

Pharmacology

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Lecture no .. 11 ...



General Pharmacology

Introduction to autonomic nervous system(ANS) and neurotransmitters

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Topic 4: Autonomic nervous system

- **Week 6**

- Day 1

- Lecture 1: Introduction to ANS and neurotransmitters.

- Lecture 2: Adrenergic and Cholinergic receptors.

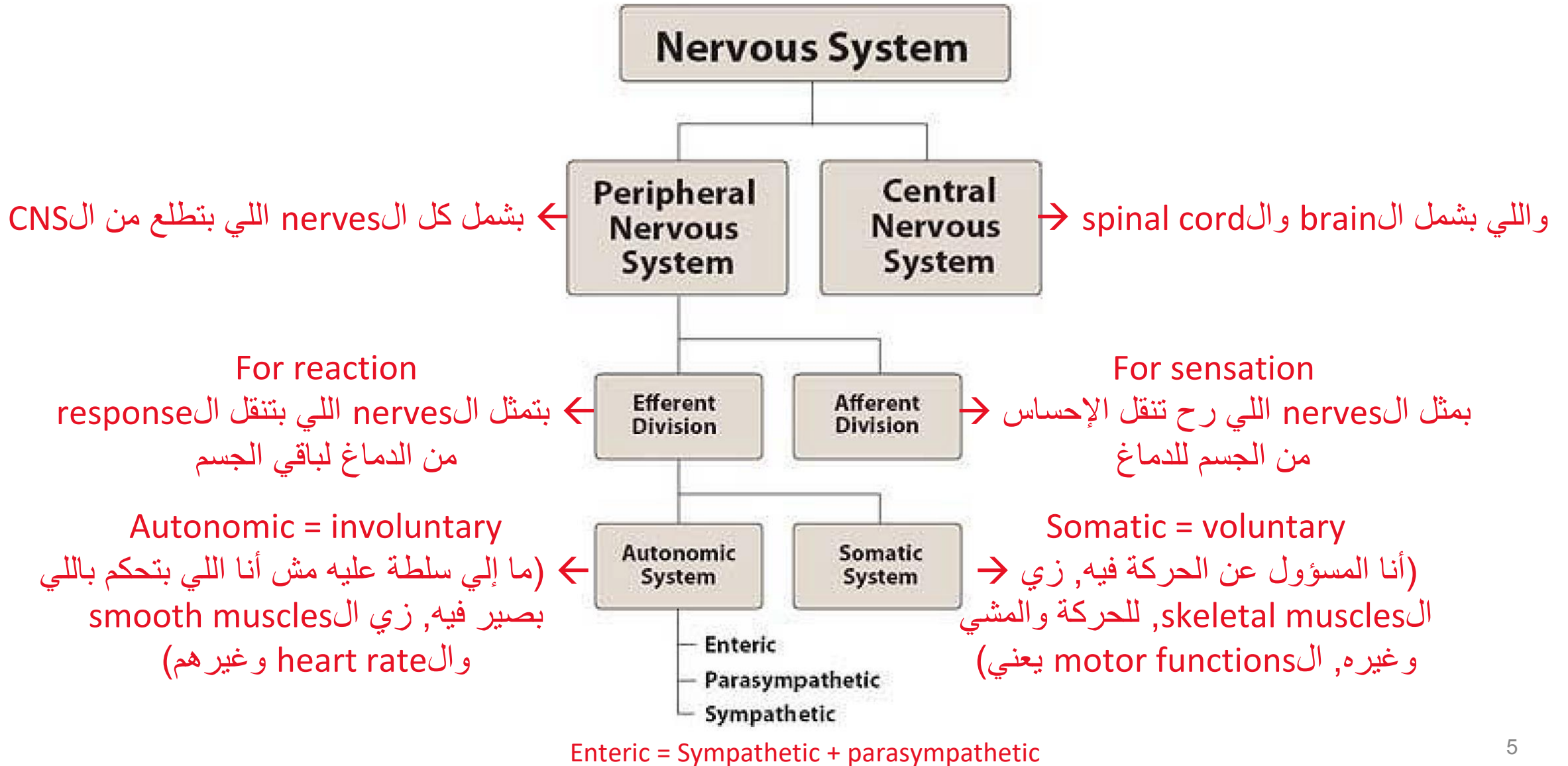
- Day 2

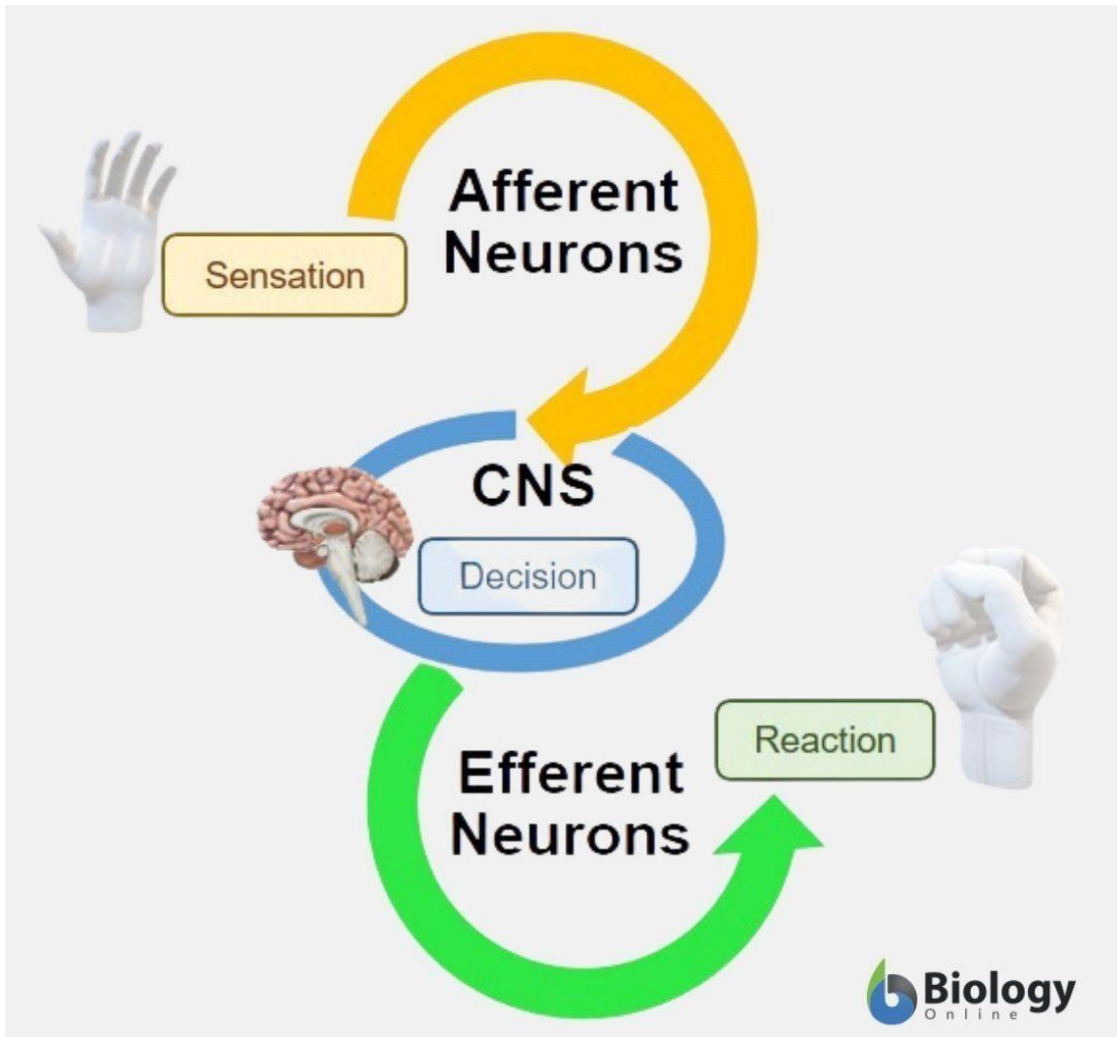
- Lecture 3: Drugs affecting cholinergic and adrenergic systems.

Introduction to ANS and neurotransmitters

- Organization of the nervous system.
- Anatomy of the autonomic nervous system(ANS).
- Action of sympathetic and parasympathetic nervous system.
- Role of CNS in the control of ANS
- Chemical signaling between cells (neurotransmitters).
- Signal Transduction in the effector cell

