PHARMACOLOGY

Assem khatatbeh

Ameera otoom

Lecture 13

CHOLINERGIC ANTAGONISTS

ANTIMUSCARINIC AGENTS

- Atropine
- Cyclopentolate
- Ipratropium
- Scopolamine
- Tropicamide

GANGLIONIC BLOCKERS

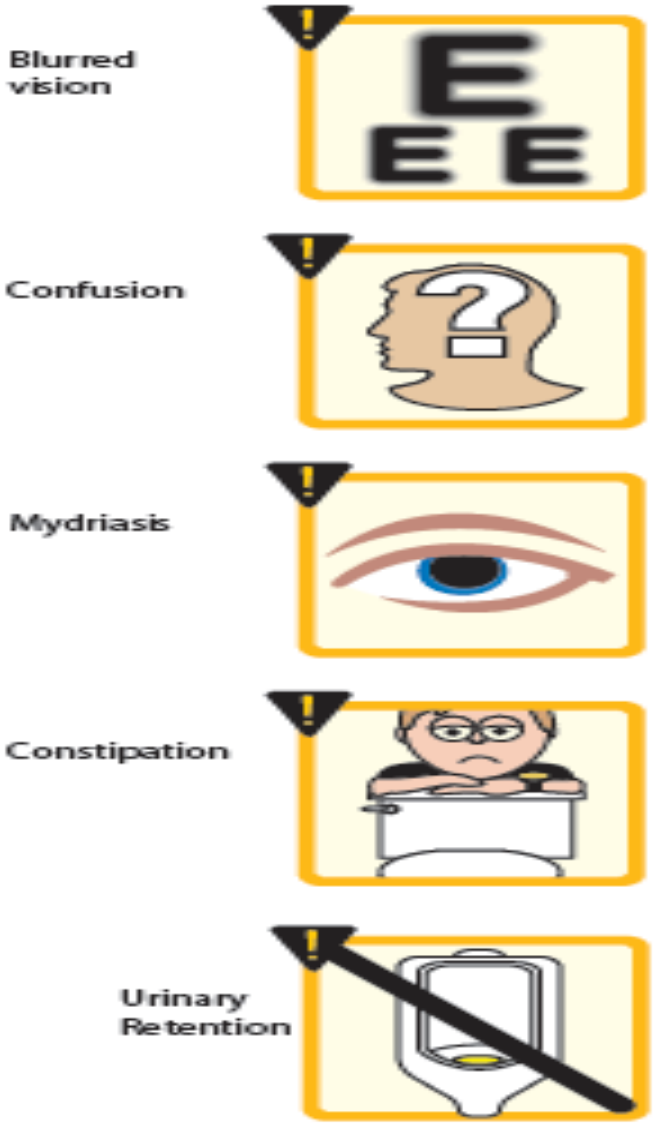
- Mecamylamine
- Nicotine

NEUROMUSCULAR BLOCKERS

- Atracurium
- Cisatracurium
- Doxacurium
- Metocurine
- Mivacurium
- Pancuronium
- Rocuronium
- Succinylcholine
- Tubocurarine
- Vecuronium

- Cholinergic agonist used mainly to treat glucoma, post operative urinary retention (because after the operation, the urinary bladder and GIT block and we want to reactivate them).

Action of anticholinergic



1. mydriasis (dilation of t he pupil)
2. antispasmodic (reduc e motility of the GI tra ct)
3. Reduce Hypermotility states of the urinary bl adder.
4. blocks the salivary gla nds secretion (cause x erostomia).

