تفريغ فارما ١

اسم الموضوع: Cholinargic Antagonists

~ lec 8 ~ Part 2 ~

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لجان الدُّفعات

Depolarizing agents

= Depolarizing & Repolarizing

عشان يصير Na+ influx لازم يكون في

مفعولها أطول لأنه AchE ما بعدر يكسرها بس في انزيم اسمه Pseudocholinesterase موجود داخل الدم

- Act as Ach , but with longer duration of action due to more resistance to AchE
- Succinylcholine is the only depolarizing agent is used.

- The depolarizing agent first causes the opening of the sodium channel associated with the nicotinic receptors, which results in depolarization of the receptor **(Phase I).** (fasciculations).

Post Somatic

Ion Gated channel

Na^+ influx

Depolarization وبيصير عنا

Phase 1 وبيدخل بال

العضلة بترتعش

كيف بعالجها؟ بعطي Small Dose of non-Depolarizing

Receptors بيرجع بفعل ال ← وبيرتبط Ach بمكانه

Action Potential بتوقف ال Neuron وال Na^+ ببطل يدخل Receptor على ال Succinylcholine ⇐ لما يطول ارتباط

Phase 2 Repolarization ← أي

- Continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses.
- **With time**, continuous depolarization gives way to **gradual repolarization** as the sodium channel closes or is blocked. This causes a resistance to depolarization **(Phase II)** and flaccid paralysis. → Weakness, ↓ mucle tone

نفس الـ non-Depolarizing

- the respiratory muscles are paralyzed last
- Normally, the duration of action of ***Succinylcholine*** *is extremely* short, because this drug is rapidly broken down by plasma pseudocholinesterase.
- Because of its rapid onset and short duration of action, *succinylcholine is useful when rapid endotracheal intubation is required*

Rapid action الـ
والله مفعول قصير جدًا
ودعم هيك مفعوله
أطول من Ach

زي لما بدنا نركب
للمريض جهاز تنفس
صناعي

داخل حنجرة إدخال الأنبوب

- *Succinylcholine is injected intravenously* IV infusion
- sometimes given by continuous infusion to maintain a longer duration of effect. Drug effects rapidly disappear upon discontinuation

يعني بعد ما أوقف الدوا
راح ينتهي مفعوله خلال فترة قصيرة

Adverse effects

- ❖ Hyperthermia T ↑
- ❖ Apnea (in genetically suseptable patients)
- ❖ Hyperkalemia K↑

صعوبة بالتنفس

↓Cholineserases
داخل الدم عندهم قليل
فتكسر الدواء راح يكون
بطيء ⇐ راح يطول مفعول الدواء عندهم