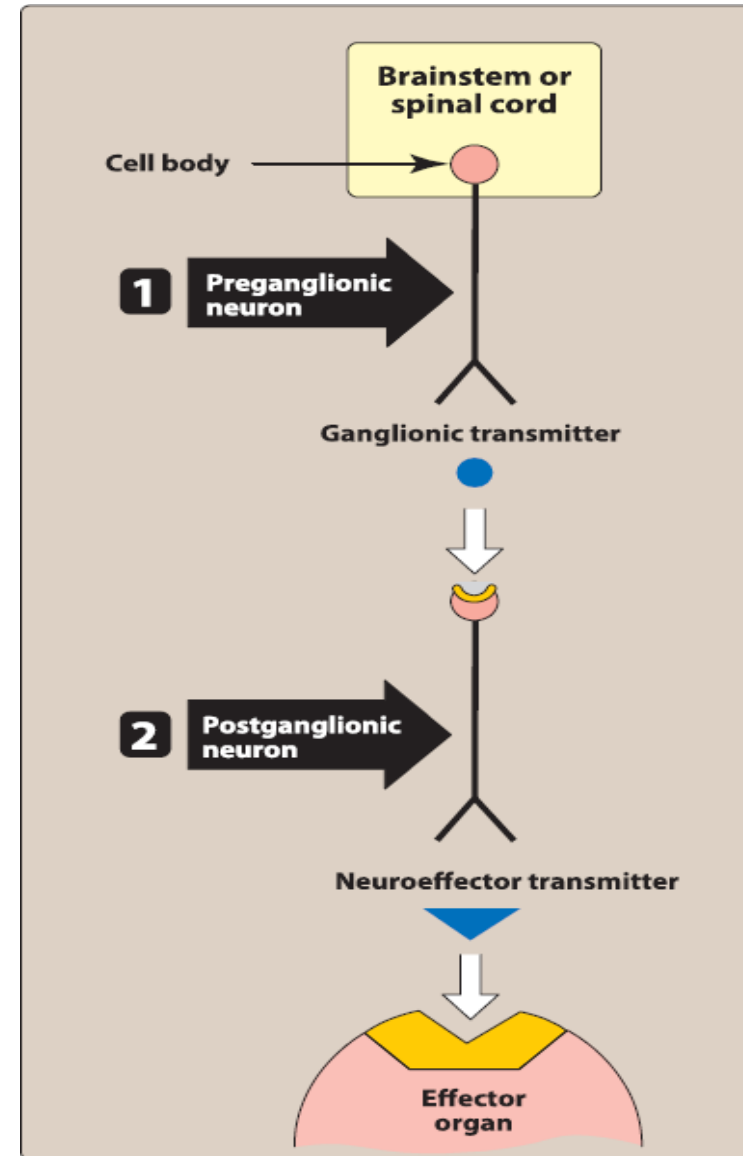
Organization of the nervous system





• Afferent and efferent Neurons

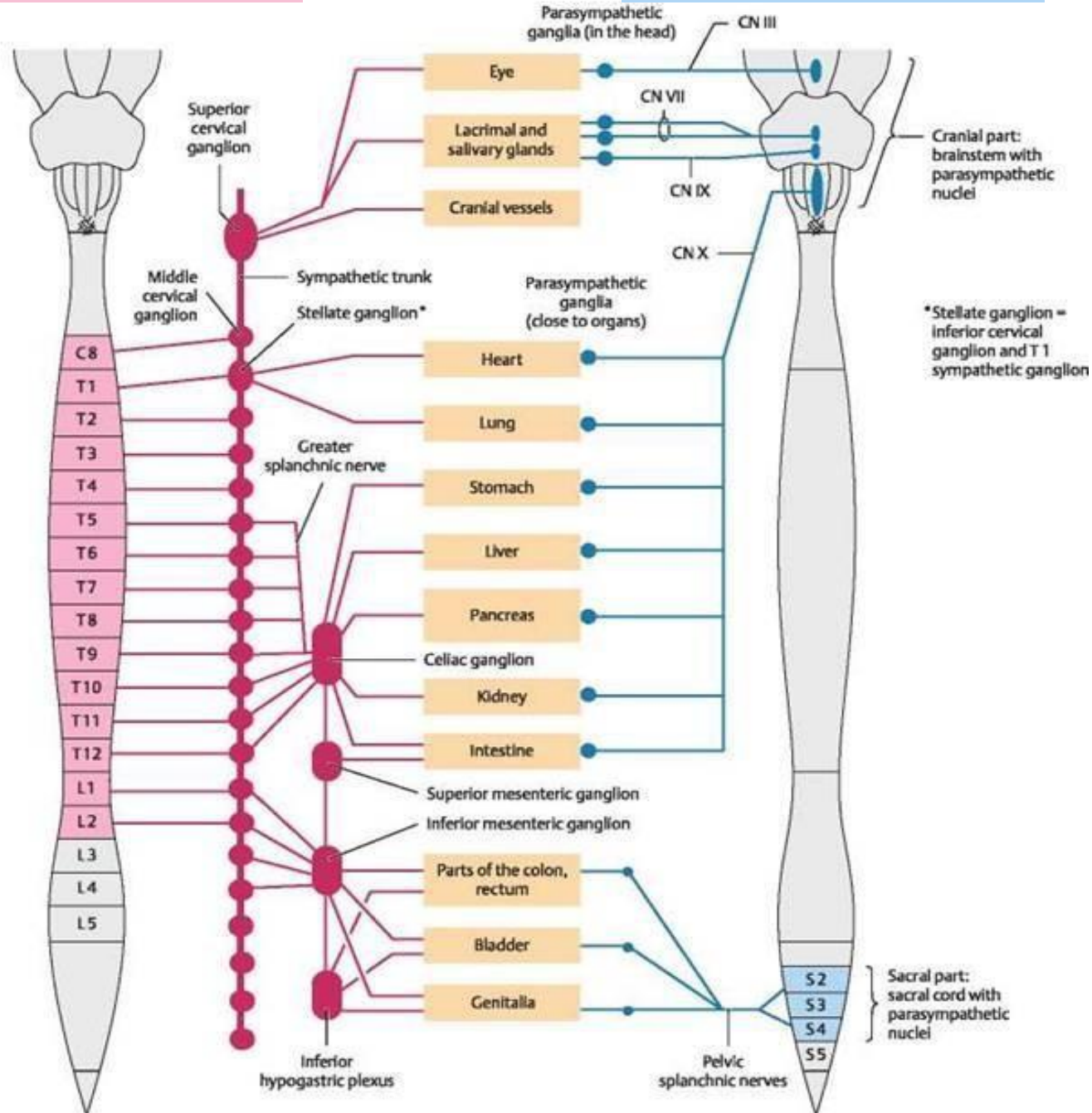
يعني على سبيل المثال لو لمست اشئ ساخن, فال sensation تنتقل بال afferent, بعدئذ ال response بإني أحرّك إيدي بكون عن طريق ال efferent



اللي بنلاحظه في ال ANS إنه في عنا جزئين.. الأول بمتد من مكان خروج ال nerve من ال CNS لحد ما يوصل ال ganglia, وبنسميه pre-ganglionic neuron الثاني بمتد من ال ganglia وصولاً إلى ال organ, وبنسميه post-ganglionic neuron

Efferent neurons of ANS

Anatomy of the ANS



ال - عبارة عن 4
 cranial nerves
 ال (الثالث) Oculomotor
 ال (السابع) Facial
 ال Glossopharyngeal
 ال (التاسع)
 ال Vagus (العاشر),
 بالإضافة لبعض ال
 nerves التي بتطلع من S2 ل S4 في
 ال spinal cord
 ال - ganglia هون أقرب
 ال لل organ, يعني
 ال preganglionic طويل
 ال - postganglionic ما
 بتفرّع و يروح على ال organ
 واحد فقط

ال - sympathetic ببلش يتفرع من
 ال C8 ولغاية ال L2 في ال spinal
 cord

ال - ganglia فيه بتكون أقرب
 لل spinal cord, عشان هيك
 ال preganglionic neuron يكون
 قصير

ال - postganglionic يكون متفرع,
 عشان هيك تأثيره أكبر (diffused)

Action of **sympathetic** and **parasympathetic** nervous system

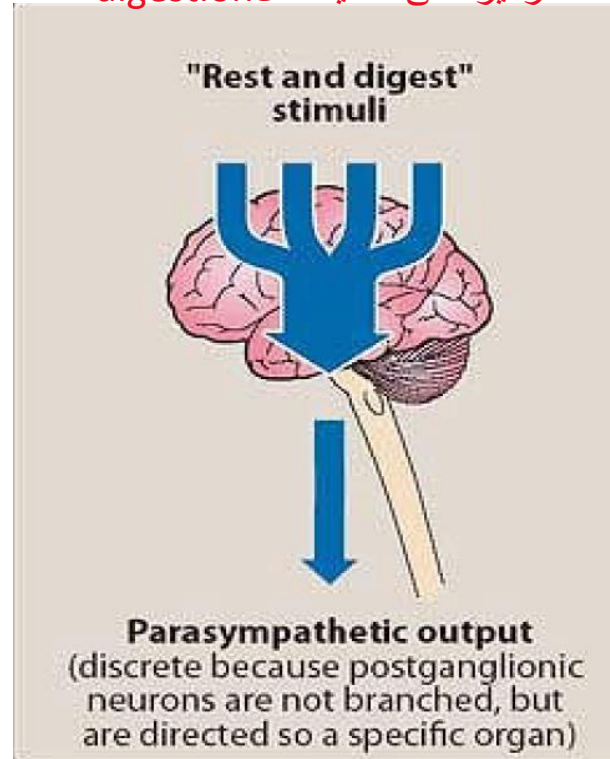
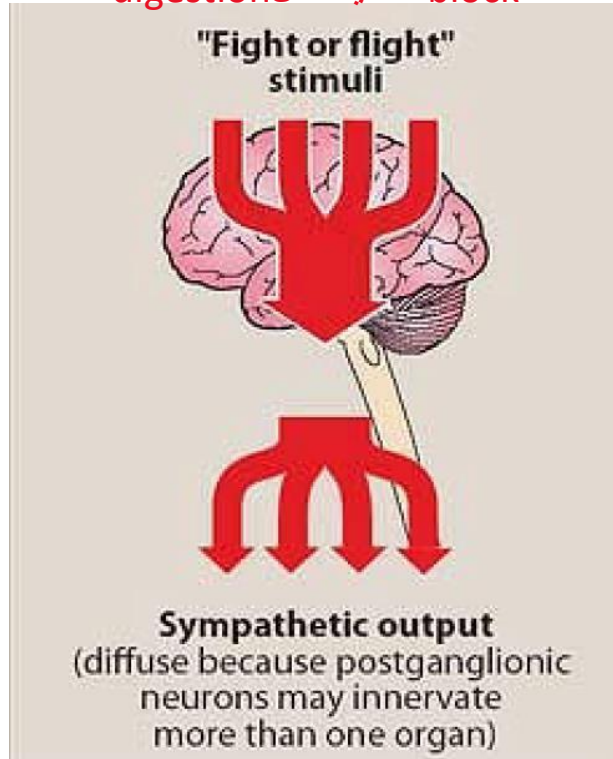
(fight or flight)

(rest and digest)

بصير فيه زيادة للHR, والBP, وبصير
digestion block لعمليات

هون رح يقل الHR, والBP, وبصير
التركيز على عمليات الdigestion

*HR = heart rate
*BP = blood pressure



- Most of the involuntary organs receive "**dual (double) innervation**".
Sympathetic and parasympathetic actions are antagonistic except the action on:
 - a. Salivary glands (**both increase salivation**)
 - b. Male sex organs is **complementary to each other**

بشكل عام الغالبية العظمى من الorgans بتستقبل stimulation من النوعين, ويكون شغلهم عكس بعض, باستثناء ال2 exceptions هضول

اللهم إني أسالك التوفيق والنجاح, في الدنيا والآخرة

Action of sympathetic and parasympathetic nervous system

Red = Sympathetic actions
Blue = Parasympathetic actions

EYE

Contraction of iris radial muscle (pupil dilates)

Contraction of iris sphincter muscle (pupil contracts)

Contraction of ciliary muscle (lens accommodates for near vision)

TRACHEA AND BRONCHIOLES

Dilation

Constriction, increased secretions

ADRENAL MEDULLA

Secretion of epinephrine and norepinephrine

KIDNEY

Secretion of renin (β_1 increases; α_1 decreases)

URETERS AND BLADDER

Relaxation of detrusor; contraction of trigone and sphincter

Contraction of detrusor; relaxation of trigone and sphincter

GENITALIA (male)

Stimulation of ejaculation
Stimulation of erection

LACRIMAL GLANDS

Stimulation of tears

SALIVARY GLANDS

Thick, viscous secretion
Copious, watery secretion

HEART

Increased rate; increased contractility
Decreased rate; decreased contractility

GASTROINTESTINAL SYSTEM

Decreased muscle motility and tone; contraction of sphincters

Increased muscle motility and tone

GENITALIA (female)

Relaxation of uterus

BLOOD VESSELS (skeletal muscle)

Dilation

BLOOD VESSELS (skin, mucous membranes, and splanchnic area)

Constriction

الثنتين بحفزاوا, بس طبيعة ال secretion مختلفة

للأسف الرسمة
مطلوبة, لازم
نعرف تأثير
ال sympathetic
وال para على كل
organ

ننتبه إنه
ال accommodated ←
بتكون para (اللي هي
مسؤولة عن الرؤية
القريبة والبعيدة)

Differences between sympathetic and parasympathetic nervous system

	SYMPATHETIC	PARASYMPATHETIC
Sites of origin	Thoracic and lumbar region of the spinal cord (thoracolumbar)	Brain and sacral area of the spinal cord (craniosacral)
Length of fibers	Short preganglionic Long postganglionic	Long preganglionic Short postganglionic
Location of ganglia	Close to the spinal cord	Within or near effector organs
Preganglionic fiber branching	Extensive	Minimal
Distribution	Wide	Limited
Type of response	Diffuse	Discrete

Innervation by the ANS

1- Dual innervation:

- Most organs
- One system usually predominates in controlling the activity of a given organ.