- General action of cholinergic antagonist:
  1) Eye ⟶ causes mydtiasis

  2) GIT ⟶ decrease GIT motility

  3) Block salivary glands secretion

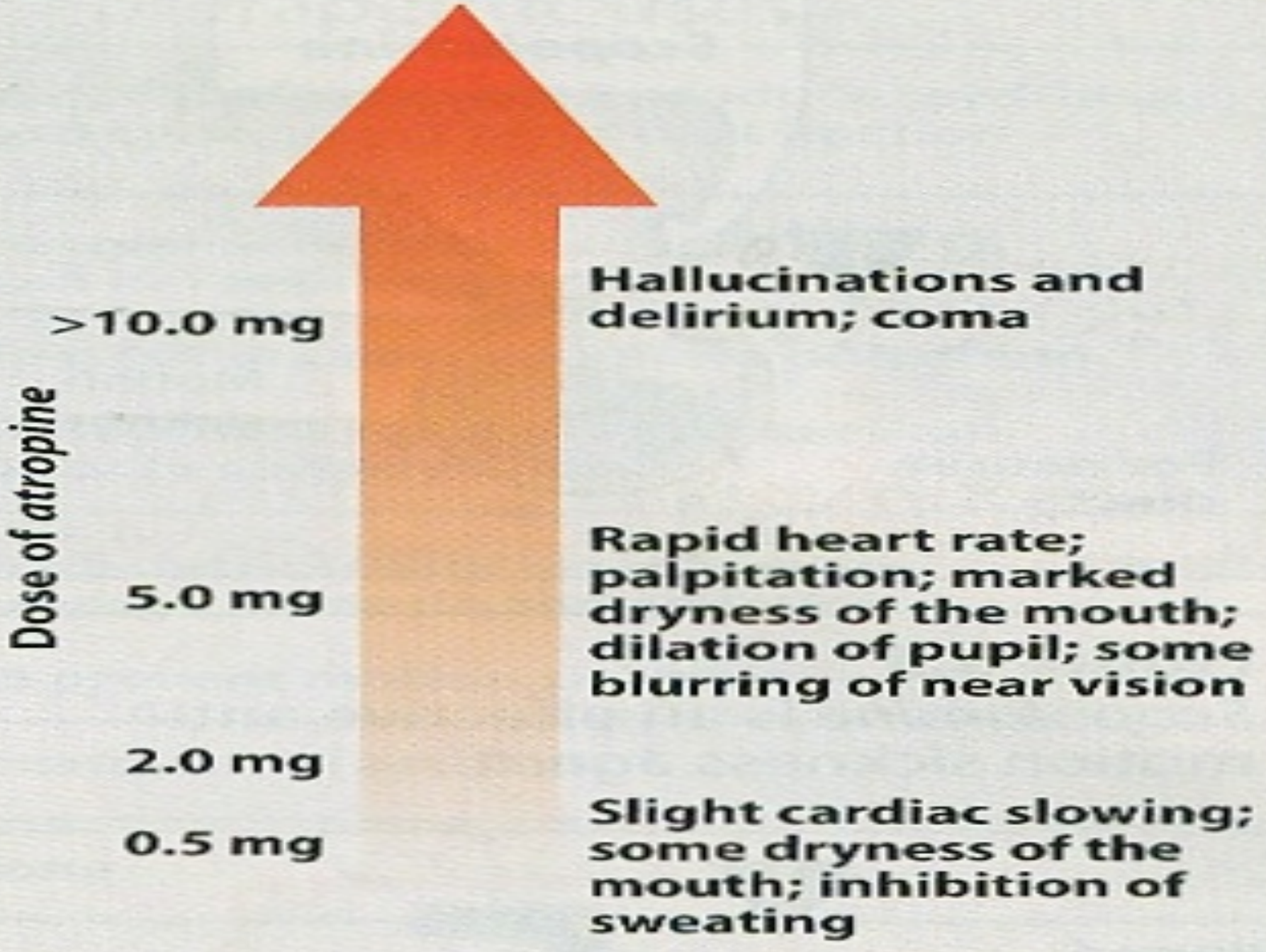
  4) Block GIT secretion

قبل أي عملية لازم نعمل تهيئة لبعض الأدوية سواء كانت على العضلات او ال GIT او ال salivary, لانه ممكن يعمل aspiration pneumonia

لانه اذا ال saliva كانت عالية او ال GIT HCL كانت عالية رح تعمل reflex وهذا رح يرجع يدخل على ال lungs ويعمل pneumonia اشي اسمه ممكن يعمل block respiration ويؤدي للاختناق, وهاي لازم نتذكرها بال Atropine اللذي يعتبر preanesthetic drug (دواء قبل التخدير)

I. Antimuscarinic Agents

- 1. Atropine:
- used as an antispasmodic to reduce activity of the GI tract
- used to reduce hypermotility states of the urinary bladder.
- Used as antidote for cholinergic agonist
- Antisecretory before surgary.
- **Contraindicated on narrow angle glucoma**


Dose of atropine
>10.0 mg
Hallucinations and delirium; coma
5.0 mg
Rapid heart rate; palpitation; marked dryness of the mouth; dilation of pupil; some blurring of near vision
2.0 mg
0.5 mg
Slight cardiac slowing; some dryness of the mouth; inhibition of sweating

- Atropine: is a pre-anesthetic drug used to decrease salivation and GIT motility.

في أدوية تعطى قبل العملية وفي أدوية تعطى بعد العملية
the post operative drugs must reverse the action of the pre operative drugs.

مثال: قبل العملية بعطي المريض muscle relaxent... بعد العملية أو خلالها بعطي المريض إبرة Antidote (neostigmine) هاي بتعمل The reverse action of muscle relaxant
يعني كل اشي بعطيه بالأول لازم أعمله reverse حتى يرجع للوظيفة الطبيعية

Atropine is known as Antidote more than as it therapeutic use.

Atropine is the major antidote for all cholinergic acting on muscarinic receptors, Ex: bethanochole is reversed by Atropine.

Atropine is an emergency drug... it is a pre-anesthetic drug used to decrease salivary and acid secretion, and it can be reversed after the surgery by other drugs.

it is also antispasmodic (مضاد للتشنج) but it has a high side effects and it is not selective (not safe), so I can use other drugs to be more selective to M_1 receptor in the gastric other than M_2 and M_3 (because atropine is generally muscarinic receptor).

- The problem with Atropine as antispasmodic that it's dose is related to response (this is not normally happen, usually we have maximum dose and it reaches after after certain concentration) but they found that the action of Atropine is changed related to the changing of the dose

- At low dose (5mg) ⟶ Atropine will act on the heart mostly, causes bradycardia (بطء في عمل القلب) and inhibit the GIT, saliva, and sweating.

- By increasing the dose, it will act on heart rate mostly ⟶ it will increase the heart rate and causes tachycardia (عدم انتظام دقات القلب)

- And at higher dose it will enter the brain (can cross the BBB because it's non polar) and causes Hallucination (هلوسة)

- This dose related response of Atropine prevents the usage of Atropine at higher doses, so we use Atropine at lower doses because we don't want to cause palpitation (زيادة في دقات القلب) or tachycardia, and I don't want to enter the brain, so it's very hard to deal with Atropine as a dose, because if we increase the dose we increase the action.

linear dose response مش رح يعطينا Atropine يعني بإختصار ال curve

- We use Atropine for emergency and toxicity

Atropine بعطيه cholinergic يعني اذا واحد تسمم بمبيدات حشرية وزاد ال asantidote

I. Antimuscarinic Agents

- **2. Scopalamine**
- used for motion sickness

- 3. **Ipratropium**
- as bronchodilators for maintenance treatment of chronic obstructive pulmonary disease (COPD)

- 4. **Benztropine**
- treatment of Parkinson disease

- The remaining drugs are synthetic compounds derevative from Atropine.
- Scopalmine or we call it hyoscine is one of the major drug used for spasmodic and it's OTC drug, and it's therapeutic window and index is very wide.
- Also, we use it for motion sickness (دوار الحركة)

يعني في ناس بصيبهم دوار لما يسافروا أو حتى بمجرد انهم بركبوا بالسيارة هذول بنعطيهم scopalamine, ولكن بشرط ما يكون هو السايق لانه بسبب نعاس

- Scopalmine is very safe for pregnancy, even in the first few months.

- Ipratropium:
- Lung is innervated by muscarinic and adrenergic receptors.
- β_2 adrenergic receptor in the lung, so when we give β_2 agonist in sympathetic, it will cause branchodilation.
- Branchodilation of Ipratropium is very important, but not like β_2 agonist, they have different efficacy, β_2 agonist is more selective and more predominant.

يعني لقوا انه β2 بالرئة عالي كثير, أكثر من M وبالتالي الفعالية اله أكثر, والدواء اللي بشتغل على β2 اسمه ventoline

- When I use Ipratropium?

In chronic obstructive pulmonary disease (حالة بتشبه الأزمة),

In this disease the problem is not in inhalation, it's in inspiration (air enters lung but can't get out), they use spirometer and then give the diagnosis.