Degoxin ⇒ Block Na-k Bump
Ca influx → ↑ Heart Contractility
+ ionotropic agent

Depolarizing agent فبشتغل عكس شغل ال

Adrenergic Agonists

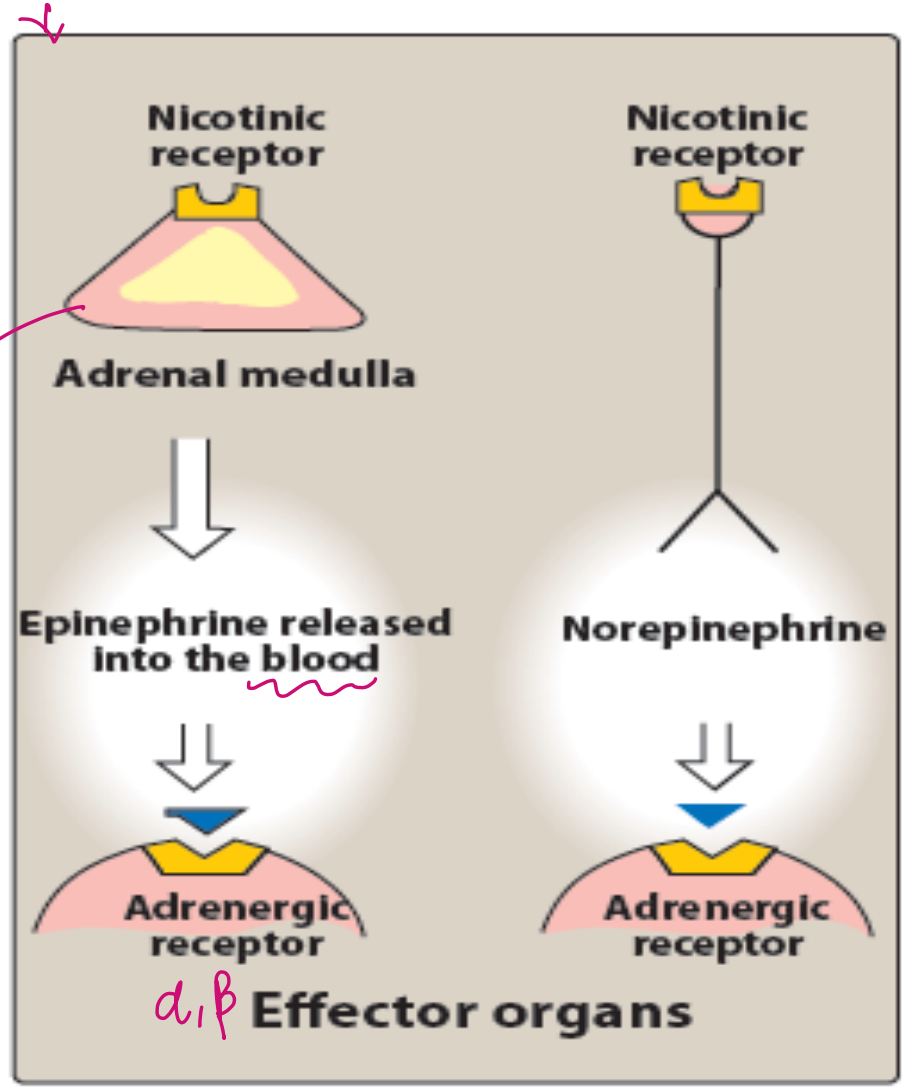
Sympathatic Pathway

الأماكن اللي بتفرز Norepinephrine

وين موجودين ؟

① Past ganglunic (Sympathatic)

② Pre ganglunic ⇒ Adrenal على الـ medulla



%80 epinephrine
%20 Norepinephrine ← endo-crine

Figure 6.2
Sites of actions of adrenergic agonists.

Adrenergic Agonists

❑ Neurotransmission at adrenergic neurons

- **N**orepinephrine is the neurotransmitter instead of acetylcholine

- The process involves :

1. Synthesis
2. Storage
3. Release
4. receptor binding
5. removal of the neurotransmitter from the synaptic gap

الترتيب مطلوب

الدكتور اختصر شرح السلايدات

بشرح الرسمة

1. Synthesis of norepinephrine

20%

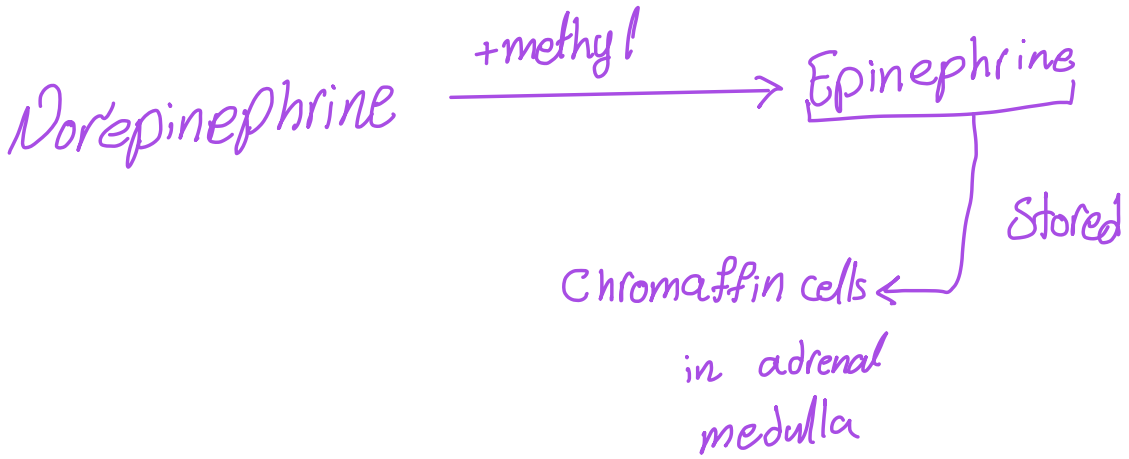
amino acid

- Tyrosine entry to the adrenergic neuron via Na+ dependent carrier
- Tyrosine hydoxylation ** RLS (+ OH)
- DOPA decarboxyation (-COOH)
- Dopamine hydroxylation(inside the vesicles)