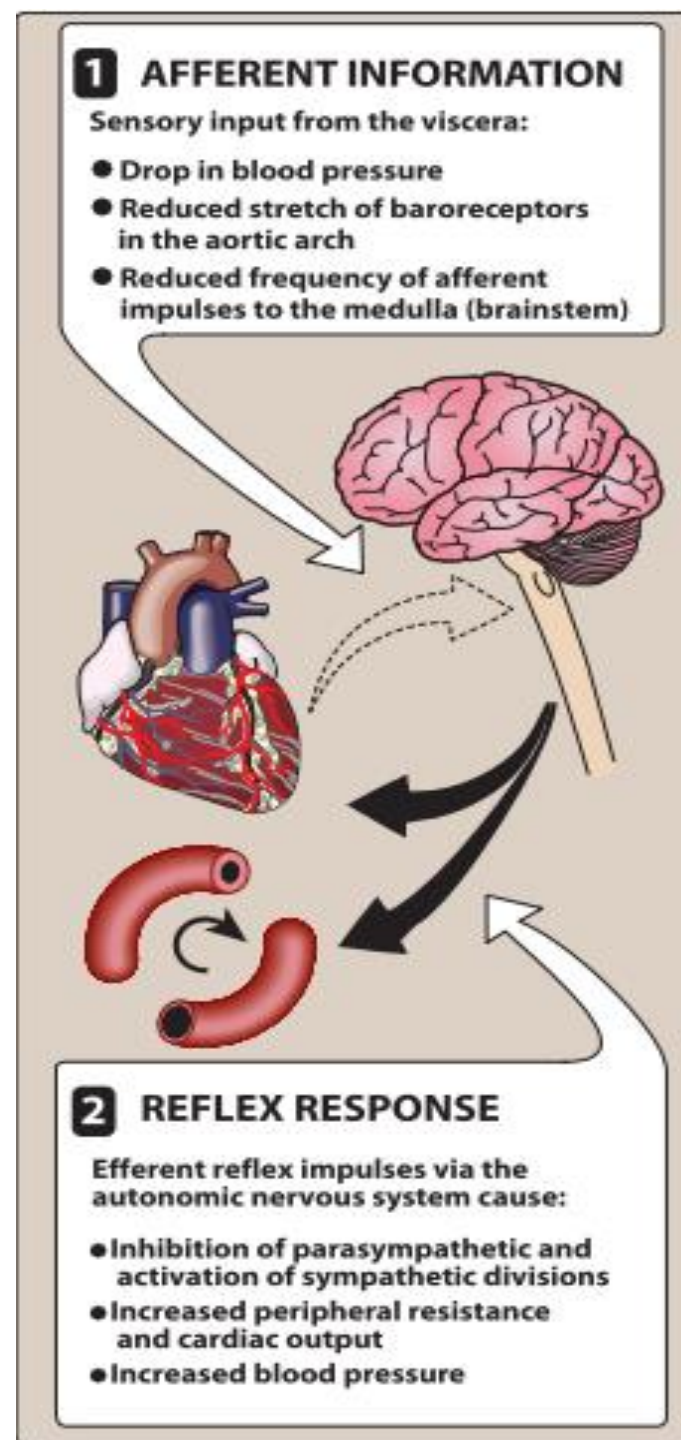
2- Sympathetic innervation:

Such as adrenal medulla, pilomotor muscles and sweat glands.

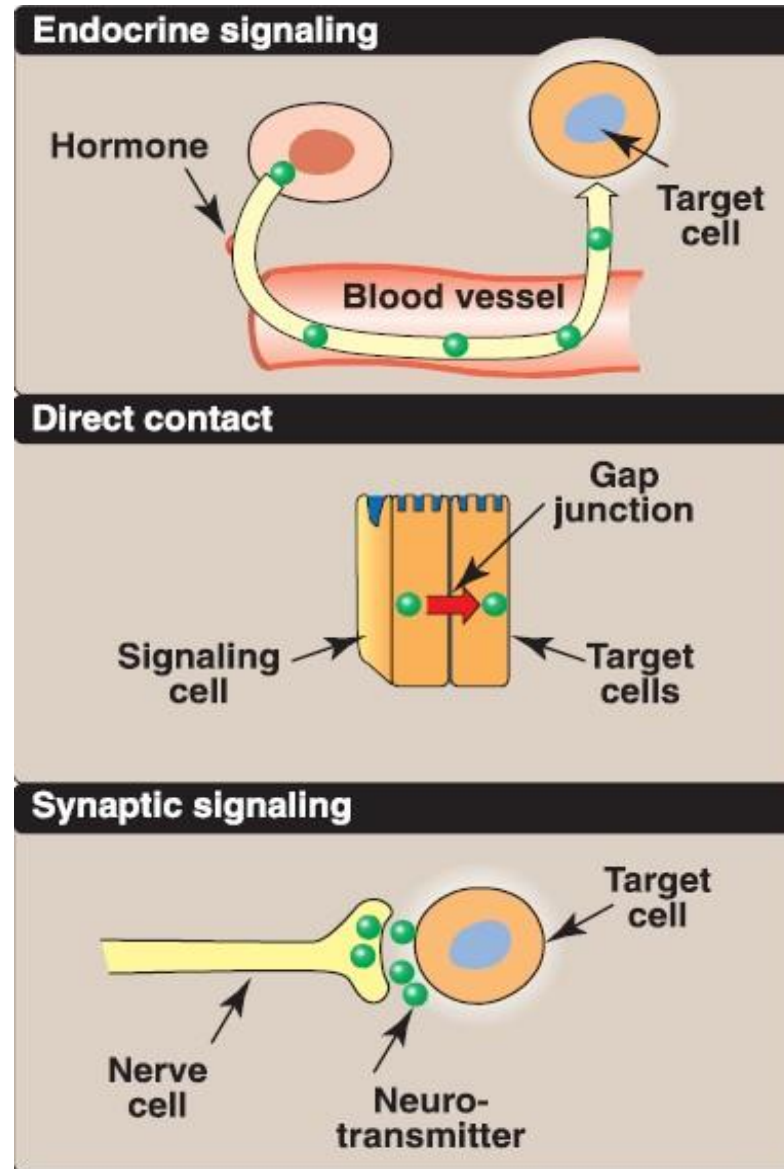
Role of CNS in the control of ANS

- **Reflex Arcs:** Most of the afferent impulses are involuntarily translated into reflex responses. *زي ما حكينا بالبداية, ال afferent هو اللي بوصل ال impulses لل brain, عشان يصير بعدها response*
- For example, a fall in blood pressure causes pressure-sensitive neurons (**baroreceptors in the heart, vena cava, aortic arch, and carotid sinuses**) to send fewer impulses to cardiovascular centers in the brain. This prompts a reflex response of increased sympathetic output to the heart and vasculature and decreased parasympathetic output to the heart, which results in a compensatory rise in blood pressure and heart rate. *فمثلا لما يقل ضغط الدم رح ترسل ال baroreceptors أمر لل brain, عشان يتخذ إجراء, حيث رح يحفز ال sympathetic ويثبط ال para, ما يؤدي لرفع ال BP*
- **Emotions and ANS:** Stimuli that evoke strong feelings, such as fear, and pleasure, can modify activities of the ANS. *أما بالنسبة لل emotions.. فمثلا ال pain ممكن يحفز ال parasympathetic ويسببلي vomiting, أو مثلا عند الحزن الشديد بعمل تحفيز لإفراز الدموع*

