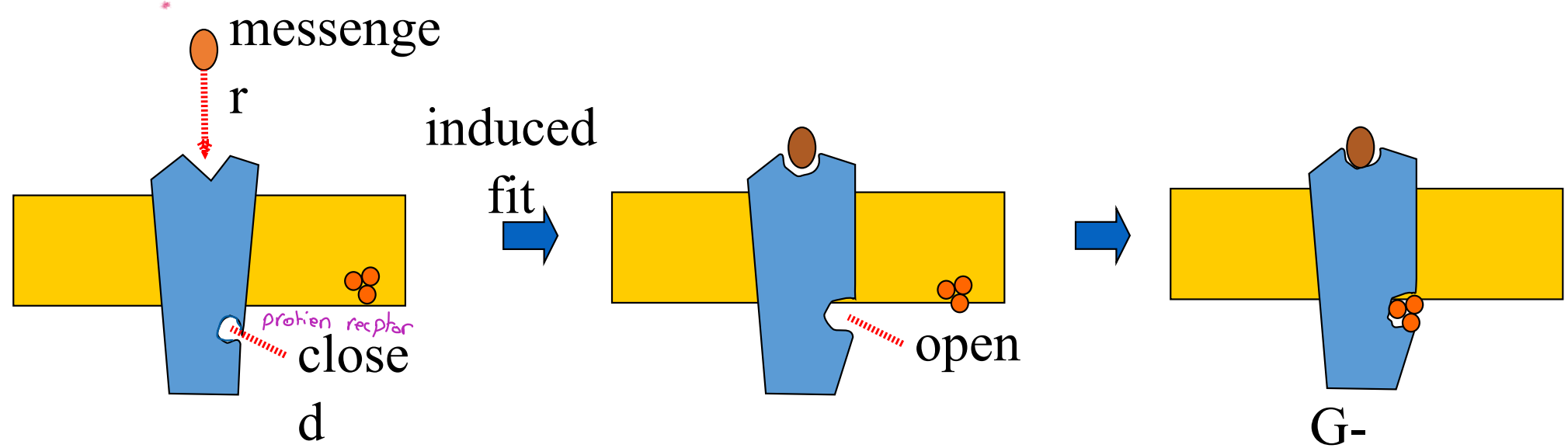
4.2 Muscarinic receptor - G Protein coupled receptor

Activation of a signal protein

شكل ال Muscrinic عبارة عن Coupled protien receptor

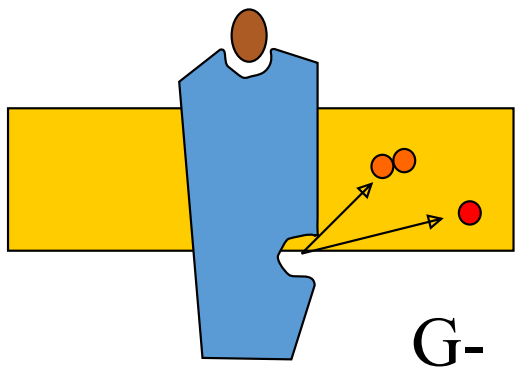
Receptor binds messenger leading to an induced fit

Opens a binding site for a signal protein (G-protein)



قبل ما يرتبط ال Message بال binding site يكون

لما يصير ، بين Closed يكون protien receptor ال



الإرتباط ح يصير ول ope ح G-protien

يرتبط فيه وصلة ال protien receptor يصير Split

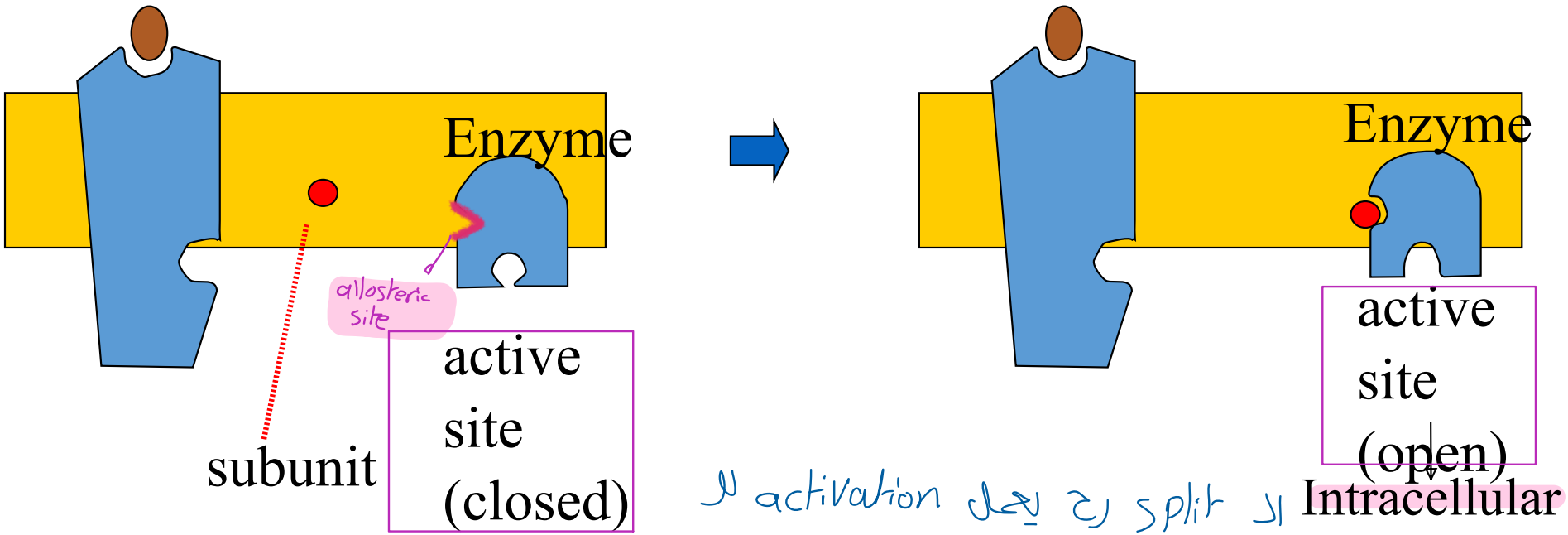
ورح يعطي intracellular_signal

G-
protein
split

4.2 Muscarinic receptor - G Protein coupled receptor

Activation of membrane bound enzyme

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



ال split رح يصل لل activation
وهيك ال allosteric site بالبروتين active site
رح يفتح ورح يعطي ال signal