- In pharmacology, when we say I use the first line, it means that I used the safest and the most effective drug, and this is agreed by many guide line.
- The first line drug=the first choice drug
- So, Ipratropium is the first choice drug for chronic obstructive pulmonary disease, secondary to asthma (means it is second line for asthma or additive for asthma, but not only for asthma).
- Benztropine:
- Treatment for Parkinson disease.
- Parkinson means decrease of dopamine and increase in acetylcholine.
- dopamine is inhibitory neurotransmitter, so it prevents acetylcholine from releasing for along time.

يعني لما امشي اجري بتنقبض وبتنبسط والمسؤول عن هذه الحركة هو acetylcholine واللي مسؤول عنه هو ال dopamine

- Dopamine regulates secretion of acetyl choline in mental nigra of the brain

بالتالي ال dopamine بتحكم في ال acetylcholine متى يزيد ومتى يقل، واذا تعطل ال dopamine ال acetylcholine

لانه spasm shuffling movement رح يزداد ويعمل انقباض كثير ويصير عنده

All the muscles contracted for the maximum without inhibition

- Treatment: by giving him dopamine and decreasing acetylcholine, and the best is giving him dopamine as Levodopa, because dopamine can't pass BBB and then I will give him adjuvant by decreasing cholinergic (acetylcholine), one of them is benztropine.
- Benzotropine doesn't cause high anticholinergic, it has effectiveness at neuromuscular and muscarinic (cause block at both of them, mostly at nicotinic), so it's helpful

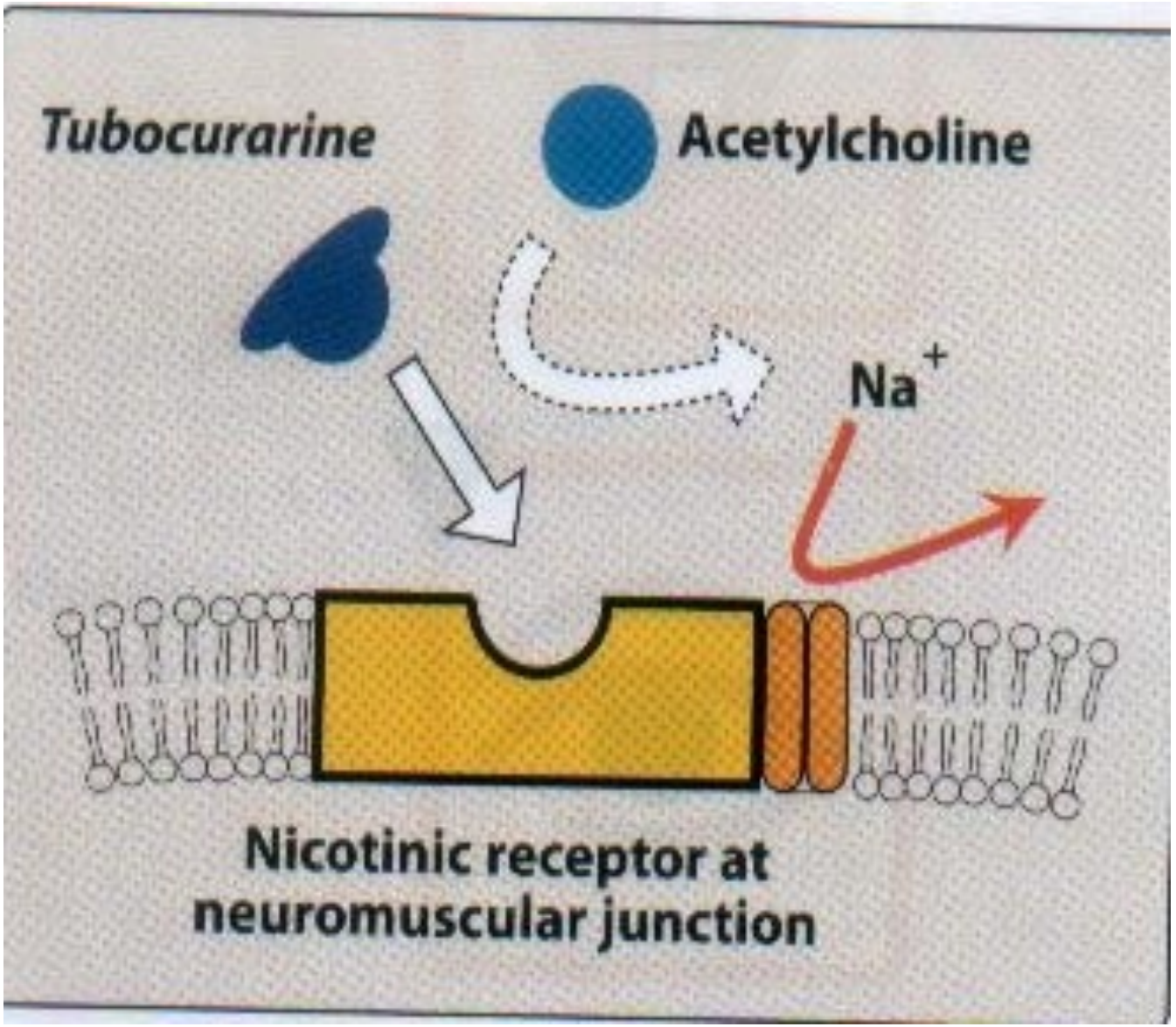
II. Neuromuscular-blocking drugs nicotinic r eceptors antagonist

1. **A. Nondepolarizing blockers**

- ***Tubocurarine*** *is* the prototype agent in this class
- interact with the nicotinic receptors to prevent the binding of Ach --- inhibit muscular contraction
- Therapeutic uses:
- as adjuvant drugs in anesthesia during surgery to relax skeletal muscle and to facilitate intubation