2.Storage of norepinephrine in vesicles

- *Dopamine is then transported* into synaptic vesicles by an amine transporter system that is also involved in the reuptake of preformed norepinephrine.
- This carrier system is blocked by *reserpine*
- *Dopamine is hydroxylated* to form norepinephrine by the enzyme, dopamine b-hydroxylase
- Stored in the vesicle untill released

- • In the adrenal medulla, norepinephrine is methylated to yield epinephrine, which is stored in chromaffin cells along with norepinephrine.



3.Release of norepinephrine

- Ca+2 influx to the cytoplasm
- Vesicles fuse with the cell membrane
- Expelling of its content

exocytosis

4. Binding to receptors

- Norepinephrine binds to postsynaptic receptors
- Elicit cascade of events including secondary messengers.
  - cyclic adenosine monophosphate cAMP
  - phosphatidylinositol cycle
- "Norepinephrine also binds to presynaptic receptors that modulate the release of the neurotransmitter"

5. Removal of norepinephrine

- Possible removal mechanisms:
  - Diffuse out of the synaptic space and enter the general circulation
  - Metabolism to O-methylated derivatives by postsynaptic cell membrane–associated catechol O-methyltransferase **(COMT)** in the synaptic space
  - Be recaptured by an uptake system that pumps the norepinephrine back into the neuron

When NE reenters Adrenergic neurons

- can be oxidized by monoamine oxidase **(MAO)** present in neuronal mitochondria.

Urine ⇐ لوين بروحوا ؟

- The inactive products of norepinephrine metabolism are excreted in urine as vanillylmandelic acid, metanephrine, and normetanephrine.

MAO inhibitors أدوية

MAO Enzyme بتوقف عمل الـ

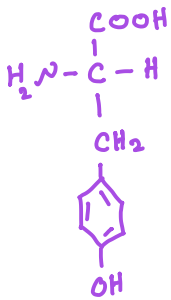
Dobamine والـ Dobal على الـ

Epinephrine بالتالي بزيد تحولهم لـ

&

Norepinephrine

Sympathatic effect وبزيد الـ



1 Tyrosin

كيف بفوت للخلية ؟

عن طريق Nachannel

Tyrosin $\xrightarrow{\text{Hydroxylation}}$ Dopa

بحوله

لـ

Rate limiting step بعملية اسمها

* واذا ما صارت ما بتكمل باقي العملية

وبعدها

Dopa $\xrightarrow[\text{Dopadecarboxylase enzyme}]{\text{Decarboxylation}}$ Dopamine

2 Vesicle بتروح لـ

* Reserpine فيا دوا من ادوية الضغط اسمه بمنع هاي الخطوة وباقي الخطوات ما راح تكمل

Dopamine

Vesicle بفوت لـ

Amin transporer عن طريق

جوا الـ Vesicle بصير عليه Hydroxylation

بواسطة انزيم اسمه Dopamine b-Hydroxylase

مسؤول عن تحويل الـ Dopamine → Norepinephrine

Viscele بتخزن داخل الـ

بانتظار action potential

3 Action potential صار Ca^{+2} influx → exocytosis

فالـ Norepinephrine بصير بالـ Synapse

عنده خيارين للربط

→ الخيار الاول :

Post-synaptic يرتبط بالـ Receptor

α or β ⇒ Gprotien

α_1, α_2 $\beta_1, \beta_2, \beta_3$

$\alpha_1, \beta_1, \beta_2, \beta_3$ Post synaptic

β_1 ⇒ موجود على الـ Heart , Kidney

Heart ⇓ Cardiac output↑

Kidney ⇓ بتحفز الـ RAAS

β_2 → موجود على Smooth musles

→ الخيار الثاني

Pre-synaptic يرتبط بالـ Receptor

α_2 Receptor

Modulation بعمل *

α_2 + NE ⇒ cAMP ↓

NE Agonist

Blockage of NE Secretion

↓ Post synaptic بالـ NE ارتباط

↓ Sympathatic stimulation

↑ Parasympathatic effect

α_2 Agonist فلما اعطي Sympathatic بوقف Parasympathatic بزيد.