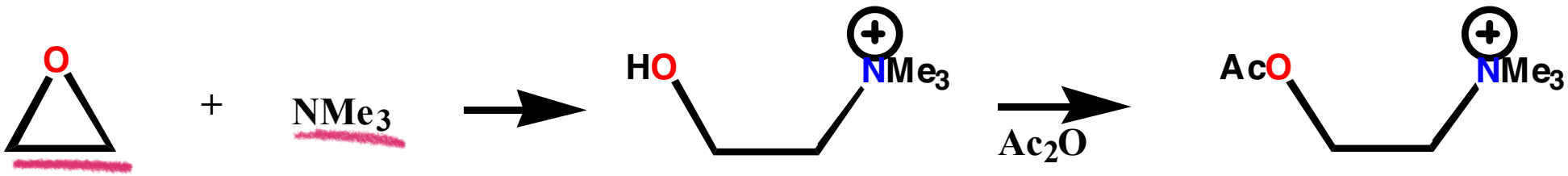
5. Cholinergic agonists

حكينا انواع الـ Ach مالله
محيث organ & selectivity

5.1 Acetylcholine as an agonist

Advantages

- Natural messenger
- 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

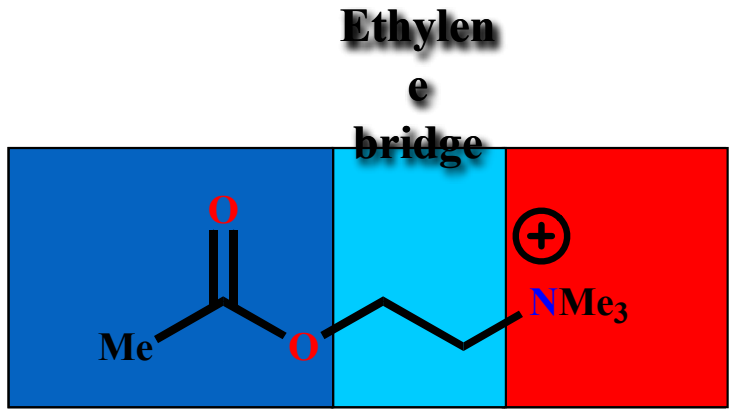
إذا بدي اعمل drug إلها cholinergic effect
هاي الخصائص اللي لازم تكون فيه

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

لازم اعرف binging site
والشكل اللي drug لازم يكون
يشبه الـ SAR تبع الـ acytetchdin

6. SAR for acetlcholine

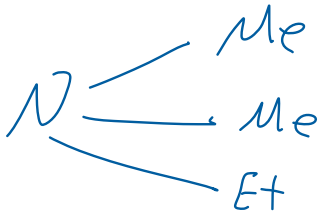
الشروط اللي لازم تكون موجودة بال N
1 charg (+)
2 اقل اشي يكون فيه Me وحدة
وممكن تكون عليها Ethyl بس
مش اكبر من هيك لانه رح يصير
antagonist



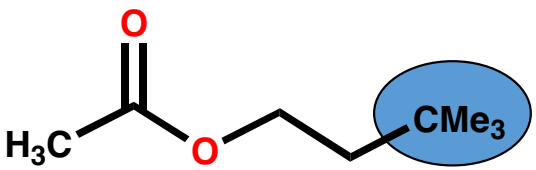
Acetoxy

4°Nitrogen

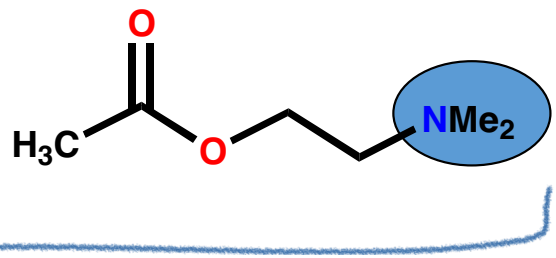
(+)charg عليها
stabel ويكون



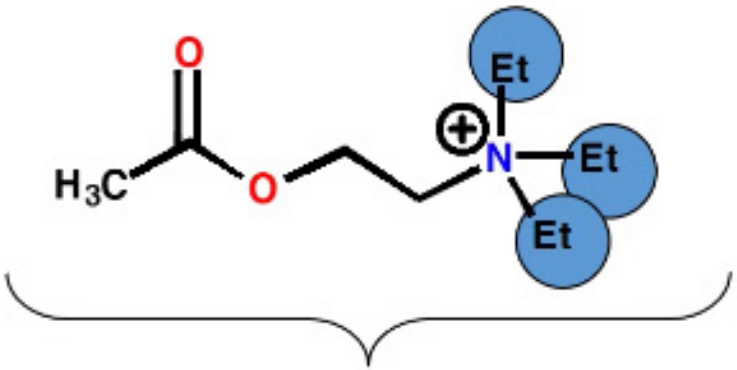
Quaternary nitrogen is essential



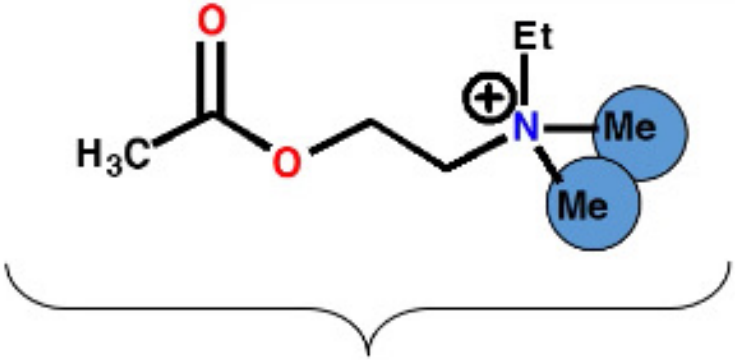
Bad for activity



active



Bad for activity



Active

رح نخسر ال activity
لازم على الاقل يكون فيه Me وحده

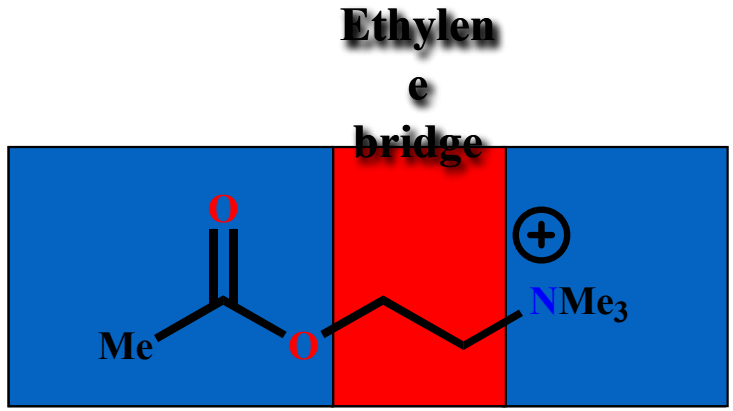
Structure–Activity Relationship (SAR) of Acetylcholine (ACh):

•**Lead compound**: Acetylcholine is used to study receptor interaction.
•SAR findings apply to both **nicotinic and muscarinic receptors**.

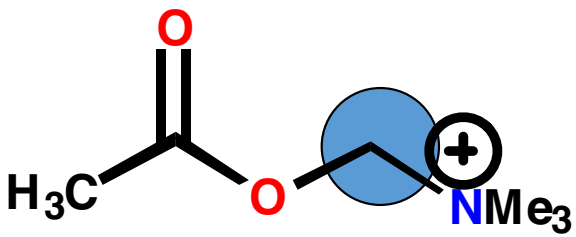
Key Features Required for Activity:

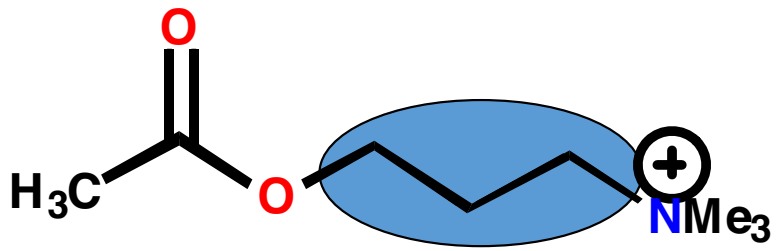
●The **positively charged nitrogen** atom is essential for activity. Replacing it with a neutral carbon atom eliminates activity.
●The **distance** between the nitrogen and the ester group is important for maintaining activity.
●The **ester functional group** is crucial to the compound's effectiveness.
●The **overall size** of the molecule cannot be altered significantly; larger molecules have poorer activity.
●The **ethylene bridge** between the ester and the nitrogen atom cannot be extended.
●There must be **two methyl groups** on the nitrogen. A larger, third alkyl group is tolerated, but more than one large alkyl group results in a loss of activity.
●**Bigger ester groups** lead to a reduction in activity.