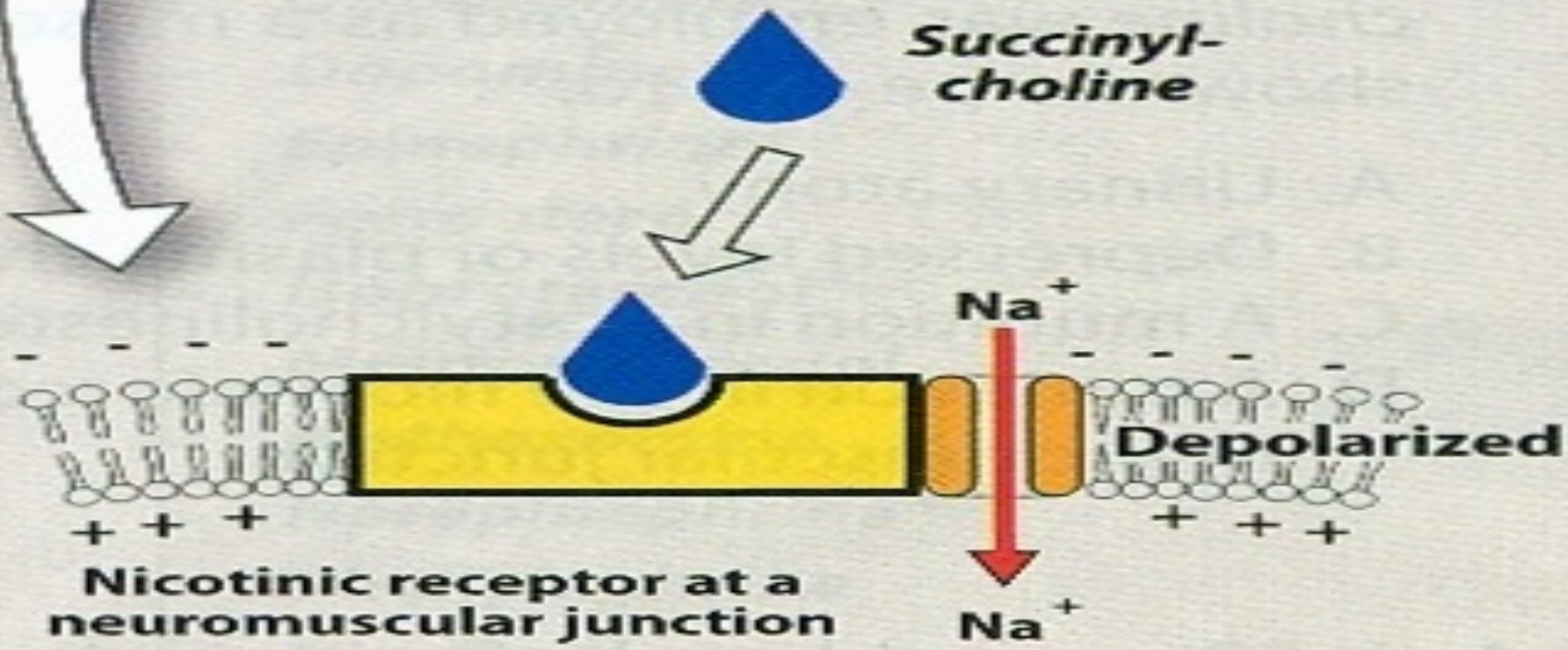
2. **Depolarizing agents**

- ***Succinylcholine***
- rapid onset and short duration of action, *useful when rapid endotracheal intubation* is required


Tubocurarine
Acetylcholine
Na+
Nicotinic receptor at
neuromuscular junction

PHASE I

Membrane depolarizes, resulting in an initial discharge that produces transient fasciculations followed by flaccid paralysis.



PHASE II

Membrane repolarizes, but receptor is desensitized to the effect of acetylcholine.

- Adjuvant: دواء مساعد وغير أساسي
- Additives: 1+1=2

- Tropicamide similar to Atropine
- Cyclopentolate has few uses in clinically

- Neurotransmitter blocker, we call it muscle relaxant
- Tubocurarine:

هذا بطلنا نستخدمه ولكن بنحتاجه ك master drug يعني هو وعيلته

Ex: we use it as antipolarizing muscle relaxing, Now the use of Tubocurarine is few because it cause a kinetic problems, it's toxic and has problems with metabolism

عشان هيك رح استخدم اخوانه, واللي هم الأدوية يلي بتنتهي ب ronium:

1) Pancuronium 2) Mivacuronium 3) Rocuronium

هذول الأدوية يعتبروا بديل لل Tubocuranine, يعني لما أحكي عنه زي كأني بحكي عنهم كلهم(the same action), ولكن بختلفوا من حيث ال metabolism

- Tubocuranine cause severe hepatotoxic (لهيك استخدامه قليل)
- It causes a muscle relaxant (so it must go to neuromuscular junction and nicotinic receptors and block them), and this is the opposite of Myasthenia gravis.

When I block it, that's mean there is no depolarizing or repolarizing, but they found that we have two groups of drugs: one can cause depolarizing and one without depolarizing, but the result is the same.

- The first and the best group is Tubocuranine that doesn't cause depolarizing.
- It is similar to acetylcholine and cause the blockage of the receptor, so there is no action, no depolarization... so it will cause muscle relaxant, by time. It will not receive any acetylcholine signals, no signals mean it will be relaxed >>>>

It will be continuous until I give the antidote, which is a neostigmine (not physostigmine)

- We give neostigmine after the operation to reverse the action, because it's acetylcholine esterase inhibitor
- Why not a physostigmine? Because the kinetic action of it is the same and distribution is also the same.

هذول الأدوية ما بعطيهم بالعمليات الطويلة بس(abdominal surgery), وأحيانا بعطيهم بال intubation, وبهاي بفضل ال short acting

- Succinylcholine:
- Has 3 side effects (read it from your book)
- Very rapid onset of action, and very short duration, so I can use it for rapid situations

مثلا بدي أدخل tube لل pharynx في ال ICU, أو بدي أعمل feeding أو في حالة عمليات التنظير, فأنا بدي اياه شوي local

وأعمل relaxation للمنطقة هاي, مش anesthetic, لا هاي relaxation وبالتالي ممكن أعطيه موضعي مثل subcutaneous

وبالتالي بعمل relaxation للمنطقة هاي, وممكن أعطيها بالوريد few drops

شكل ال succinylcholine بشبه ال acetylcholine فبالأول ال receptors بفكره acetylcholine فلما يرتبط بعمل شوي sensitization

فبتعمل depolarization ولكن بعدها بصير oversensitize, فخلص عمل ال depolarization وبعدها ما بقدر يستقبل اي اشارة, فهو بالتالي عمل شغلة اسمها flaccid paralysis وهاي معناها انه العضلة انقبضت لحد الشلل ولكنه شلل مش دائم يعني زي كأنها صارت over the threshold وارتخت, ونفس الاشي بقدر أعكس ال action