صح هي Agonist لكن اشتغلت as Adrenargic Antagonist

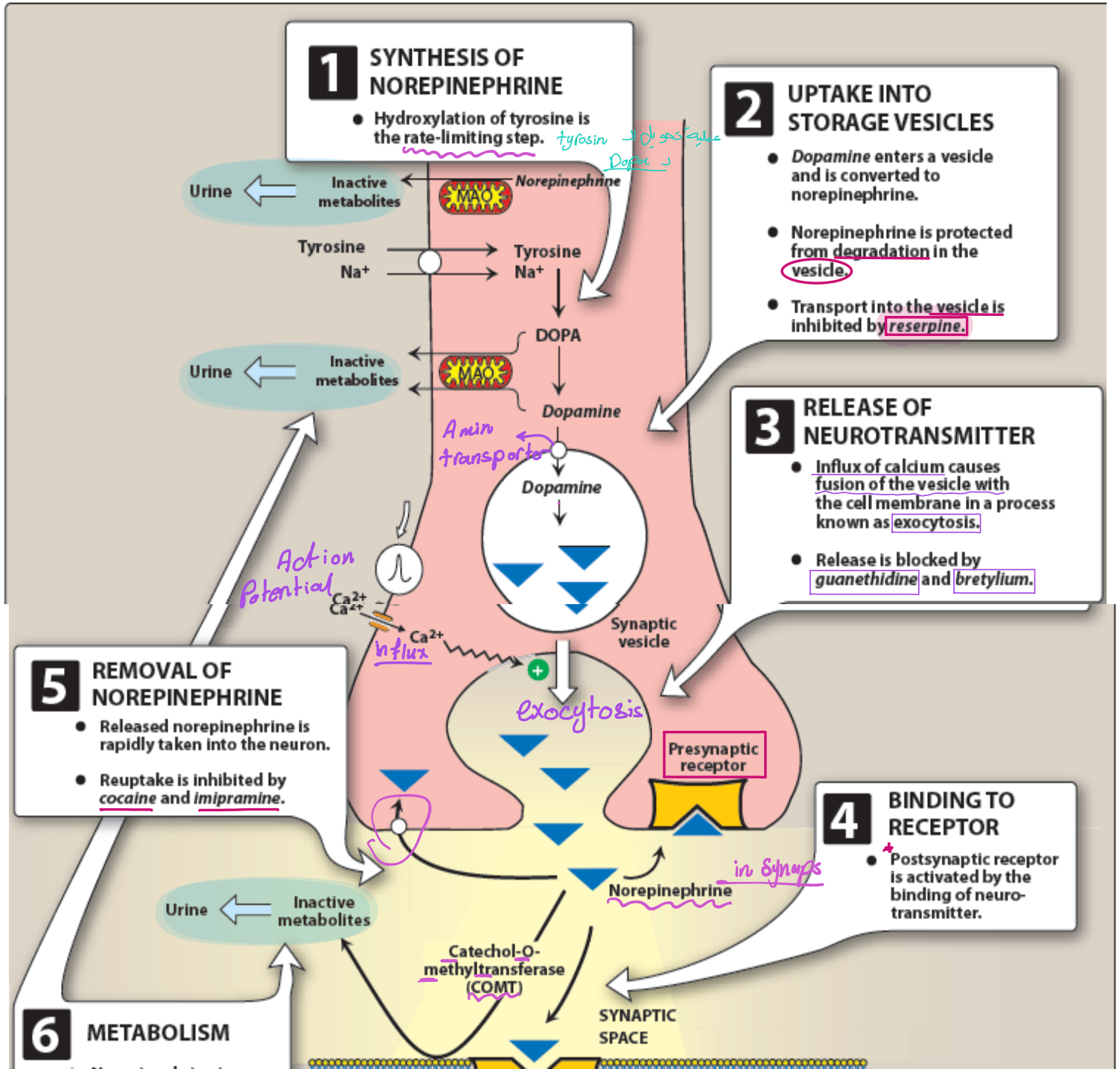
بعد ما ربط NE على ال
Adrenargic Receptor
عنده ٣ خيارات

① Diffusion → Blood circulation
ممكن بعدها يصير عليه metabolism او يرتبط
بمكان ثاني