6. SAR for acetylcholine



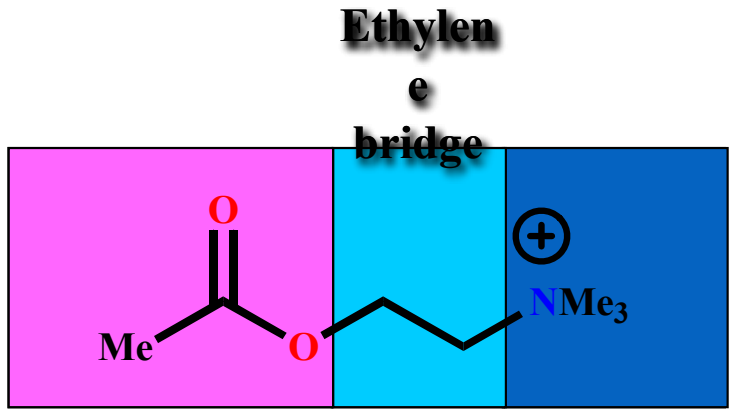
- Distance from quaternary nitrogen to ester is important
- Ethylene bridge must be retained



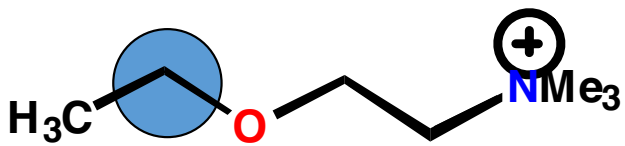


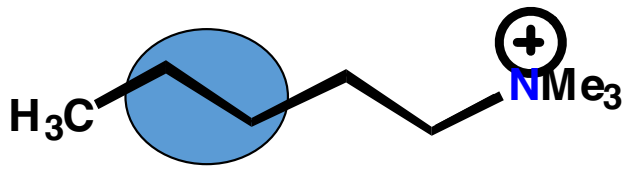
Bad for activity

6. SAR for acetylcholine



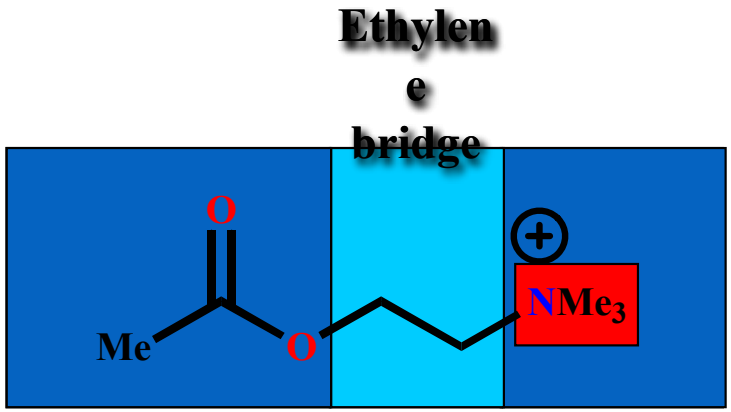
Ester is important



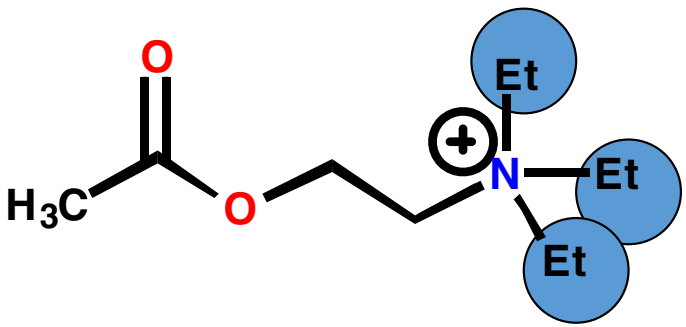


Bad for activity

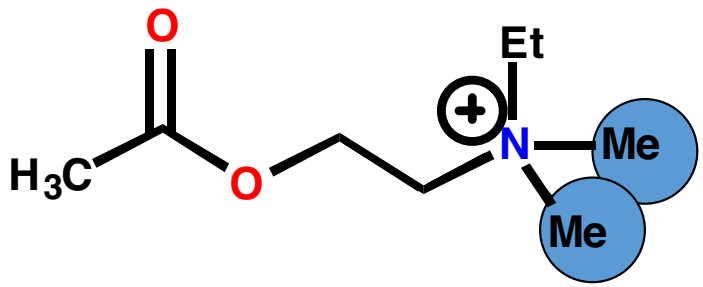
6. SAR for acetylcholine



Minimum of two methyl groups on quaternary nitrogen

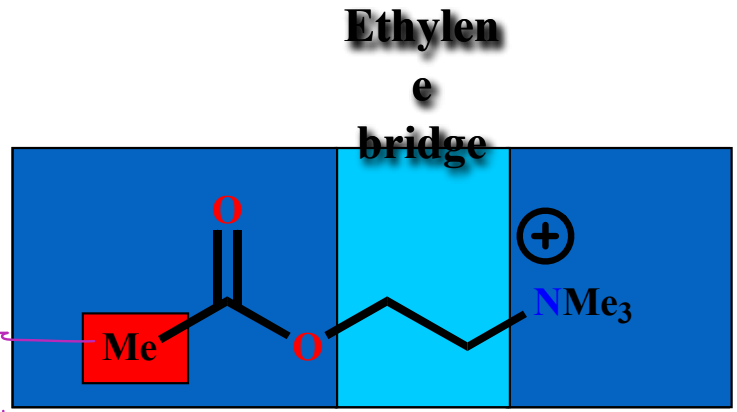


Bad for activity



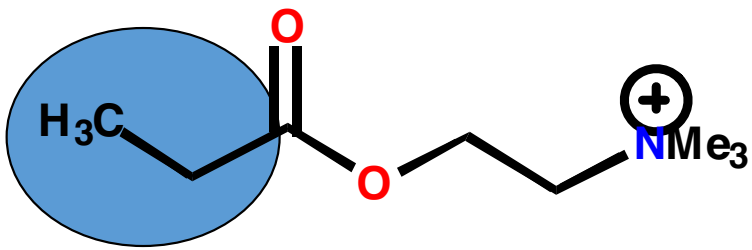
Active

6. SAR for acetylcholine



معظم كثير Me هاي ال
hydrophobic بال ترتبط ارتباط
receptor الموجود بال Pocket

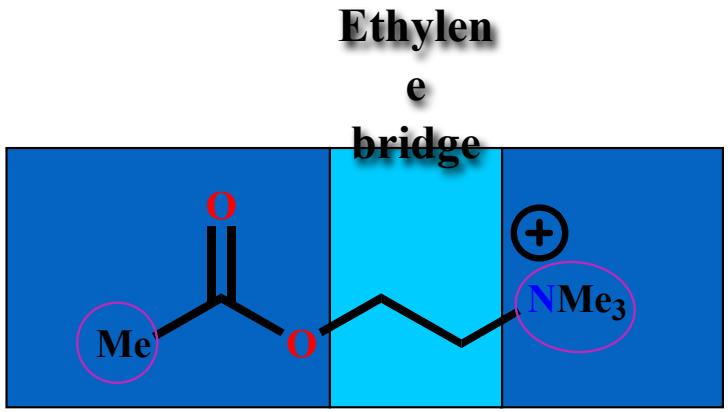
Methyl group of acetoxy group cannot be extended