Baroreceptors reflex arc



Signaling between cells



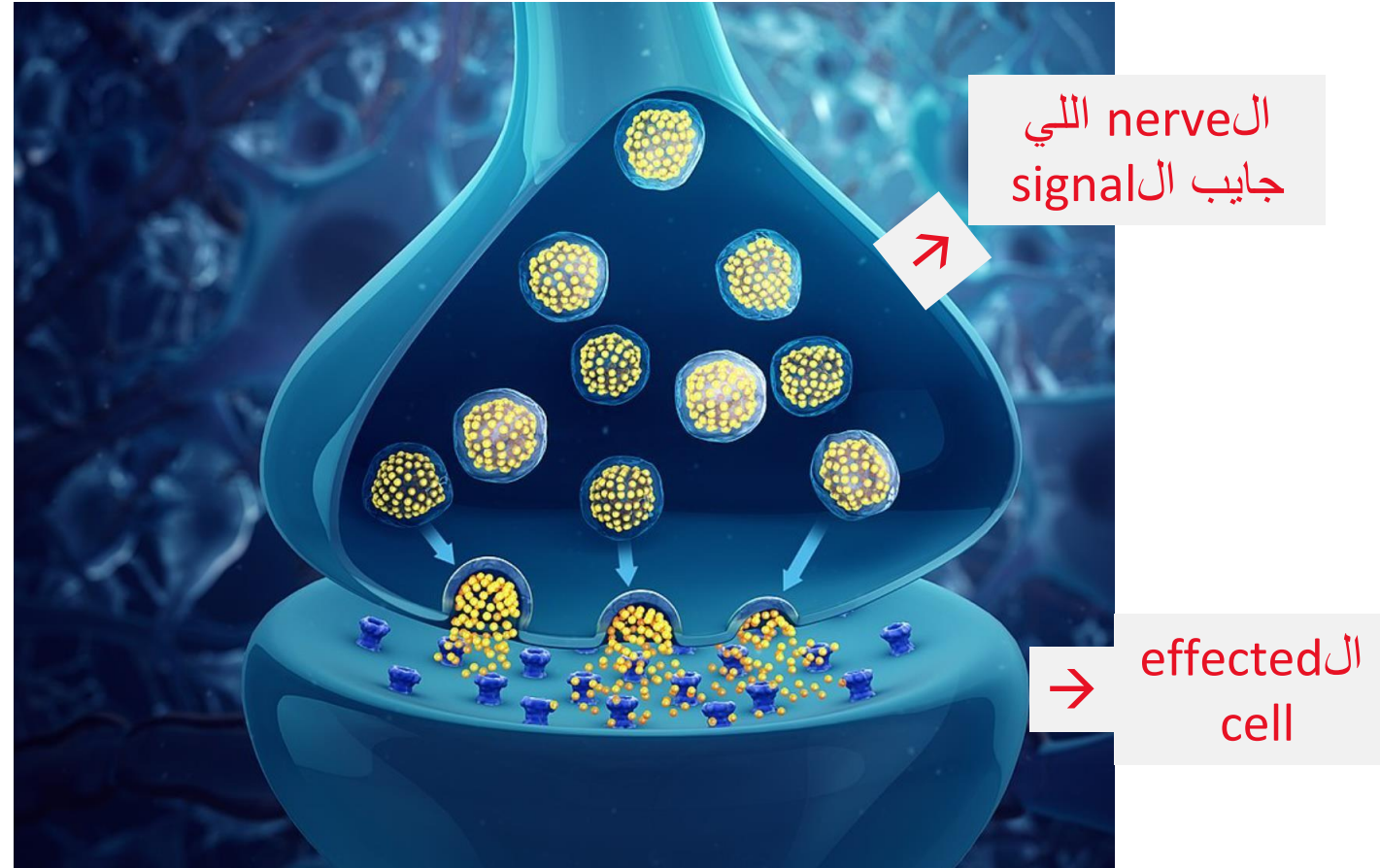
في ال endocrine, ال stimulus عبارة عن hormone, يدخل ال blood, بعدين بوصل ال effected organ, ويرتبط بال target

في ال direct contact يتم النقل عبر ال gap junctions

واللي بهمنا هون هو ال synaptic, حيث ال neuron (بغض النظر pre/post) بطلع منه neurotransmitters, اللي رح ترتبط بال target cell, اللي ممكن تكون effected organ أو ganglia (اذا كان pre)

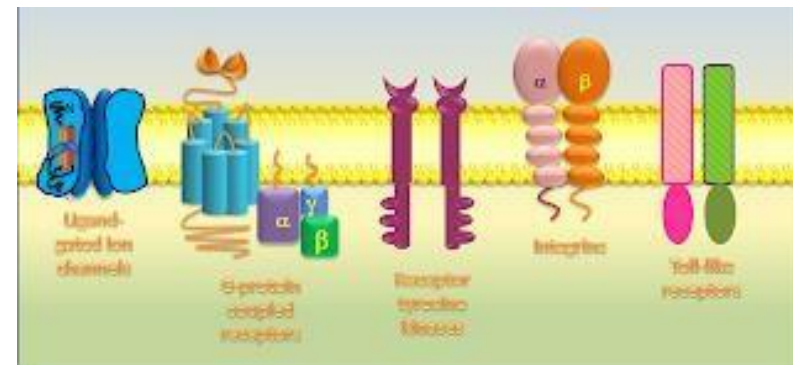
Chemical signaling between cells (neurotransmitters).

The activity of ANS is based on the presence of **specific "neurotransmitters"** acting on **specific "receptors"**



Membrane receptors

- All neurotransmitters are too hydrophilic to penetrate the lipid bilayers of target cell plasma membranes.
- Neurotransmitters signal is mediated by binding to specific receptors on the cell surface of target organs.
- **Receptor**: is a recognition site for a substance. It has a binding specificity and is coupled to processes that eventually evoke a response.
- **Most receptors are proteins.**



بما إنه ال neurotransmitters مواد hydrophilic فهاض يعني إنه ما رح تقدر تعبر ال cell membrane, عشان هيك في receptors عشان يساعدوا بنقل هاض ال neurotransmitter

ال receptors ممكن تكون : protein kinase C / G protein / ion channels , واللي آلية عملها مختلفة, حيث ممكن تغير بال permeability, أو تكون 2nd messengers

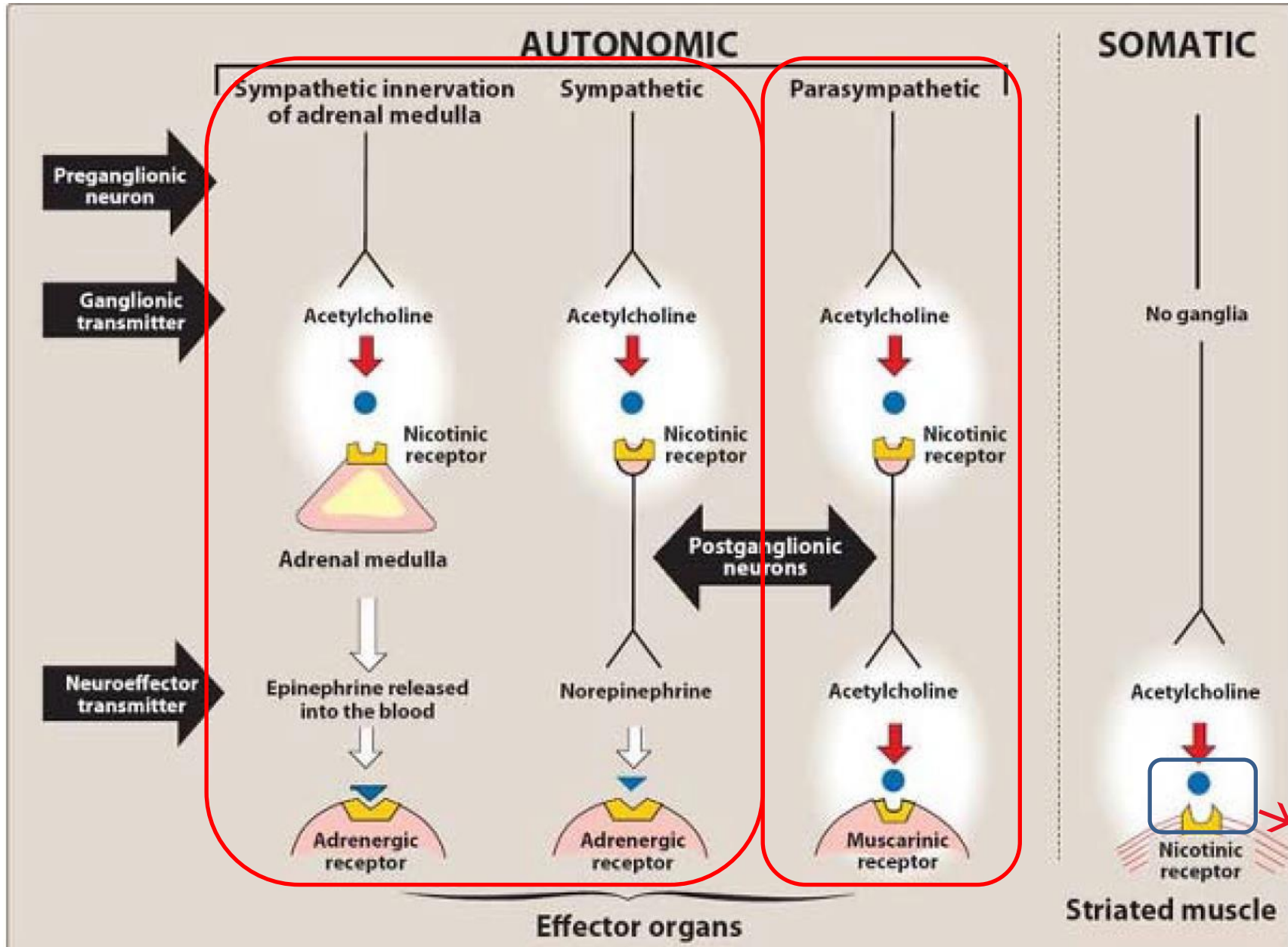
Types of Neurotransmitters

- The **most commonly neurotransmitters** involved in the actions of therapeutically useful drugs are **acetylcholine**, **norepinephrine**, **epinephrine**, dopamine, serotonin, histamine, glutamate, and γ -aminobutyric acid.
- **Acetylcholine** and **norepinephrine** are the **primary chemical signals in the ANS.**
epinephrine بالإضافة لل
- If **transmission** is mediated by **acetylcholine**, the neuron is termed **cholinergic neuron**.
- If **transmission** is mediated by **norepinephrine**, the neuron is termed **adrenergic neuron**.