② Metabolism by enzyme اسمه
COMT - Catechol O-Methyl
Trasferase
يكون موجود بال Synaps

③ Reuptake to the Presynaptic
neuron ⇒ NE يرجع على شكل
وبس يفوت يتأكسد بواسطة MOE

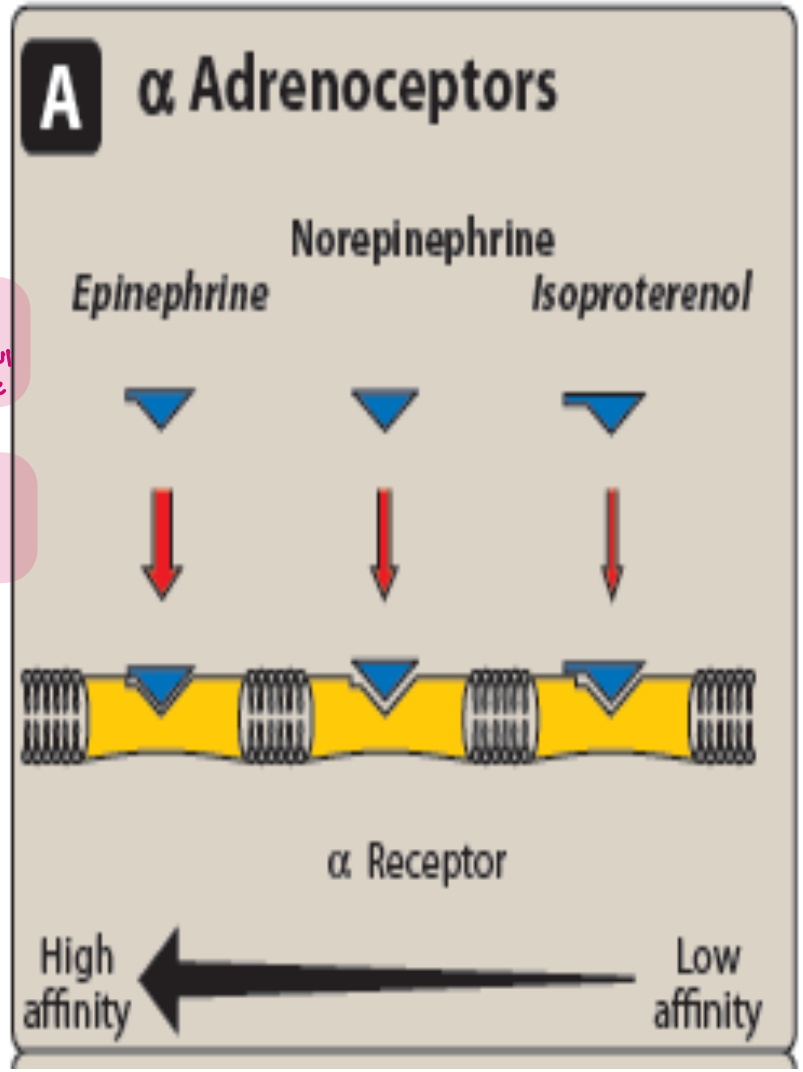
الرسمة مهمة جدًا

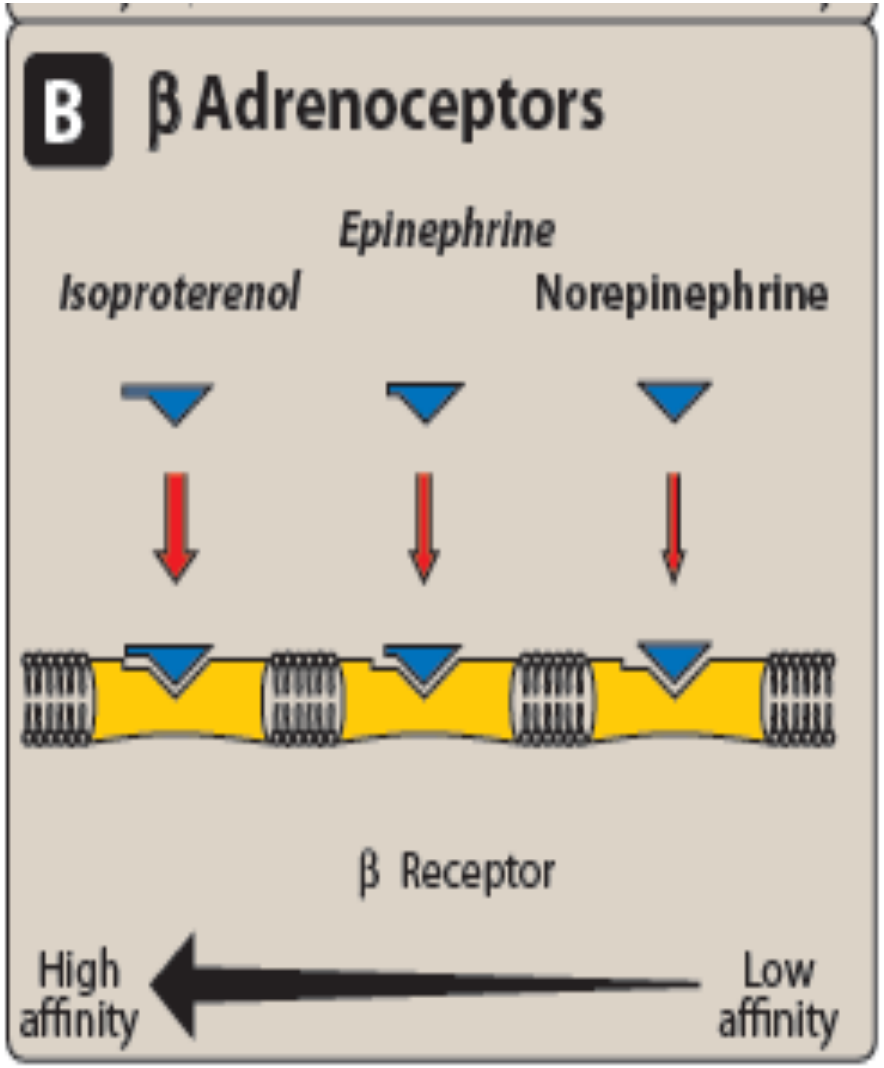


Adrenergic receptors (adrenoceptors)

Epinephrine دائمًا
الـ Affinity لأنه اعلى من Norepinephrine

isoporterenol بتختلف
α, β من





Epinephrine
↓
Norepinephrine
↓
isoproterenol

Adrenergic receptors (adrenoceptors)

α Receptors

- α 1 :
  - postsynaptic effector organs
  - contraction of smooth muscles
  - Activation increases IP3 and DAG and Calcium release from the ER to cytplasm

$Gq \uparrow \Rightarrow IP_3 \uparrow , DAG \uparrow \Rightarrow Ca^{+2} \uparrow$

Secreation ↑, Contraction ↑

- α 2 :
  - located presynaptically
  - Beta cell of the pancreas and on certain vascular smooth muscle cells, control adrenergic neuromediator and insulin output,
  - feedback inhibition on NE
  - fall in the levels of intracellular cAMP.