Et هون بدلت الـ Me بـ
صارت اطول وخسرت
الـ activity اذا لازم
تكون Me فقط

Bad for activity

6. SAR for acetylcholine



Conclusions:

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

بال (+)charg و ال ester bond و طول ال structur و ال ethylen bridg هاكـ الاشياء كلها بتخليه thigh fit

7. Binding site (muscarinic)

•**Ester group** forms **hydrogen bonds** with an **asparagine residue**.
•A **hydrophobic pocket** accepts the **ester methyl group**, especially in **muscarinic receptors**.
•The **NMe_3^+ group** fits into a hydrophobic pocket lined with **aromatic residues** (e.g., tyrosine).
•Two methyls on NMe_3^+ occupy sub-pockets; the third is exposed and modifiable.
•Likely interactions include:

Ionic interaction with **aspartate** (classical view).
Induced ion–dipole interaction with **aromatic rings** (modern view), due to the **diffuse positive charge** of NMe_3^+.

Receptor Binding:
•The **hydrophobic pocket** of the receptor contains **three aromatic amino acids**, supporting the idea of **induced ion–dipole interactions** with the **NMe_3^+ group** on acetylcholine.
•Both **ionic** and **ion–dipole** interactions may occur in the binding site.

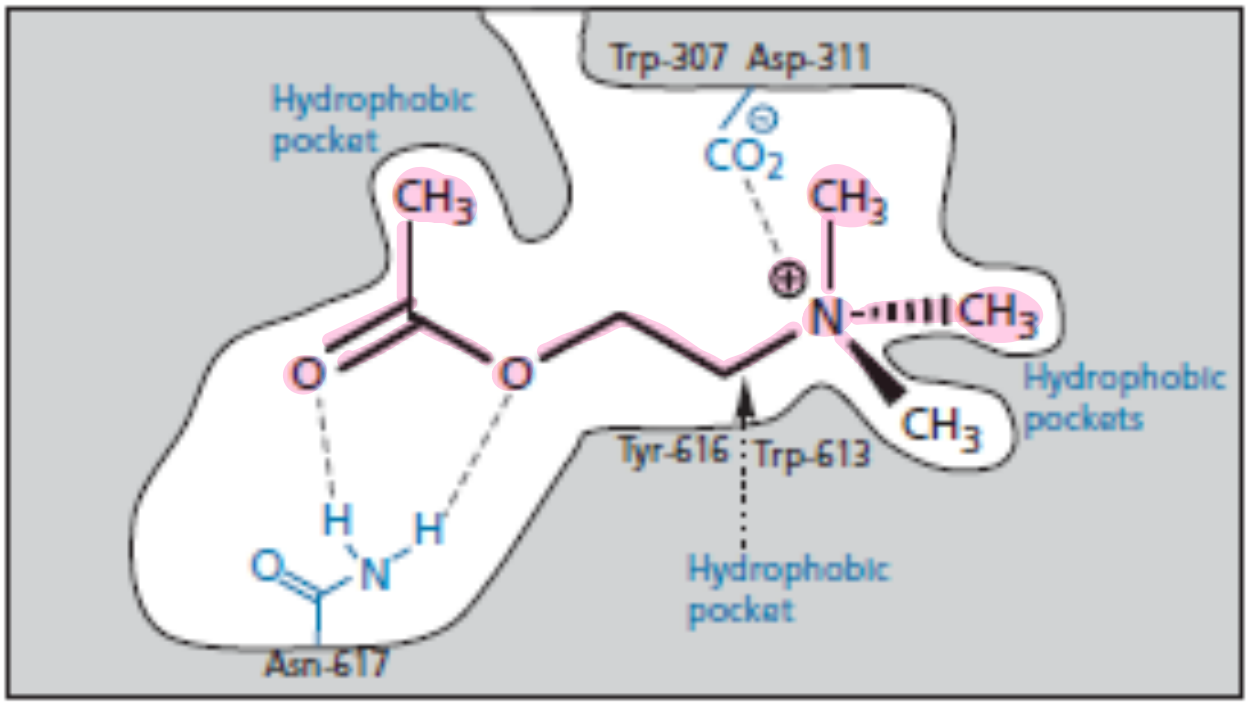
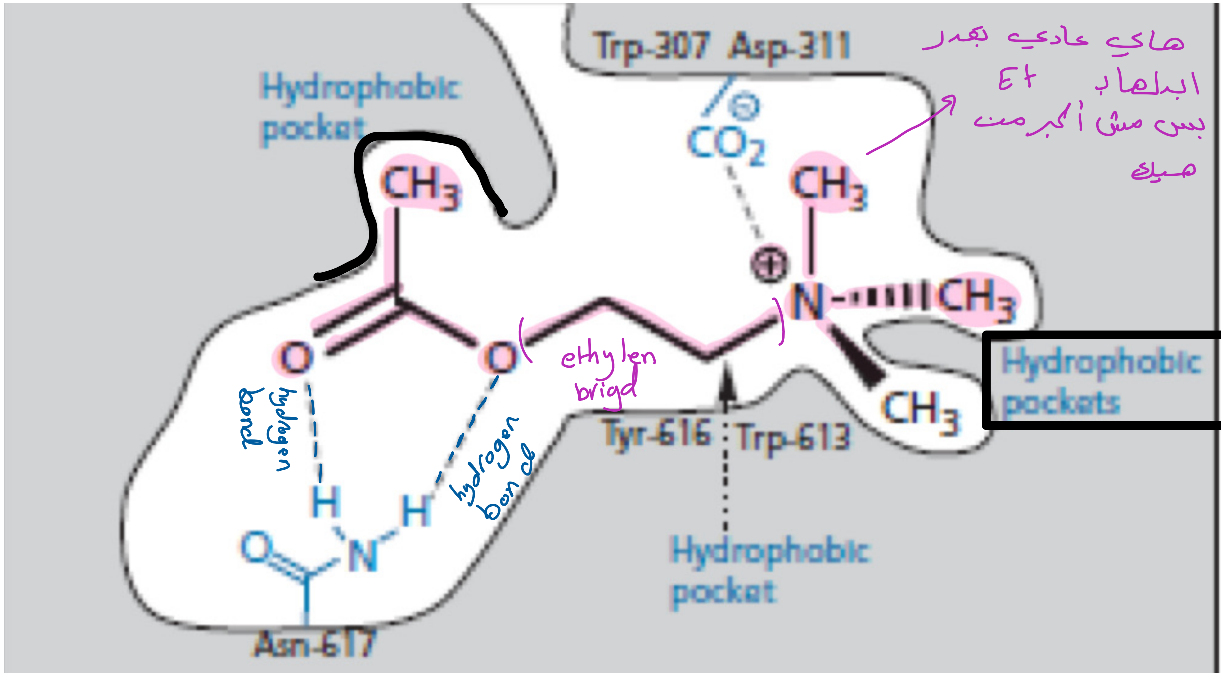


FIGURE 22.10 Muscarinic receptor binding site.