Summery of the neurotransmitters release within the ANS

- هسا

بالpreganglionic,
 ال transmitter رح
 يكون دائما
 acetylcholine (يعني)
 ال receptor رح يكون
 (nicotinic
 ganglia ال - بينما بعد
 في فرق , حيث في
 ال sympathetic رح
 يكون epinephrine
 (اذا الشغل
 بال adrenal
 او medulla)
 norepinephrine
 (عبر post-neuron),
 ال receptor في
 الحالتين adrenergic

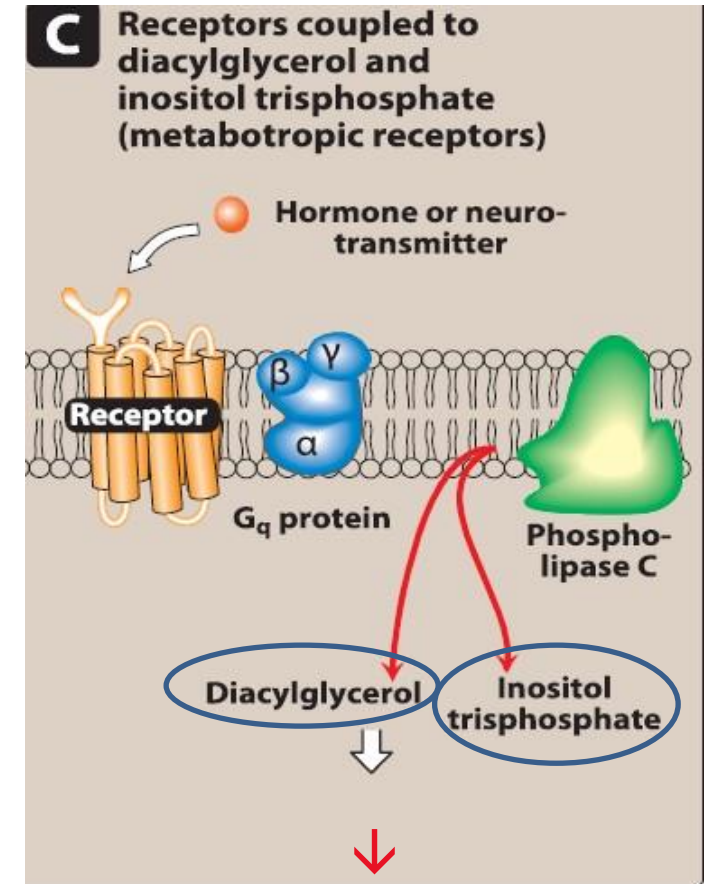
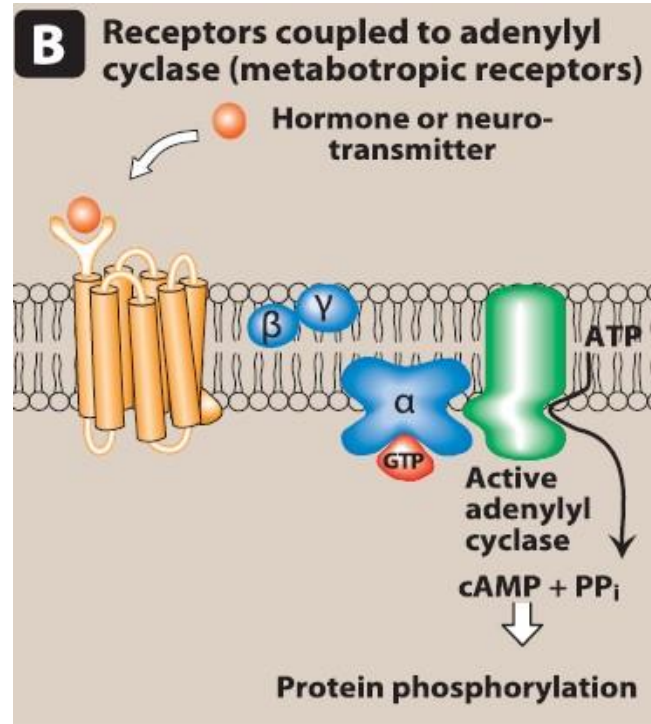
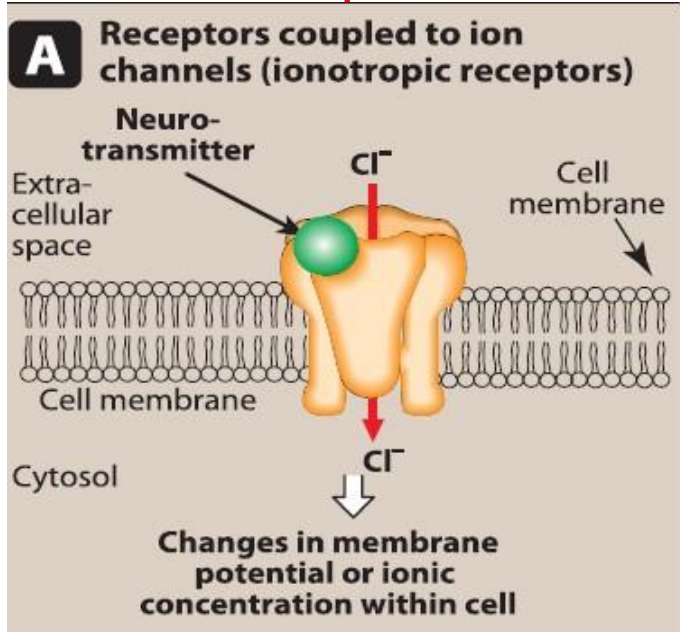


- أما ال para
 ال post-neuron
 رح يفرز
 acetylcholine
 وال receptor
 يكون muscarinic
 أو nicotinic
 - في حالة
 ال somatic ما في
 عنا ganglia,
 وال neuron بفرز
 acetylcholine
 وال receptor
 يكون nicotinic
 neuromuscular
 junction

* المنطقة التي يرتبط فيها ال transmitter على ال muscle بنسبها neuromuscular junction , وهي التي بنسبها عند التخدير عشان نعملها block ونرخي العضلات

Signal Transduction in the effector cell

ال ion channel receptors بتغير
ال membrane potential
وال permeability عشان تعطي ال action



ال G-protein بعمل conformational changes بال proteins الموجودة, وبتحفز ال 2nd messenger الذي هو عبارة عن adenylyl cyclase, فيزيد ال cAMP وبصير protein phosphorylation

ممكن ال G-protein يعمل تحفيز ال phospho-lipase ويعطينا 2nd messengers آخرين زي الذي بالصورة

اللهم إني أسألك الهدى والتقى والعفاف والغنى

General Pharmacology

Adrenergic and cholinergic receptors

Faculty of Medicine

The Hashemite University

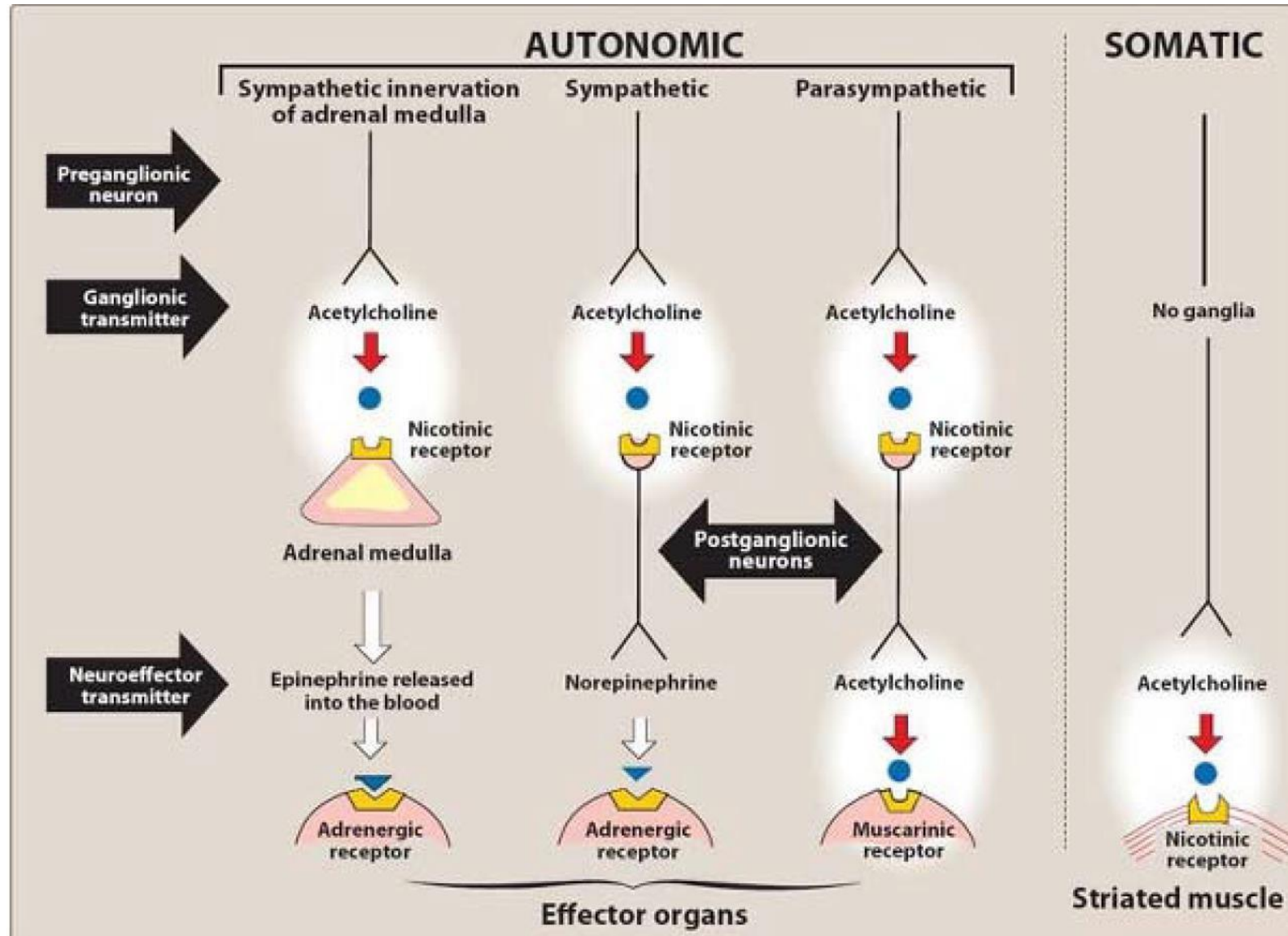
Arwa Al Anber(MD, PhD)