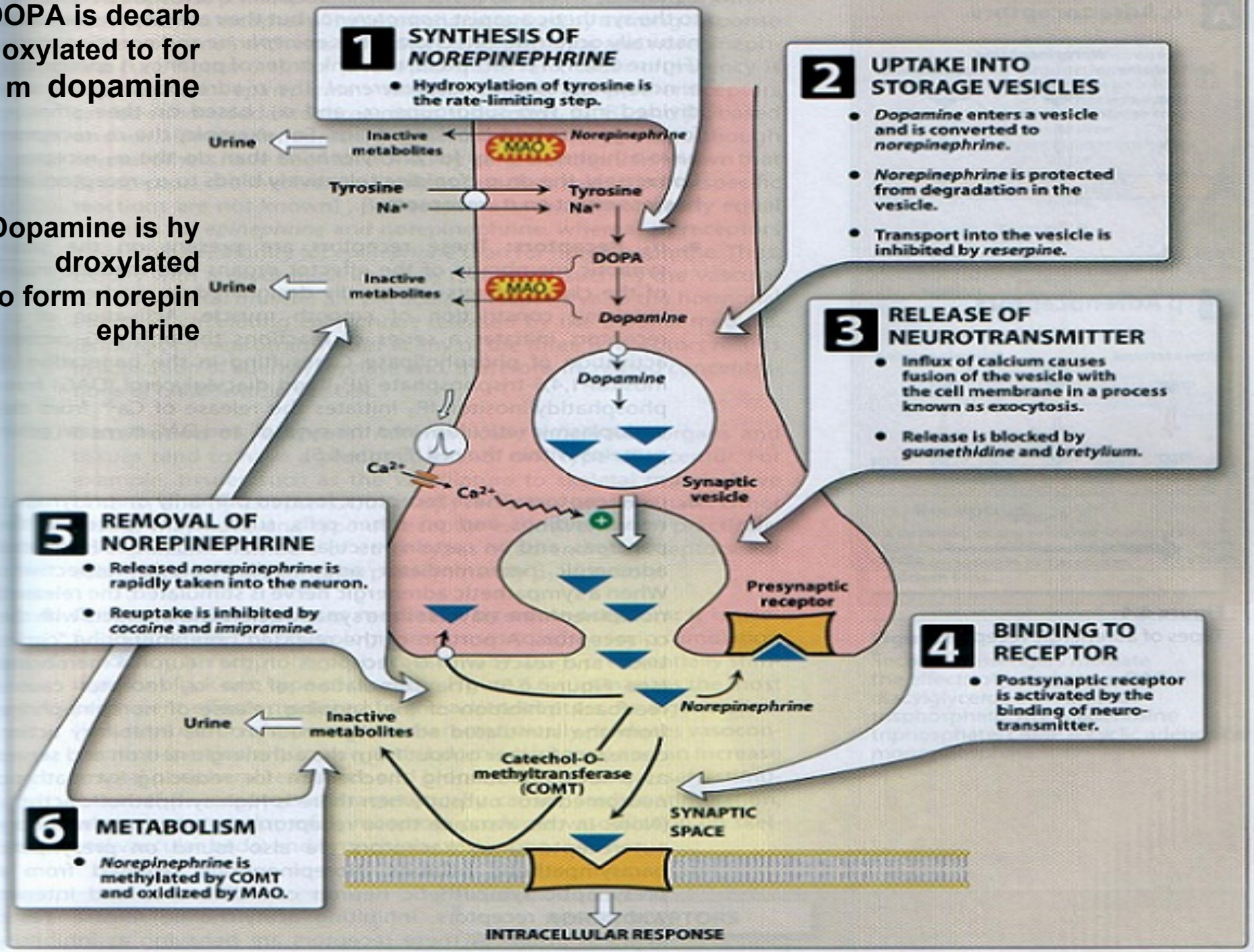
Succinylcholine doesn't need antidote, because it's degraded by the same acetylcholine esterase enzyme (pseduesterase enzyme), so it will not be longer, So we use it for procedures less than 10 minutes.

- It has some side effects for multi use

history of the patient يعني لا يفضل استخدامه أكثر من مرة فبشوف ال
اذا استخدمه قبل هاي المرة

DOPA is decarb oxylated to for m dopamine

Dopamine is hy droxylated to form norepin ephrine



ال sympathetic يعتبر تقريبا زي ال anticholinergic ولكنه أشمل

- Sympathetic innervation is more predominant than cholinergic innervation
- Some organs are not innervated by cholinergic

- Synthesis of norepinephrine:
- The neurotransmitter of sympathetic is epinephrine and norepinephrine (the main and the most important one) and isoproterenol
- We synthesize norepinephrine, and when it reaches the blood, it can be metabolized to epinephrine, and epinephrine is mainly secreted by the adrenal medulla
- The precursor of acetylcholine is Choline, then we do acetylation
- The precursor of norepinephrine is Tyrosine:

the first step is hydroxylation of tyrosine, and it is the rate>>>

Limiting step, means no hydroxylation of tyrosine, no norepinephrine, then it will be converted to deopa (levodopa), that will be decarboxylated to synthesize dopamine, so dopamine is one of the neurotransmitter, also work on sympathetic, and dopamine will still present in the blood vessels, maybe levodopa synthesis dopamine only or maybe transmitted into norepinephrine, these steps of synthesis could be inhibited by drugs.

- Note: remember that levodopa we use it to enter the brain.
- Dopa=levodopa
- Levo or dextro = the mean of rotation
- Reserpine: is the drug for hypertension, it prevents the transportation of dopamine into the vesicles (prevent the storage of it), so it prevents the sympathetic, so it reduces the blood pressure.
- Bretylium: it prevents the releasing of norepinephrine.

- After releasing of the norepinephrine, what is the fate?