① ال ethylen bridg متناسب مع ال structure (fit)

② ال ester linkag عملت H-bond مع ال a.a → Asn

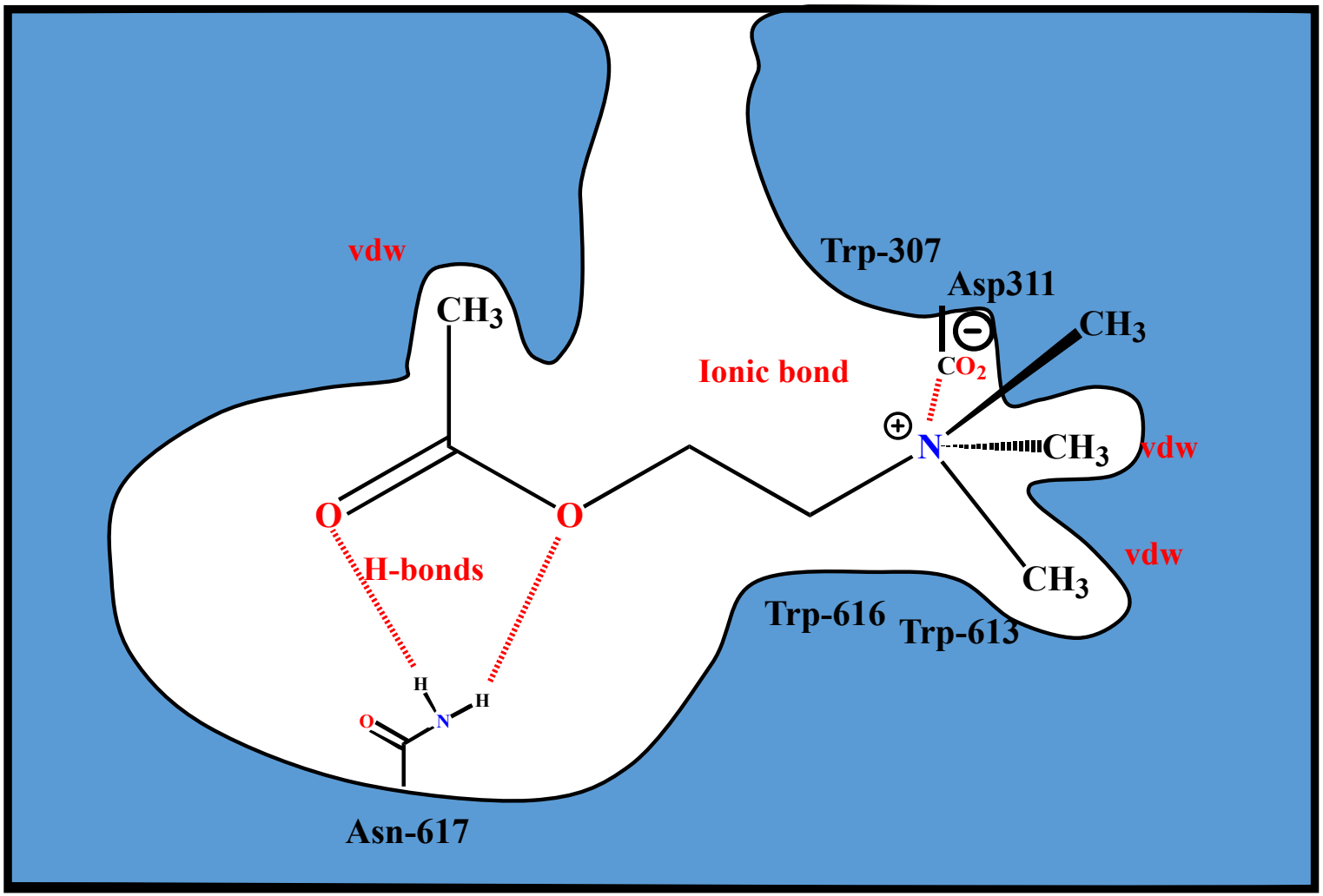
③ ال Me رح ترتبط بال hydrophobic pocket

④ ال charg (+) رح تعمل ionic bond مع a.a → Aspartate

ال Hydrophobic pocket يحتوي كل aromatic a.a بعمل induced-ion dipol interaction مع ال Me المرتبطة بال N او مع ال Me المرتبطة بال ester

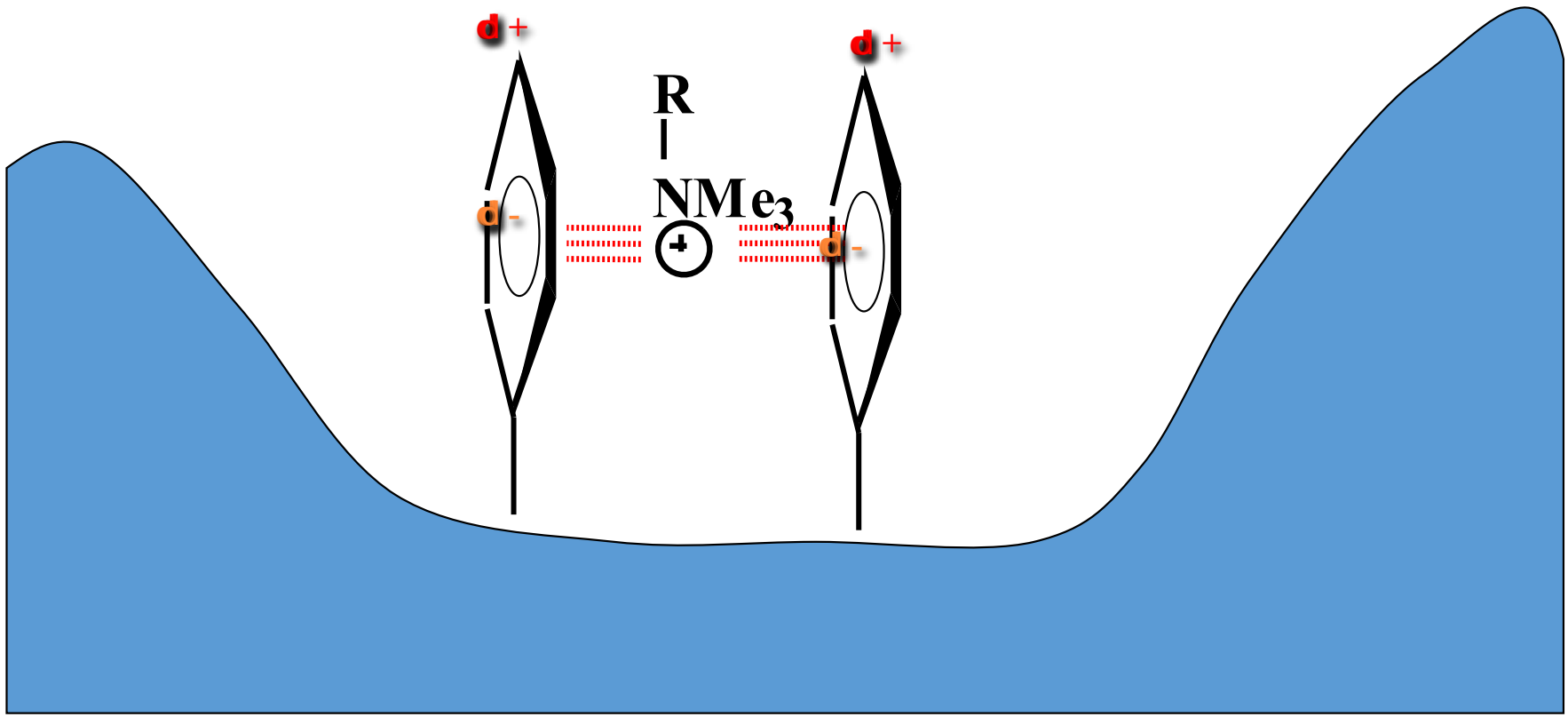
مثال على induced-ion dipol ← vander reaction (Vdw)