تفريغ : ندى خليفات

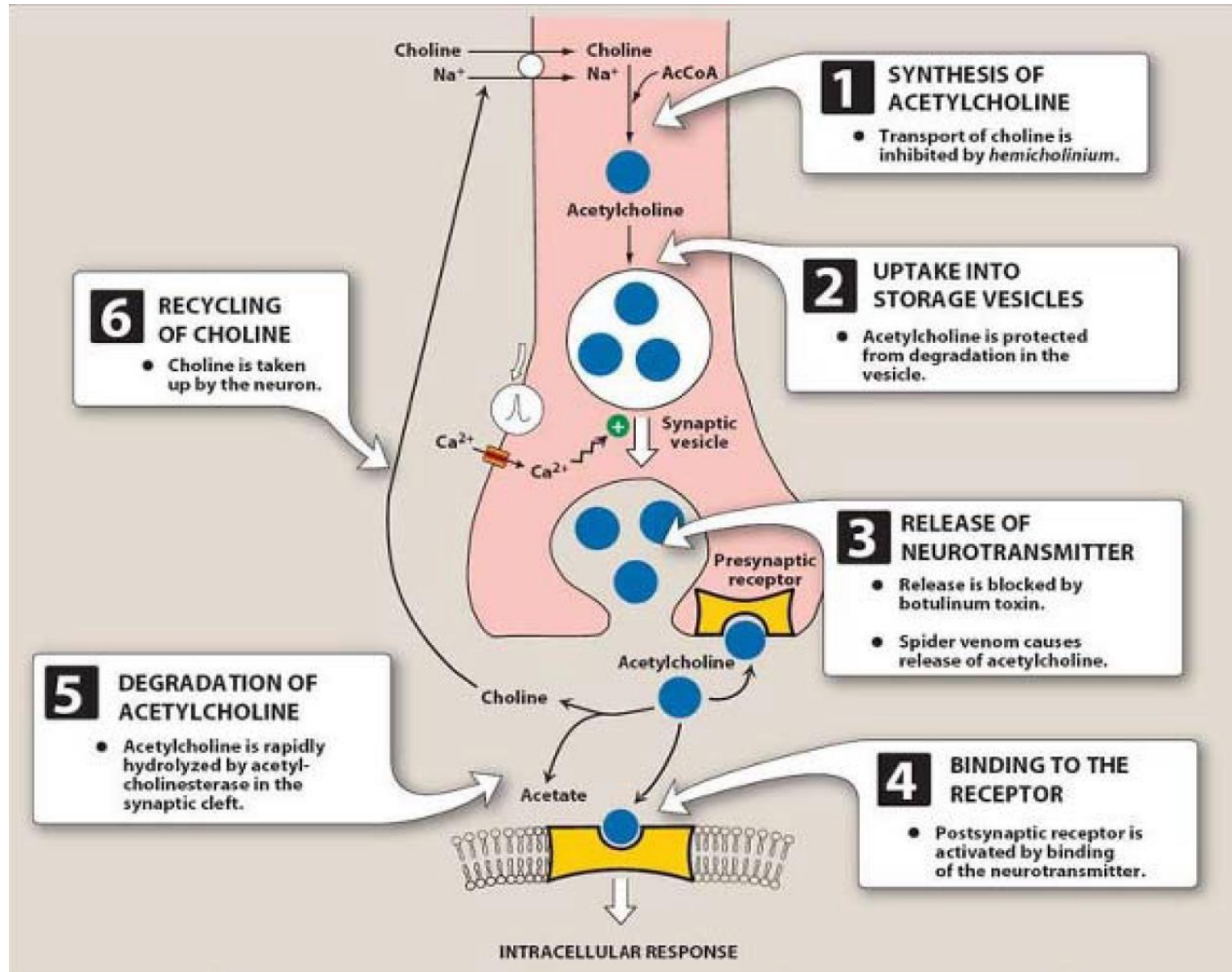
Adrenergic and cholinergic receptors

- **Introduction to cholinergic neurons.**
- **Synthesis and release of acetylcholine.**
- **Types of cholinergic receptors**
- **Introduction to adrenergic neurons.**
- **Synthesis and release of adrenaline.**
- **Types of adrenergic receptors.**

Introduction to cholinergic neurons



Synthesis and release of acetylcholine



الcholine موجود بالcytoplasm حتى يدخل الneural cell يحتاج ATP و Na ويدخل
عن طريق الcotransport وحسب قديش عندي choline available رح اضل اصنع Ach



حتى ما يصيرله degradation لازم يدخل الvesicles, تعمله update ويتخزن

Action potential \rightarrow influx of ca^{++} \rightarrow release of ach

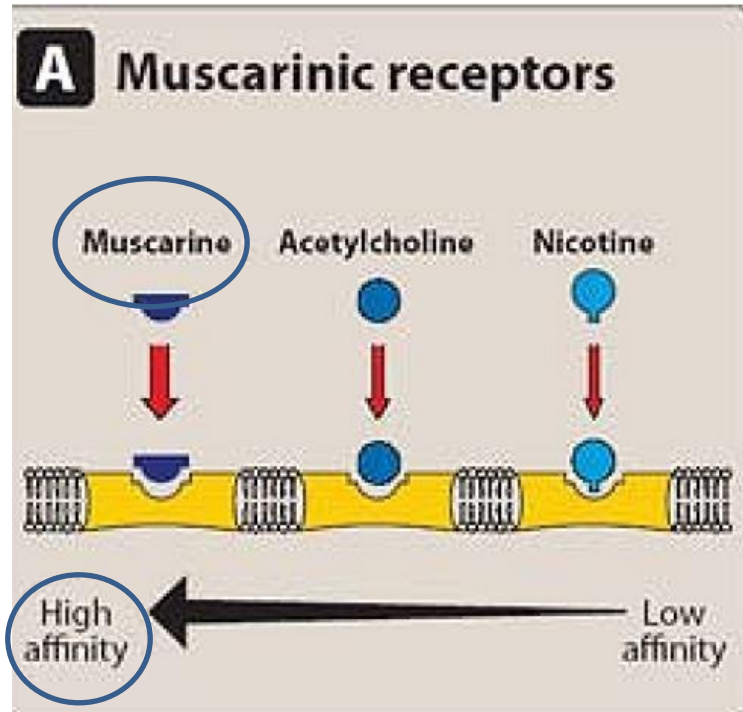
رح يرتبط يا مع الganglia او الorgan effected بالMuscarinic والganglia او M
skeletal بالnicotinic بعدين يصير عندي الaction

Ach is degraded by ach esterase

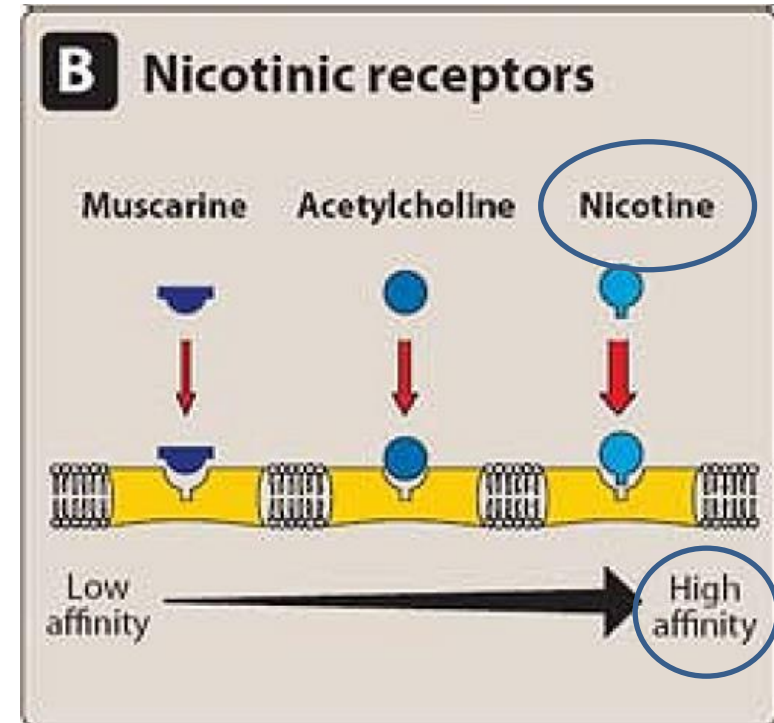
في ادوية تمنع شغل الانزيم هاد الي بكسر الach عشان يضل وقت اطول (agonists)

ولو صارله degradation رح يصيرله recycling into new ach

Types of cholinergic receptors



Located in: Autonomic effector organs such as heart, smooth muscles, brain and exocrine glands.



Located in: CNS, adrenal medulla, autonomic ganglia and neuromuscular junction (NMJ) in skeletal muscles.

Muscarinic receptors

الalkaloids سام لأنه لو ربط مع الreceptors رح تكون الaffinity كثير عالية فيصير عندي
Continuous parasympathetic stimulation

- These receptors belong to the class of G-protein—coupled receptors (**metabotropic receptors**).
- These receptors recognize **muscarine, an alkaloid in certain poisonous mushrooms**.
- There are five subclasses of muscarinic receptors; however, **only M1, M2 , and M3** receptors have been functionally characterized.

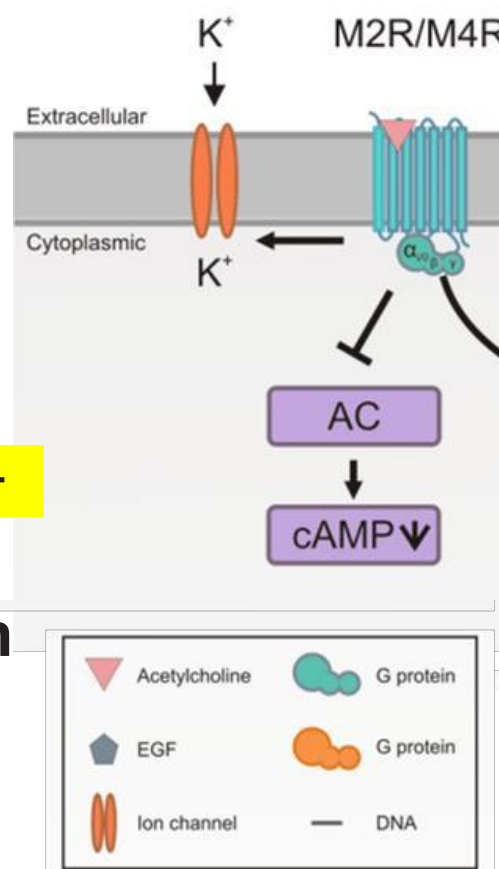
M1: Gastric Parietal cells هاي الM1 مهمة للsecretion of acids فتساعد عالdigestion

M2: Cardiac cells and smooth muscles

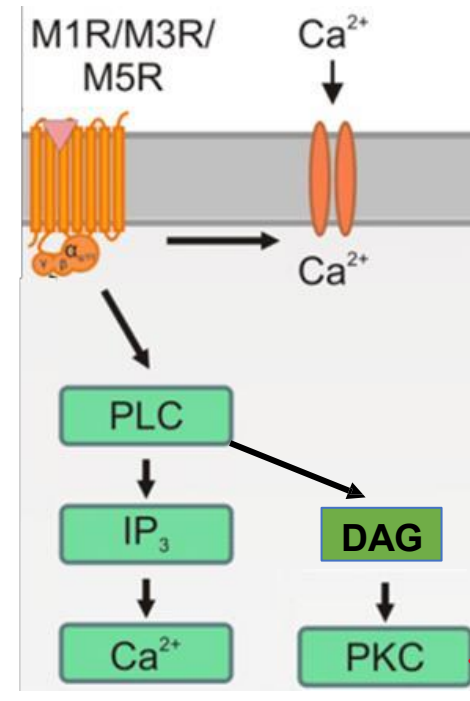
M3: Bladders, exocrine gland and smooth muscles

Mechanism of acetylcholine signal transduction

Activation of the **M2** subtype on the **cardiac muscle stimulates a G-protein that inhibits AC and increases K⁺ conductance**. The heart responds with a decrease in rate and force of contraction.