First, it will bind with postsynaptic receptor, and will make IPP and G protein, and do the action depending on it's target

In cardiac ⟶ it will increase heart rate

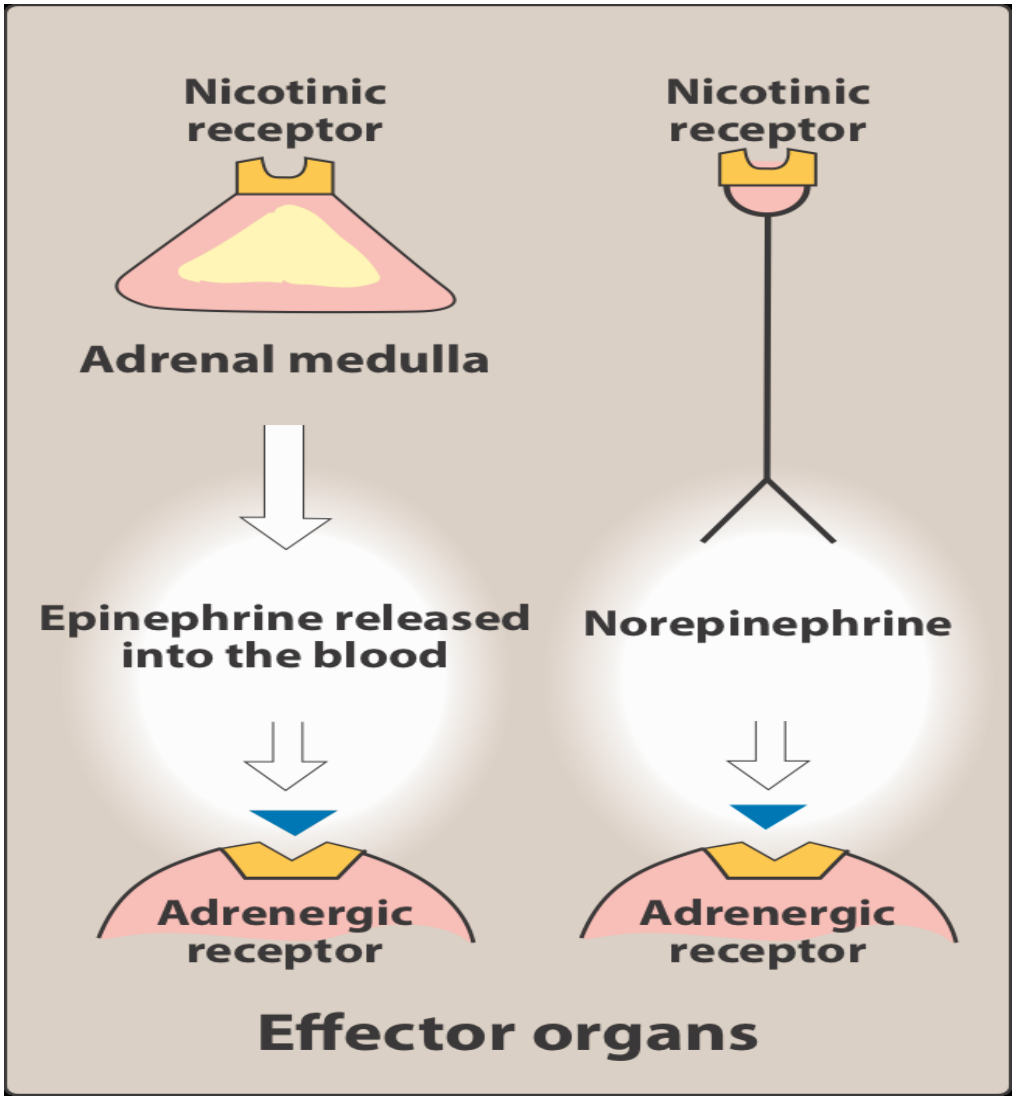
In smooth muscles ⟶ it will increase the contraction

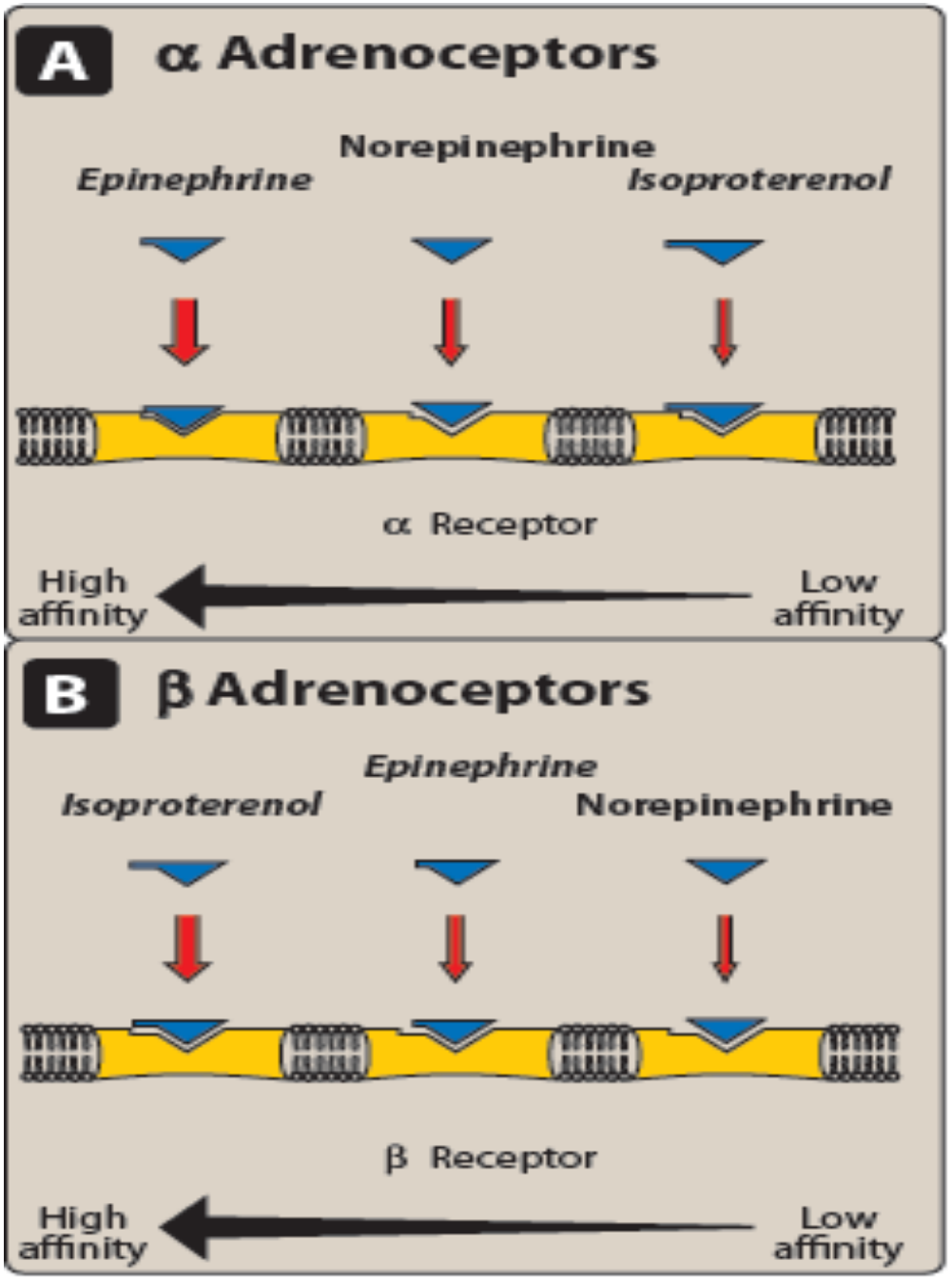
- We have two enzymes:

1) COMT (catechol-o- methyltransferase)
2) Mao (monoamineoxidase)

- Mao and COMT these abbreviation is international, these two enzymes can metabolize norepinephrine and terminate the action.
- So, we have Mao inhibitor drug (for depression) and COMT inhibitor drug.
- We must remember that norepinephrine and dopamine are degraded by COMT and Mao

- Mao inhibitor drug prevents the degradation of dopamine and norepinephrine and we know dopamine is secret for depression, so if I want to prevent depression, I must increase dopamine.

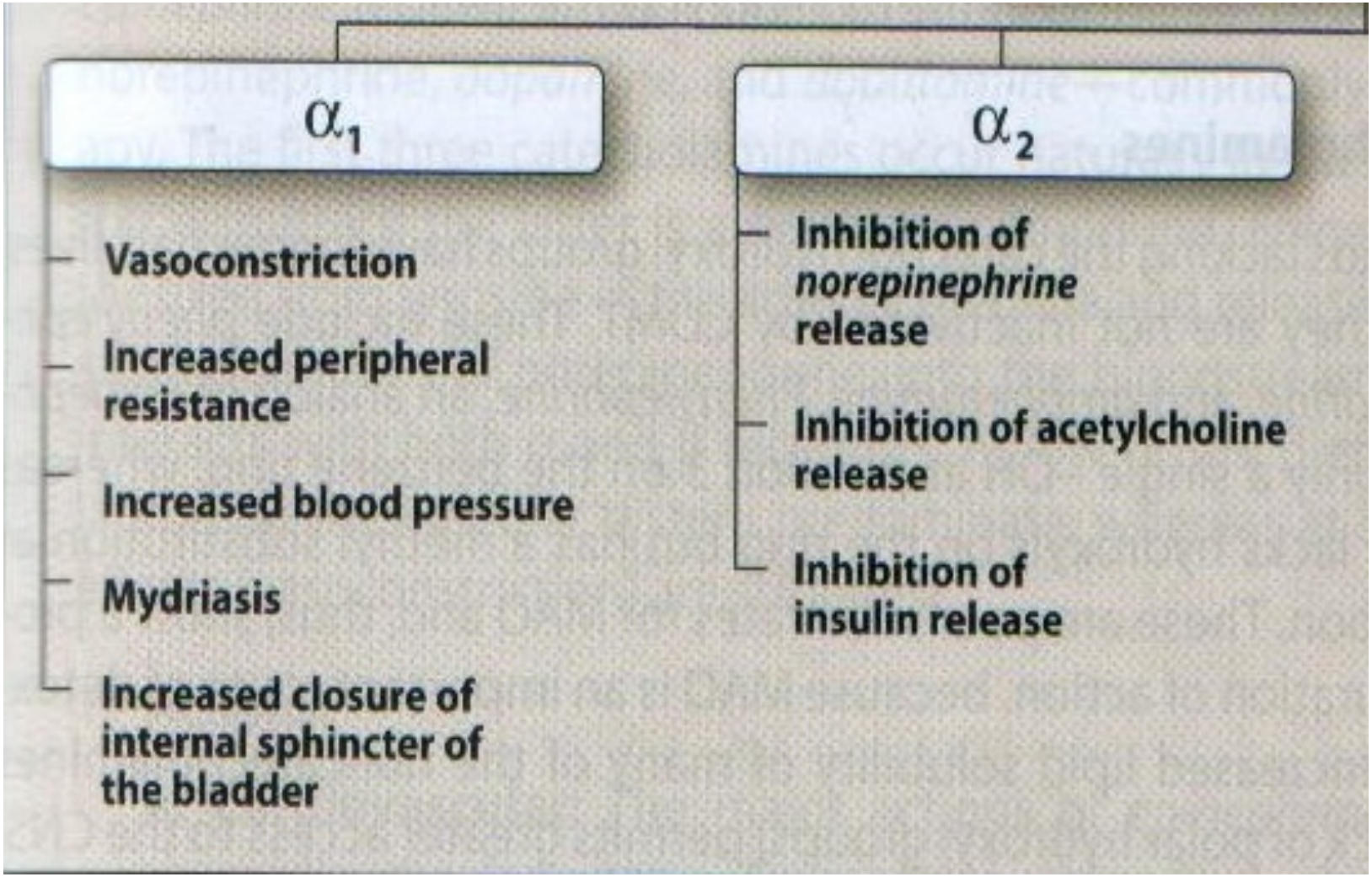

Nicotinic receptor
Nicotinic receptor
Adrenal medulla
Epinephrine released into the blood
Norepinephrine
Adrenergic receptor
Adrenergic receptor
Effector organs