7. Binding site (muscarinic)



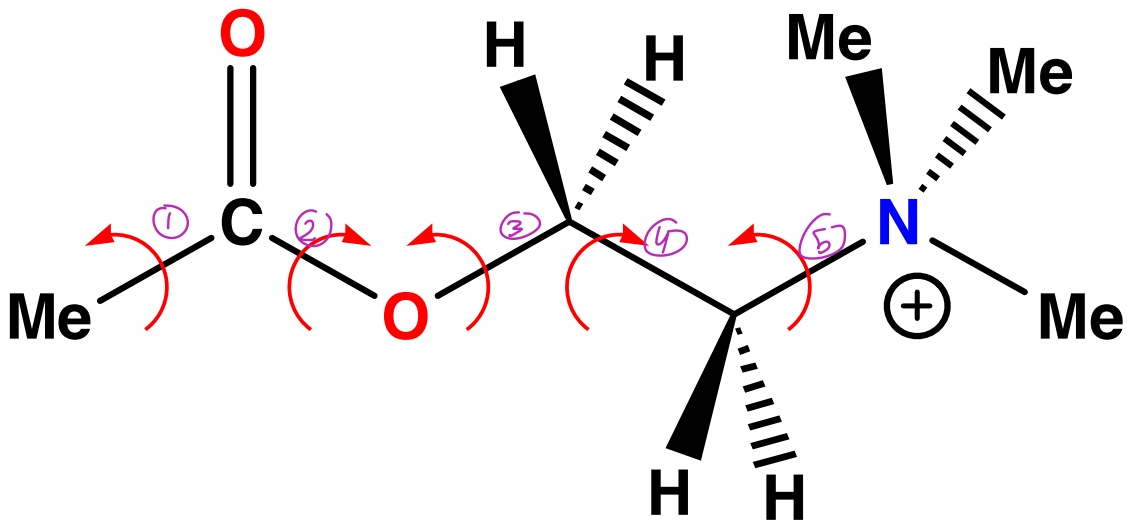
7. Binding site (muscarinic)

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



8. Active conformation of acetylcholine

الـ Ach عنده 5 singel bond اللي رح يعملوا rotation للمركب وهيك رح نعطي Larg conformation



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

Active Conformation of Acetylcholine:

•**Acetylcholine** is highly **flexible**,

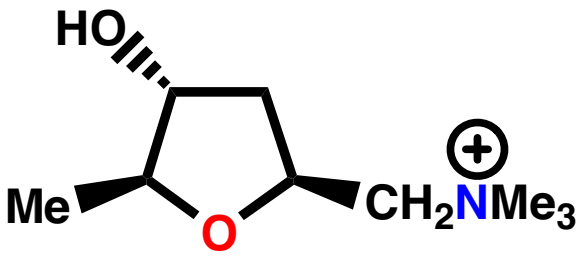
- The most stable conformation (sawhorse/Newman projection) was originally assumed to be the active one, but the energy difference between stable conformations is **minimal**.
- The **gauche conformation** might also play a role in receptor binding.

•To identify the active conformation, **rigid cyclic molecules** mimicking acetylcholine's structure, like **muscarine**, have been studied.

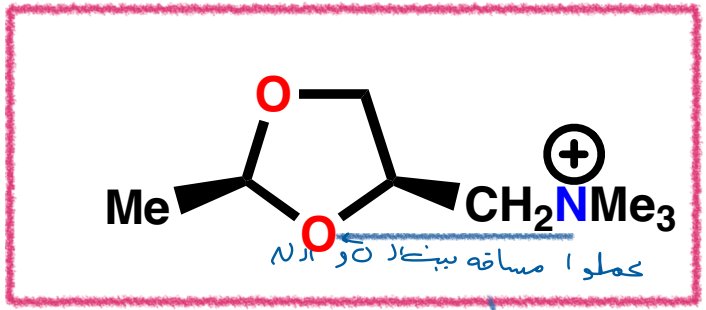
- These rigid molecules bind to the cholinergic receptor, indicating that the specific conformation they adopt is **functional**.

8. Active conformation of acetylcholine

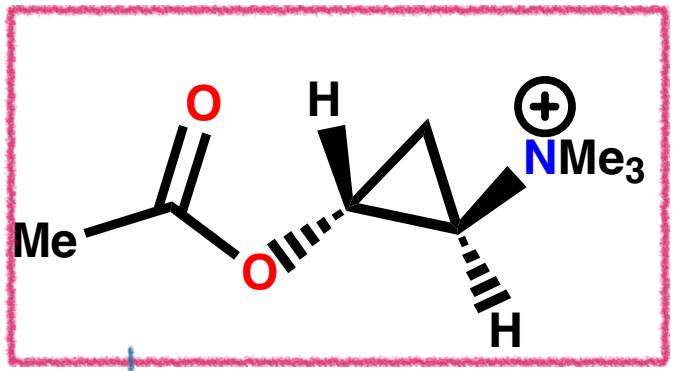
Rigid Analogues of acetylcholine — تلف singel bond ال ما بتخلي



MUSCARINE



عملوا مسافة بين الـ O و الـ N



Rotatable bonds 'locked' within ring

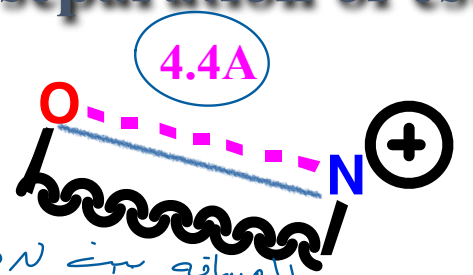
Restricts number of possible conformations