AC: Adenylyl cyclase .



Activation of M1 or M3 subtypes are activated, the receptor undergoes a conformational change and interacts with a G-protein that activates PLC.

مسؤول عن ال phosphorylation لل protein

IP₃: inositol-1,4,5,-triphosphate

PLC: Phospholipase C.

PKC: protein kinase c

الي بالheart تفرق عن الي بالmuscle smooth

اللي بالheart تعمل inhibition of adenylyl cyclase فيقل عندي الCAmp
فيزيد الHeart rate والContractility

اما الآخر فيعمل activation للplc وهاد يعمل second messenger system
من خلال الip3 الي يحفز الca secretion فيصير عندي response او DAG
الي يعمل phosphorylation لل protein kinase

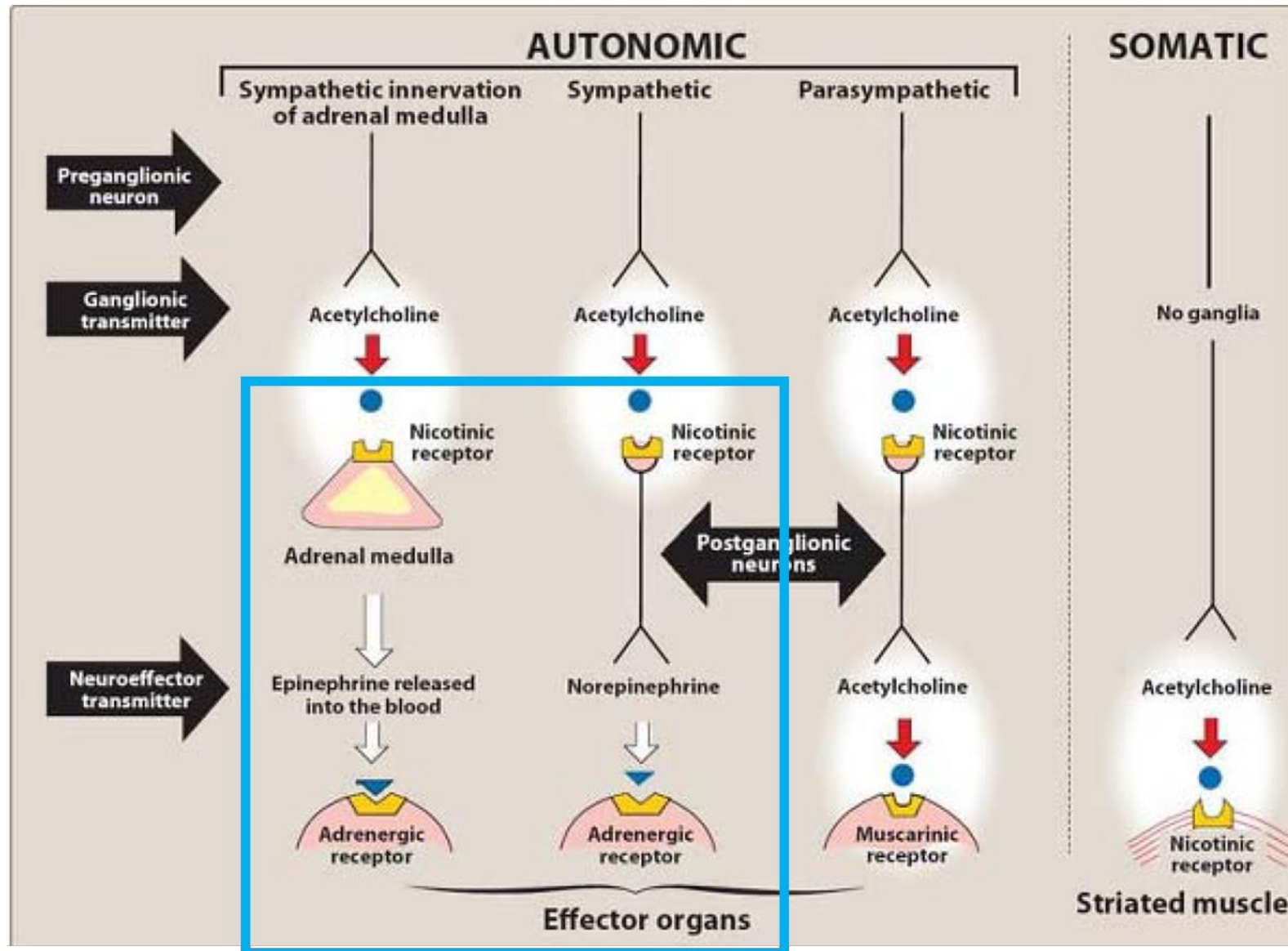
Nicotinic receptors

- The nicotinic receptor is composed of five subunits, and it functions as a **ligand-gated ion channel (ionotropic receptor)**.
- Binding of two Ach molecules elicits a conformational change that allows the **entry of sodium ions, resulting in the depolarization of the effector cell.**
- **Nicotine at low concentration stimulates the receptor, whereas nicotine at high concentration blocks the receptor.**
- The nicotinic receptors of autonomic ganglia differ from those of the NMJ.

Adrenergic neurons

- Adrenergic neurons **release norepinephrine as the primary neurotransmitter**. These neurons are found in the sympathetic nervous system, where they serve as links between ganglia and the effector organs.
- The adrenergic drugs affect receptors that are stimulated by **norepinephrine or epinephrine**.
- **Sympathomimetics**: adrenergic drugs act directly on the adrenergic receptor (adrenoceptor) by activating it. → Act as agonist to the sympathetic system
- **Sympatholytic**: block the action of the neurotransmitters at the receptors.
→ Act as antagonist (نوعا ما)

Adrenergic neurons



Synthesis and release of norepinephrine from the adrenergic neuron

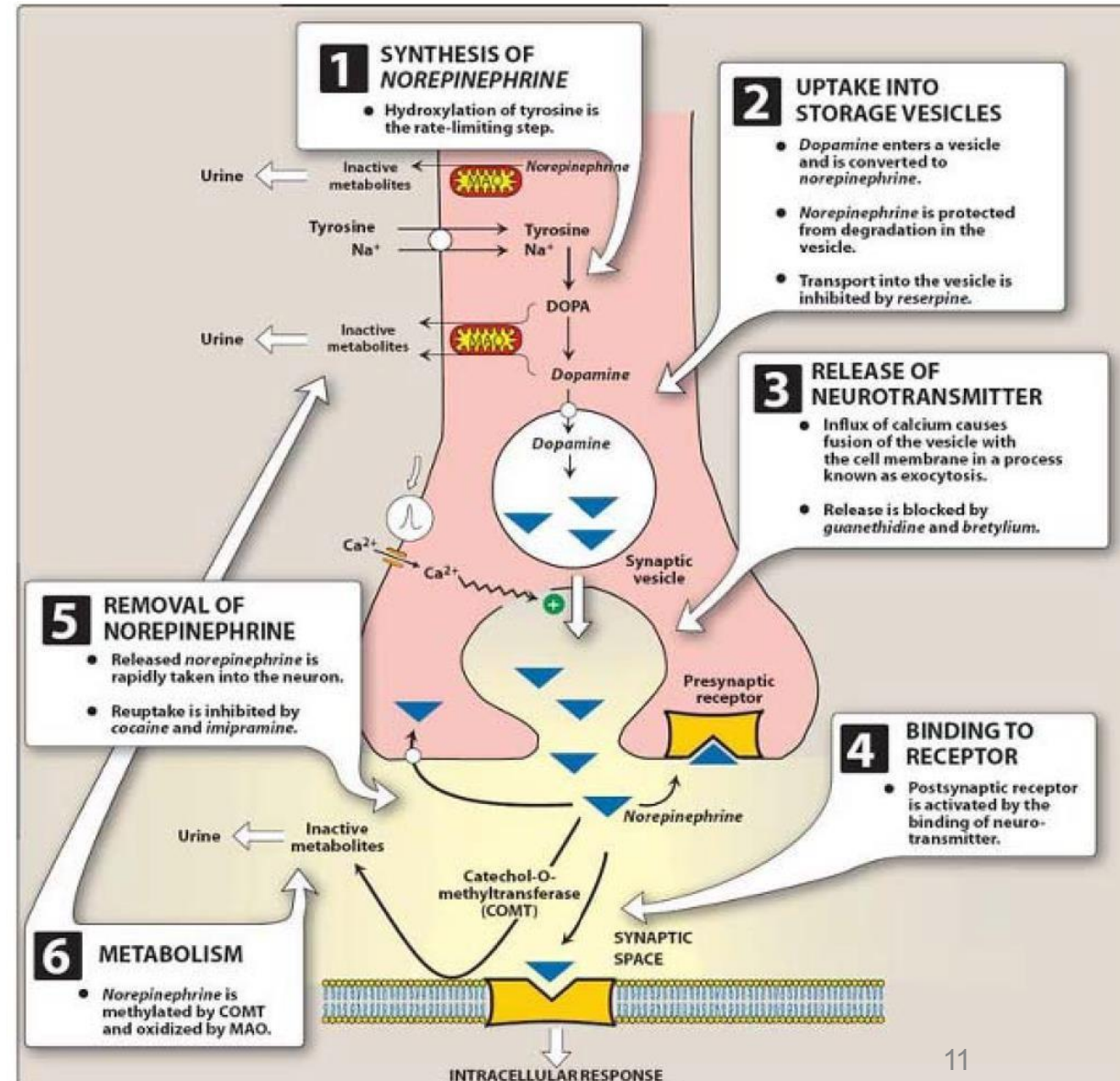
*NE = norepinephrine

Synthesis of NE 1-uptake of tyrosine then it's hydroxylated into dopa then it's either degraded by MAO to inactive metabolite then secreted to urine or decarboxylated into dopamine

بعدين الدوبامين نحطه جوا vesicles (كوتي كوتي ههه مثل دمى امزح) المهم هاي ال vesicles معها ATP تضلها موجودة حتى يصير عندي AP فيطلع ال Ca^{2+} ويصير عندي neurotransmitter بعده release of norepinephrine

هاد ال NE يا يرتبط مع ال α_1 عال postsynaptic بعدين يصير له metabolism by COMT, THEN ITS SECRETED INTO URINE