$G_I \Rightarrow cAMP \downarrow$

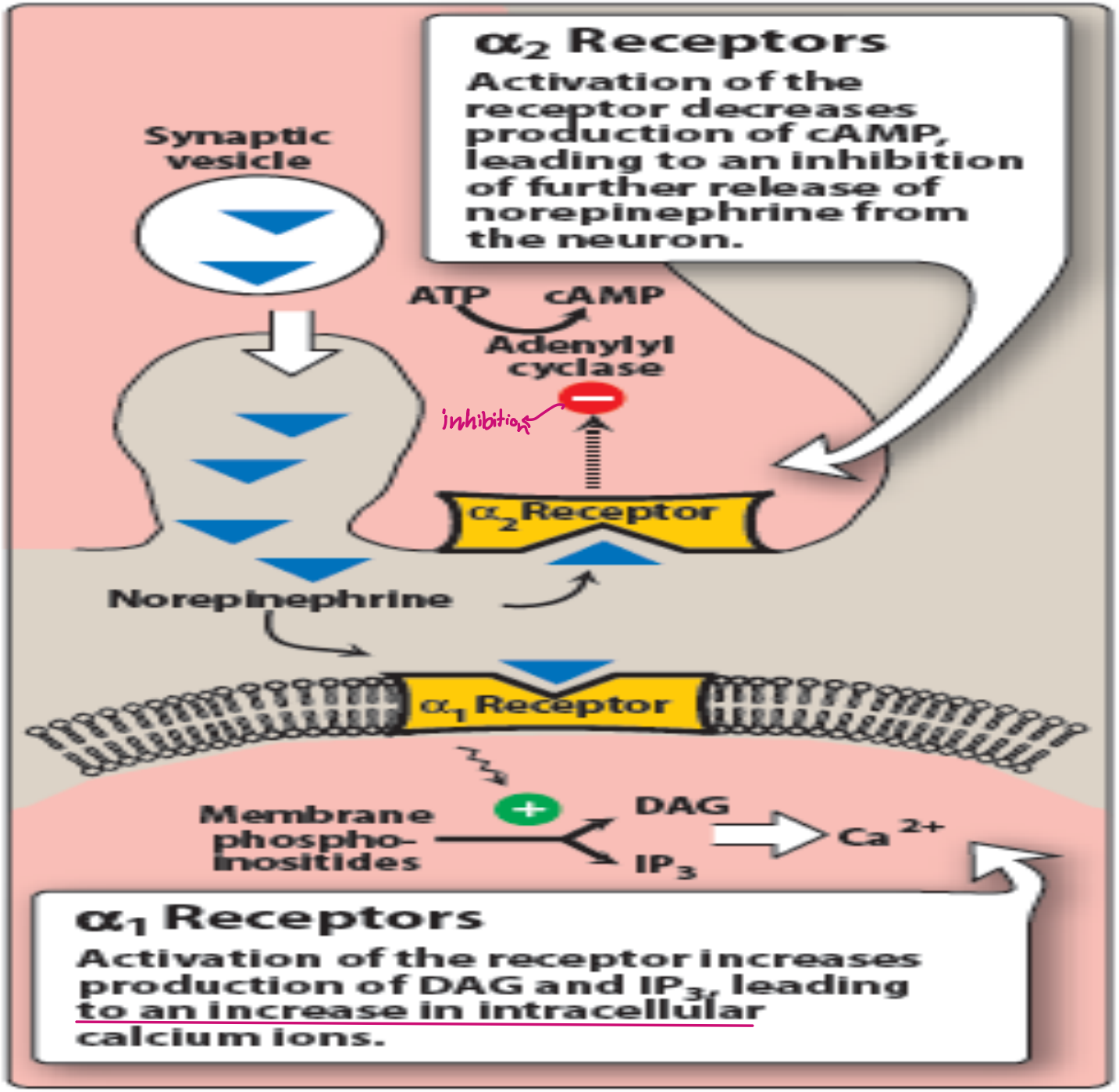
Heart contractility ↓

↑ Smooth muscles Contraction

α_1
α_2 ⇒ G-protien
2nd massanger يعني عنا
DAG , IP_3 , cAMP

إذا: cAMP زاد

inhibition of smooth بعيق
muscles contraction
Relaxation يعني بعمل
عليه
يكبح على القلب
Contractility بزيد ال



→ A , B , C, D

- The α1 and α2 receptors are further dividedinto α1A, α1B, α1C, and α1D and into α2A, α2B, and α2C. This extended classification is necessary for understanding the selectivity of some drugs.
- For example, ***tamsulosin*** *is a* ***selective α1A*** **antagonist** that is used to treat **benign prostate hyperplasia**. The drug is clinically useful because it targets α1A receptors found primarily in the urinary tract and prostate gland.