Defines separation of ester and N

كيف عملوا block الـ Rotatable bond ؟

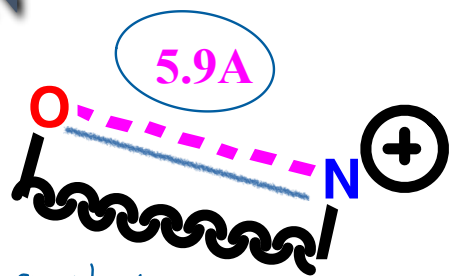
1. عملوا الـ singel bond داخل Ring

2. عملو مسافة بين N و O



المسافة بين N و O لما تكون 4.4A رح تكون muscarine بتكون

Muscarinic receptor



المسافة بين N و O لما تكون 5.9A رح تكون Nicotinic بتكون

Nicotinic receptor

10. Design of cholinergic agonists

Requirements

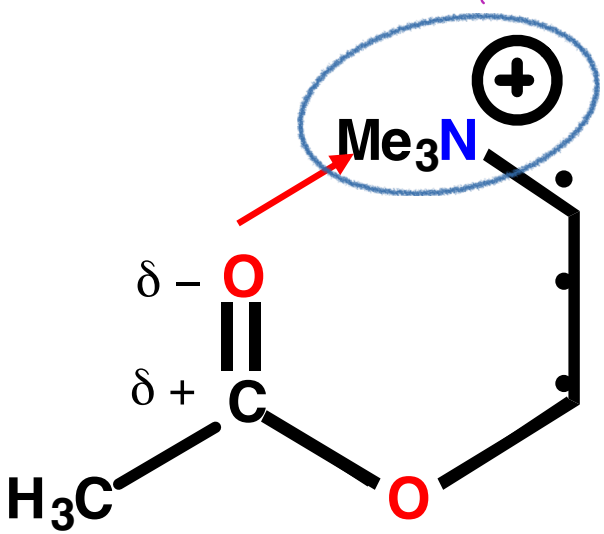
- Correct size
- Correct pharmacophore - ester and quaternary nitrogen
- Increased stability to acid and esterases
- Increased selectivity

9. Instability of acetylcholine

Acetylcholine is prone to hydrolysis because of its molecular conformation. In one conformation, the positively charged nitrogen interacts with the carbonyl oxygen, creating an electron-withdrawing effect. This makes the adjacent carbon atom electron-deficient and more susceptible to attack. While water is generally a weak nucleophile, the increased electrophilicity of the carbonyl carbon makes it more likely to undergo hydrolysis. This process is driven by neighbouring group participation, where the nitrogen ion assists in the reaction.
While this understanding came later through structure-activity relationship (SAR) studies, initial efforts to address the issue of hydrolysis were made without fully knowing the receptor binding site structure.

لما ا صنع drug يعطي Cholinergic effect لازم يتشبه وما اخلف الـ ester carbonyl قريب على الـ N^+

هاي الـ N^+ لح تتفاعل هي الـ ester carbonyl لح تخلي الـ carbonyl hydrophilic وهيك اي compound قريب منه لح يكسر



Neighbouring group participation

Increases electrophilicity of carbonyl group

Increases sensitivity to nucleophiles

10. Design of cholinergic agonists

كيف اصنع drug بتعطي Cholinergic effect

A Use of steric shields

بزيد جزء للمركب يسبب تقليل الـ hydrophility للـ Carbonyl

بس انه اقلل الـ hydrolyses وازيد الـ Stability ؟؟

Rationale

1- **Shields protect ester from nucleophiles and enzymes**

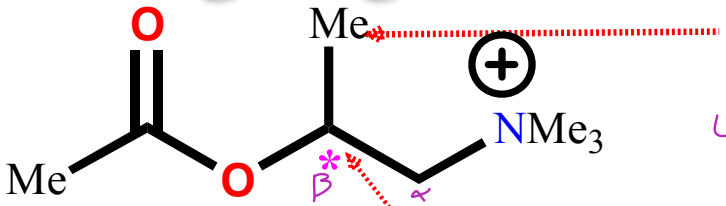
2- **Shield size is important** → اذا كان كبير رح يحوله لـ antagonist

3- **Must be large enough to hinder hydrolysis**

4- **Must be small enough to fit binding site**

10. Design of cholinergic agonists

Steric shield — مثال على الادويه اللي إستخدمت فيها



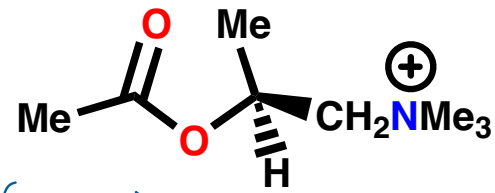
hinders binding to esterases and provides a shield to nucleophilic attack

هون ضيفت Me لل β carbon الموجوده على الـ Ach وهيك منعت الـ esterase من الإرتباط بالمركب ومنعت nucleophilic attack

Methacholine

asymmetric centre

Methacholine demonstrates steric shielding with an extra methyl group on the ethylene bridge. This shield prevents nucleophiles from attacking the carbonyl group and reduces binding to esterases, making methacholine three times more stable to hydrolysis than acetylcholine.

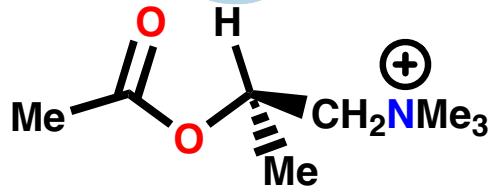


(active)

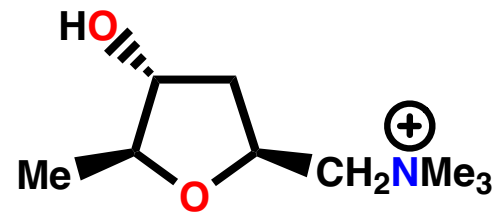
Properties

1. Three times more stable than acetylcholine
2. Increasing the shield size increases stability
3. Larger substituents will give more stability but decreases activity
   ↳ Me بدل Et ضيفت اذا يعني مثلاً
4. Selective for muscarinic receptors over nicotinic receptors
5. *S*-enantiomer is more active than the *R*-enantiomer
6. Stereochemistry matches muscarine
7. Not used clinically

(*S*)



(*R*) → (inactive)