او مع ال α_2 على ال presynaptic الي يضل بال synaptic region يصير له metabolism

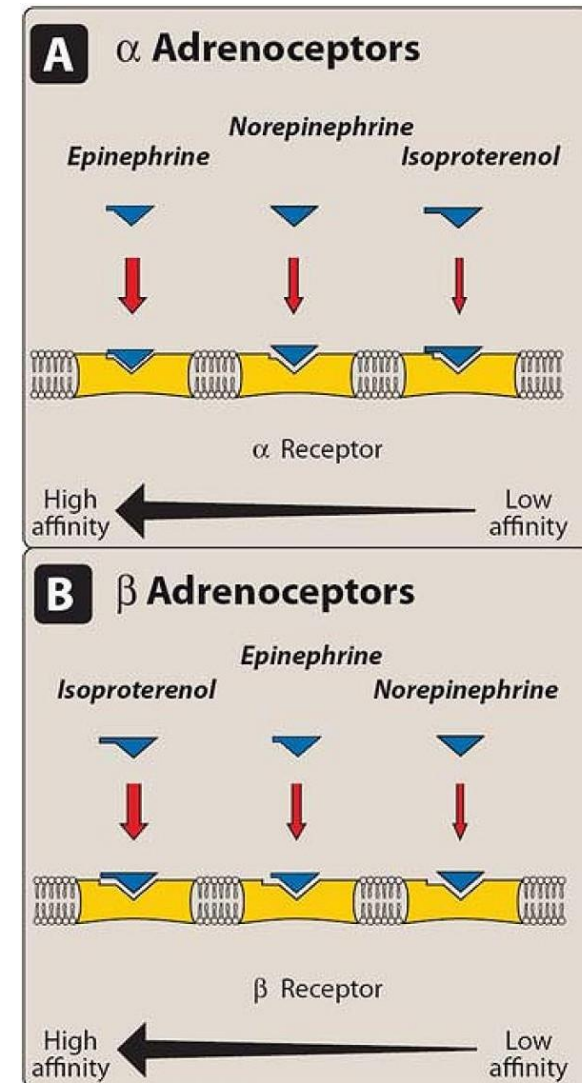


Adrenergic receptors (adrenoceptors)

- Two families of receptors, designated α and β , were initially identified based on their responses to the adrenergic agonists: epinephrine, norepinephrine, and isoproterenol.
- Alterations in the primary structure of the receptors influence their affinity for various agents.

لازم نعرف ال classification حسب ال specificity
وكل adrenoceptor يكون specific لشو

اللهم إني أستودعك أموري كلها, فوقفتني لما تحبه وترضاه



Adrenergic receptors (adrenoceptors)

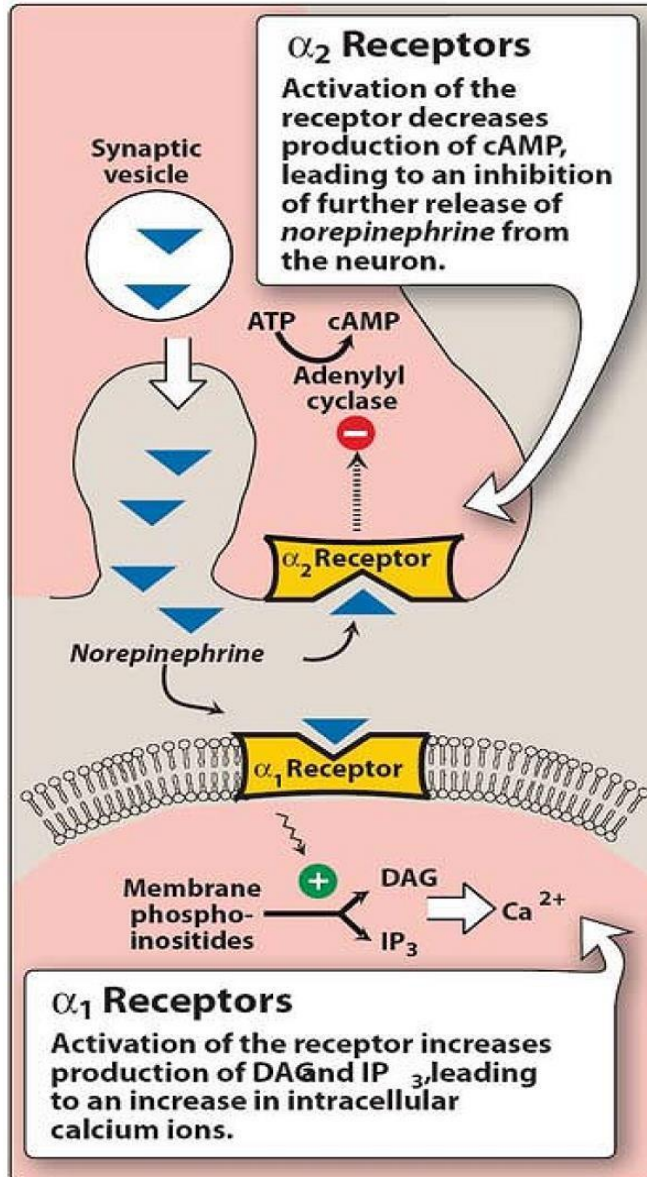
- The **α -adrenoceptors** are subdivided into two subgroups, **$\alpha 1$ and $\alpha 2$** , based on their **affinities for α agonists and antagonists**. The $\alpha 1$ and $\alpha 2$ receptors are further divided into $\alpha 1A$, $\alpha 1B$, $\alpha 1C$, and $\alpha 1D$ and into $\alpha 2A$, $\alpha 2B$, $\alpha 2C$, and $\alpha 2D$
- The **β -adrenoceptors** are subdivided into two subgroups, **$\beta 1$, $\beta 2$ and $\beta 3$** , based on their **affinities for β agonists and antagonists**.

Beta-1 → in heart

Beta-2 → mainly in skeletal muscles

Beta-3 → mainly in adipose tissue

Second messengers mediate the effects of α receptors



لو صار عندي release of norepinephrine ممكن تروح ترتبط
 بال alpha-1 receptor بال effected organ و يعمل activation
 لل phospho-inositides فيفرز DAG و IP₃ , فيزيد الكالسيوم فيصير
 عندي Cellular response in effected Oregon

لو ارتبط بال a2 , هاد , mainly inhibitory رح يعمل inhibition of
 cyclase adenylyl , فيقل ال cAMP , فيقل ال NE او يمنع release of

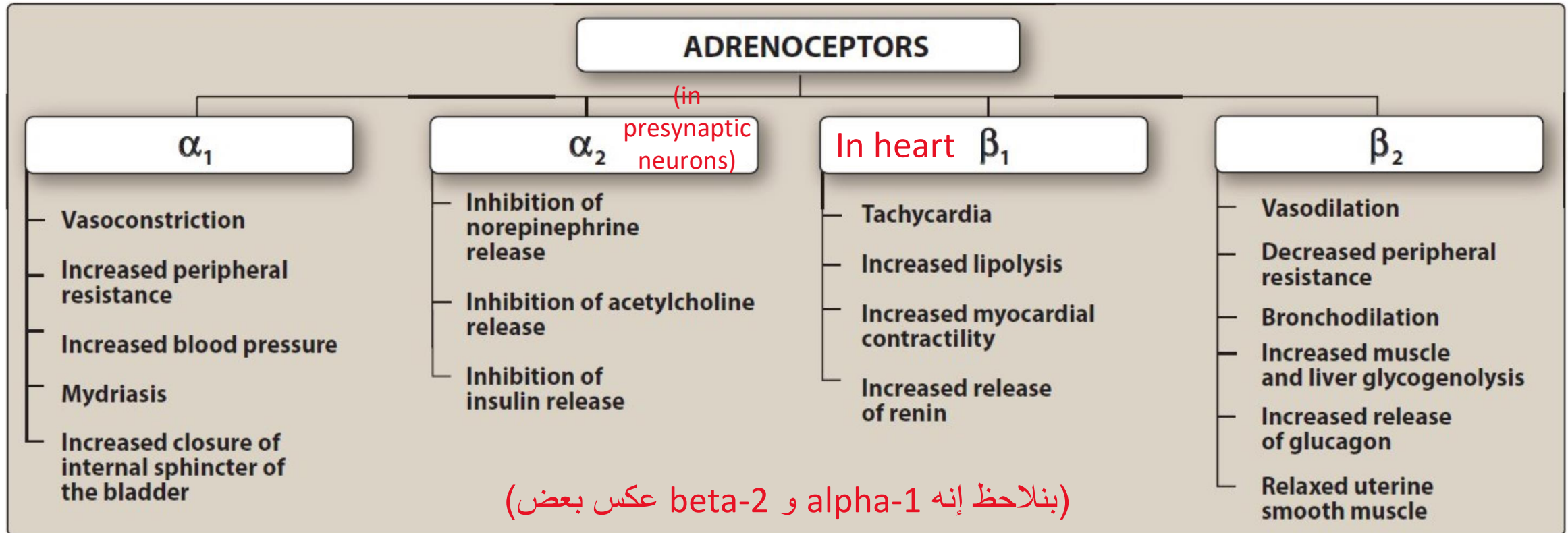
DAG = diacylglycerol
 IP₃ = inositol trisphosphate
 ATP = adenosine triphosphate
 cAMP = cyclic adenosine
 monophosphate.

Adrenergic receptors (adrenoceptors)

- **β_1 Receptors** have approximately equal affinities for epinephrine and norepinephrine, whereas **β_2 receptors** have a higher affinity for epinephrine than for norepinephrine.
- Tissues with a predominance of **β_2 receptors (such as the vasculature of skeletal muscle)** are particularly responsive to the hormonal effects of circulating epinephrine released by the adrenal medulla.
- **Binding of a neurotransmitter at any of the three β receptors results in activation of adenylyl cyclase and, therefore, increased concentrations of cAMP within the cell.**

Adrenergic receptors (adrenoceptors)

****Very important slide****



Heart: predominantly β_1 receptors

Vasculature of skeletal muscle: α_1 and β_2 , $\beta_2 > \alpha_1$

ال β_2 بنستخدمها مع مرضى ال asthma (الربو),
السبب إنه يكون عندهم bronchoconstriction

Adrenergic receptors (adrenoceptors)

Desensitization of receptors

- Prolonged exposure to **the catecholamines reduces the responsiveness of these receptors, a phenomenon known as desensitization.**
- Three mechanisms have been suggested to explain this phenomenon:
 - 1) **Sequestration of the receptors** so that they are unavailable for interaction with the ligand.
 - 2) **Down-regulation**, that is, a disappearance of the receptors either by destruction or decreased synthesis
 - 3) An **inability to couple to G protein**, because the receptor has been phosphorylated on the cytoplasmic side.