يعالج تضخم البروستات ⇩ α1A antagonist

مش موجود بالقلب

فهو Selective

بدل مايخرب الدنيا ويأثر على القلب

أثر بس على Site of action

ويحل المشكلة بأقل آثار جانبية

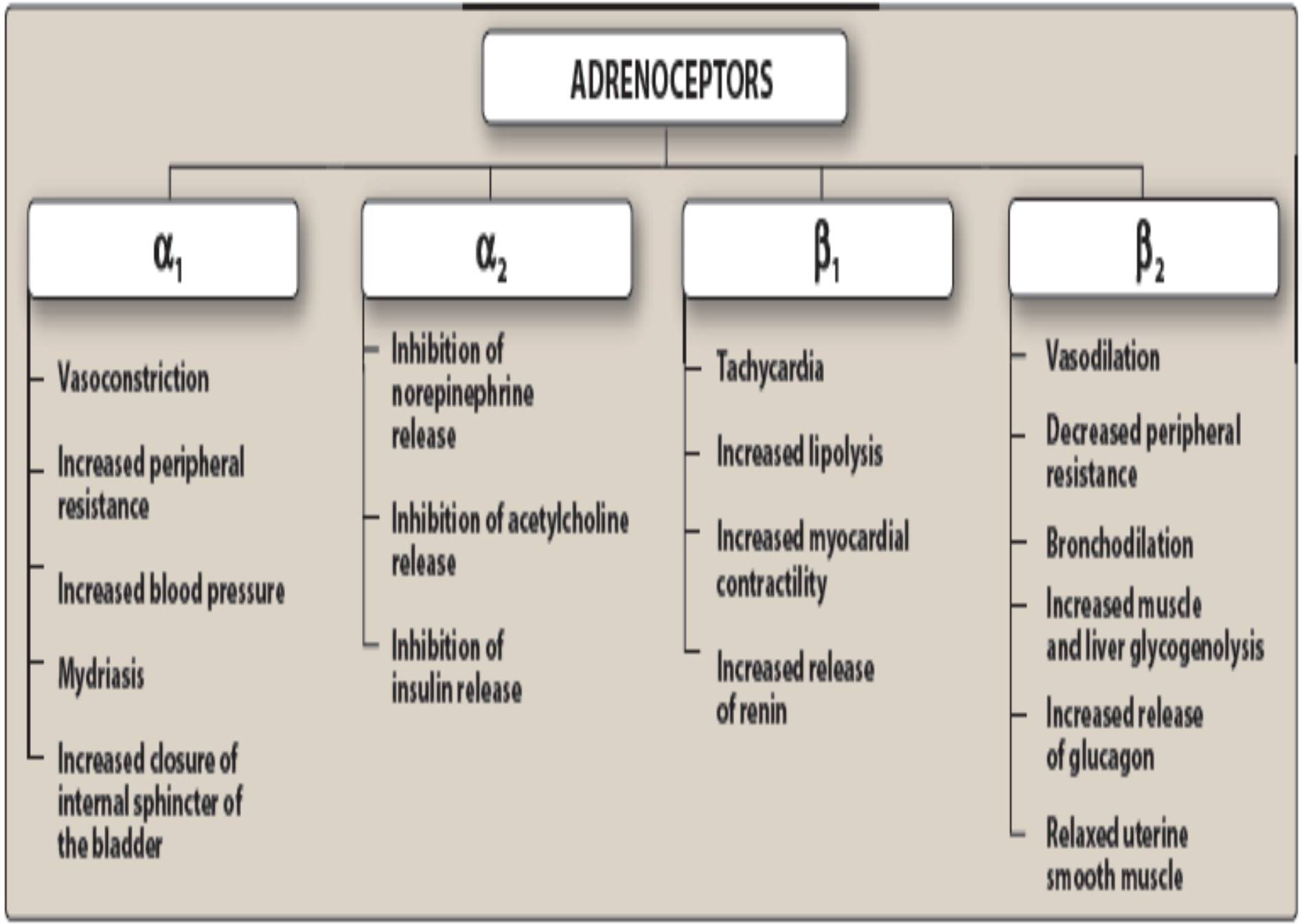
β Receptors

⇒ G_s protien ⇒ ↑cAMP → Heart Contractility ↑
→ Smooth muscle Relxation↑

- Strong response to **isoproterenol** rather than to epinephrine
- The β-adrenoceptors can be subdivided into three major subgroups

- **β1 (heart, kidney)**
- **β2 (lung, blood vessels)**
- **β3 (AD)**

Binding of a neurotransmitter at any of the three β receptors results in increased concentrations of cAMP within the cell


ADRENOCEPTORS
α1
Vasoconstriction
Increased peripheral resistance
Increased blood pressure
Mydriasis
Increased closure of internal sphincter of the bladder
α2
Inhibition of norepinephrine release
Inhibition of acetylcholine release
Inhibition of insulin release
β1
Tachycardia
Increased lipolysis
Increased myocardial contractility
Increased release of renin
β2
Vasodilation
Decreased peripheral resistance
Bronchodilation
Increased muscle and liver glycogenolysis
Increased release of glucagon
Relaxed uterine smooth muscle