MUSCARINE

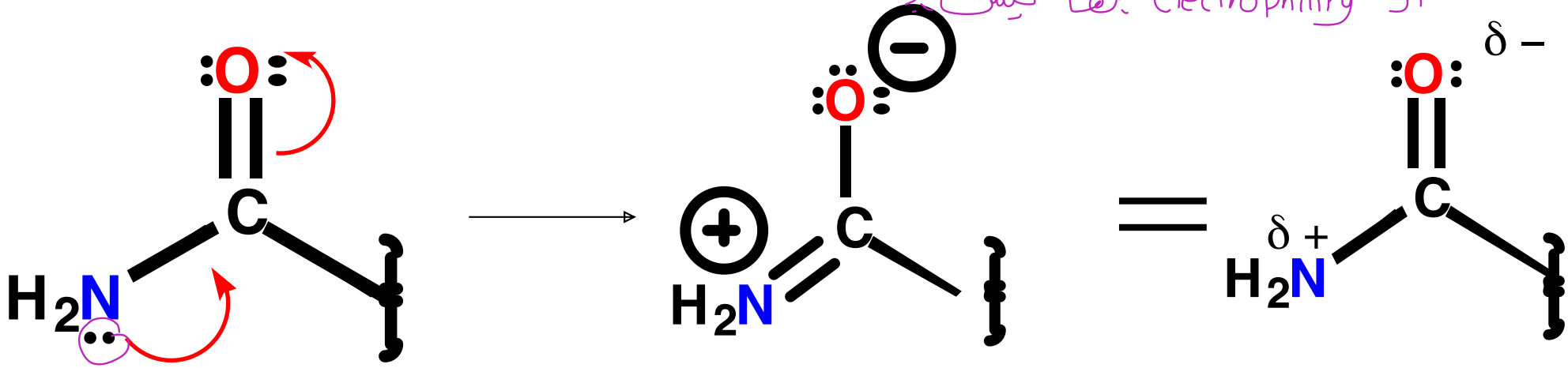
10. Design of cholinergic agonists

3 Use of electronic effect

هاي طريقة ثانية لتحسين الـ drug ←

Replace ester with urethane ← استبدلت الـ ester بـ amin groub

Stabilises the carbonyl group ← فالـ carbonyl صارت أكثر stabel وقلت الـ electrophility الها ليش؟



الـ amin groub بـ تعطي الـ pair of ē للـ doubel bond

فالـ C بـ تصير rich of ē

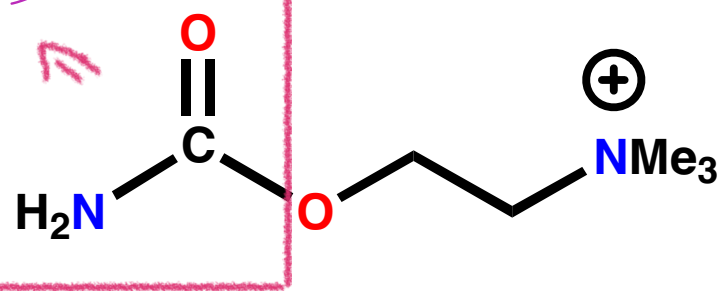
فوج تمنع اي nucleophil انه يكسرها

10. Design of cholinergic agonists

Electronic Effects

Carbachol is a long-acting cholinergic agent designed to resist hydrolysis by replacing the acyl methyl group with an NH2 group, creating a carbamate (urethane) group. The lone pair on nitrogen reduces the electrophilicity of the adjacent carbonyl, making it more stable

The amino group is a bioisostere for the methyl group, allowing it to fit into the binding site despite being polar, unlike the hydrophobic methyl group. This change enhances stability without affecting receptor activity but does not improve selectivity between muscarinic and nicotinic receptors.



Carbachol

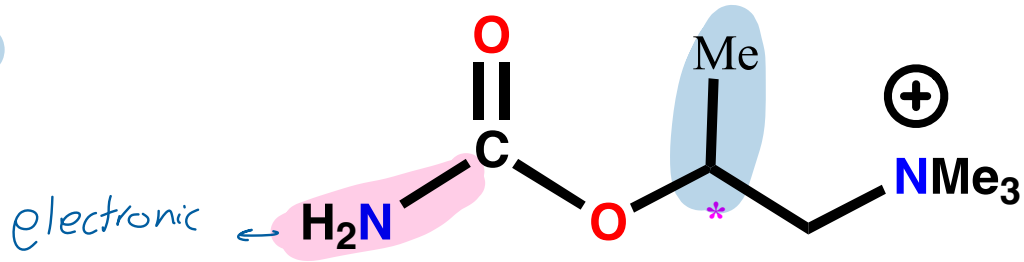
Properties

- Resistant to hydrolysis
- Long lasting
- NH2 and CH3 are equal sizes. Both fit the hydrophobic pocket
- NH2 = bio-isostere
- Muscarinic activity = nicotinic activity
- Used topically for glaucoma by locally reducing intraocular pressure,

10. Design of cholinergic agonists

shiled

Steric + Electronic factors



electronic

Bethanechol

Properties

Very stable to hydrolysis and selective in its action

Orally active

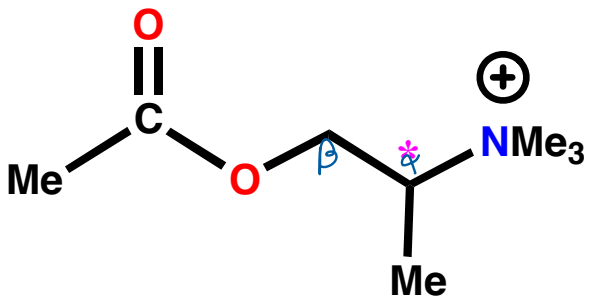
Selective for the muscarinic receptor

Used to stimulate GI tract and urinary bladder after surgery as these organs are often temporarily 'shut down' by drugs during surgery.

لانه بعد ال surgery بصير خطر بال bladder وال GI tract
وهذا الدوا رح يعطل الهم stimulation

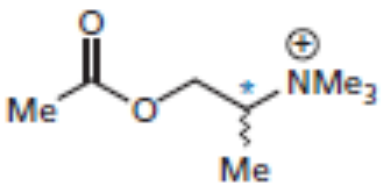
10. Design of cholinergic agonists

Nicotinic selective agonist

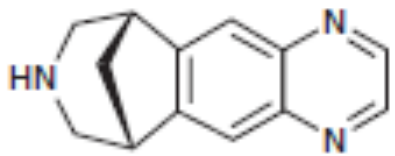


* **asymmetric centre**

- Nicotinic agonists help treat myasthenia gravis, an autoimmune disease where antibodies destroy cholinergic receptors, causing muscle weakness. These agonists boost the chance of activating the few remaining receptors.
- A selective nicotinic agonist, similar to methacholine but with a different methyl position, changes receptor selectivity.
- Despite this, it's not used clinically—anticholinesterases are preferred. Varenicline, a partial nicotinic agonist approved in 2006, is used to aid smoking cessation.



* Asymmetric centre



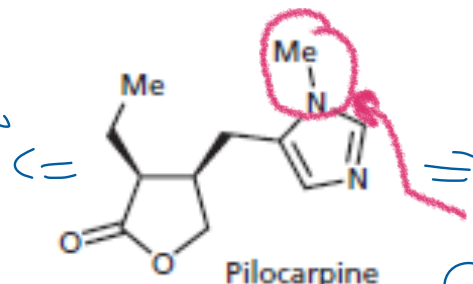
Varenicline

FIGURE 22.23 Examples of selective nicotinic agonists.

10. Design of cholinergic agonists

Muscrinic selective agonist

Pilocarpine an alkaloid from Pilocarpus shrubs, is used to treat glaucoma. **It lacks a quaternary ammonium group but is assumed to be protonated before binding to the muscarinic receptor.** Molecular are being considered for Alzheimer's disease treatment, though anticholinesterases are shows that pilocarpine fits the pharmacophore for muscarine receptors

muscarinc ال شكله بشبه <= 

Pilocarpine

=> ج receptor قبل ما يرتبط بال
يصير N ال Me من Protanation
وصيك ج يصير عليها Charg (+)

FIGURE 22.22 Examples of muscarinic agonists.

اعزوني اذا فيه اي خطأ املائي

لا تنسو زميلنا ايهم من دعائكم