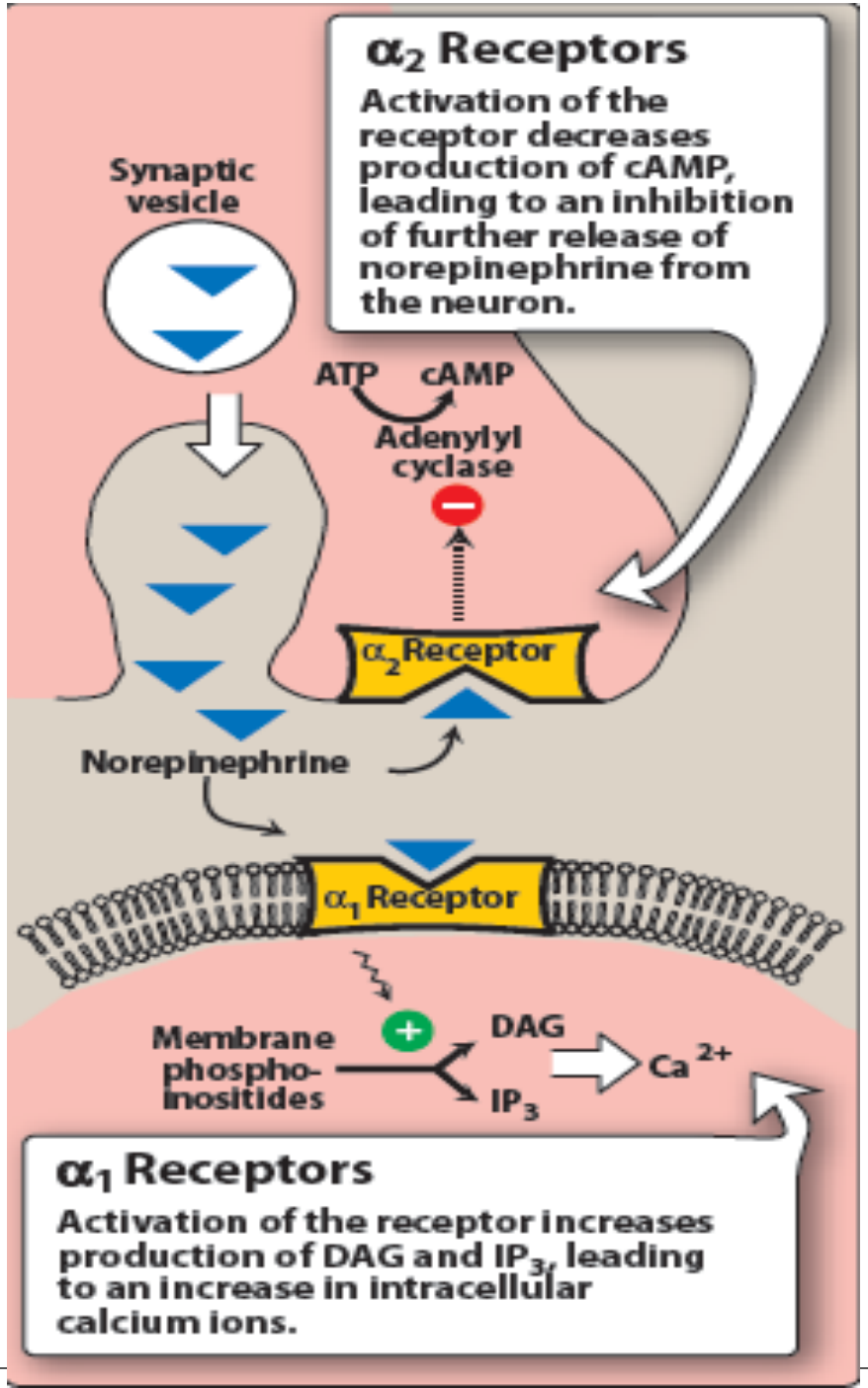

A
α Adrenoceptors
Norepinephrine
Epinephrine
Isoproterenol
α Receptor
High affinity
Low affinity
B
β Adrenoceptors
Epinephrine
Isoproterenol
Norepinephrine
β Receptor
High affinity
Low affinity

α-Adrenergic Receptors

	α_1	α_2
Location	Postsynaptic membrane of the effector organs	−Presynaptic neuron membrane: sympathatic and parasympathatic −Pancreas β cells −At certain vascular smooth muscle cells
Binding to agonist	Adrenergic effect	Feedback inhibition: --↓ sympathatic output --↓ cholinergic output (minimal(
Effect	Classic adrenergic effect (e.g. Contraction of the smooth muscles(	−Control adrenergic neuromediator −Control insulin output

ADRENOCEPTORS




α2 Receptors
Activation of the receptor decreases production of cAMP, leading to an inhibition of further release of norepinephrine from the neuron.
Synaptic vesicle
ATP
cAMP
Adenylyl cyclase
α2 Receptor
Norepinephrine
α1 Receptor
Membrane phospho-inositides
DAG
IP3
Ca 2+
α1 Receptors
Activation of the receptor increases production of DAG and IP3, leading to an increase in intracellular calcium ions.

- We have a site called a presynaptic receptor
- There is a rapid way for termination the action (not by Mao or COMT), this way is by presynaptic receptor α_2 receptor
- The reason of presence of α_2 receptor in our body is inhibition.
- So when it binds to this receptor, it will cause it to stop and it will not release
- α_2 inhibitory for cholinergic
- α_2 receptor present in presynaptic neuron for cholinergic
- α_2 receptor receive both acetylcholine and norepinephrine, so it cause the inhibition of both
- Mao and COMT will degrade norepinephrine and dopamin to tyrosine
- Nicotinic receptor in adrenal medulla mainly release epinephrine, but in adrenergic the main neurotransmitter is norepinephrine.

- But it has affinity for both epinephrine and norepinephrine
- We have 3 neurotransmitters, and all of them work at α and β receptors.
- Epinephrine has a higher affinity to α and β receptors than norepinephrine
- α_1 is mainly in postsynaptic in smooth muscles
- α_2 is mainly in presynaptic, so it is inhibitory action for both sympathetic and parasympathetic, it causes the termination of the action by stopping the release of neurotransmitter
- α_2 is very predominant in pancreas for insulin release
- In general the action of α_1 :

1) α_1 stimulation cause vasoconstriction of smooth muscles
2) The pressure will increase
3) The peripheral resistance will increase

These 3 are important for cardiogenic shock.

- Cardiogenic shock= hypovolemic shock, that means the patient has hypotension, hypovolemia → so I have to increase it
- α_1 in urinary bladder causes closure of internal sphincter, it's important for urination.
- α_2 → inhibition for acetylcholine norepinephrine, and insulin release
- When the α_2 will work as insulin inhibitor?

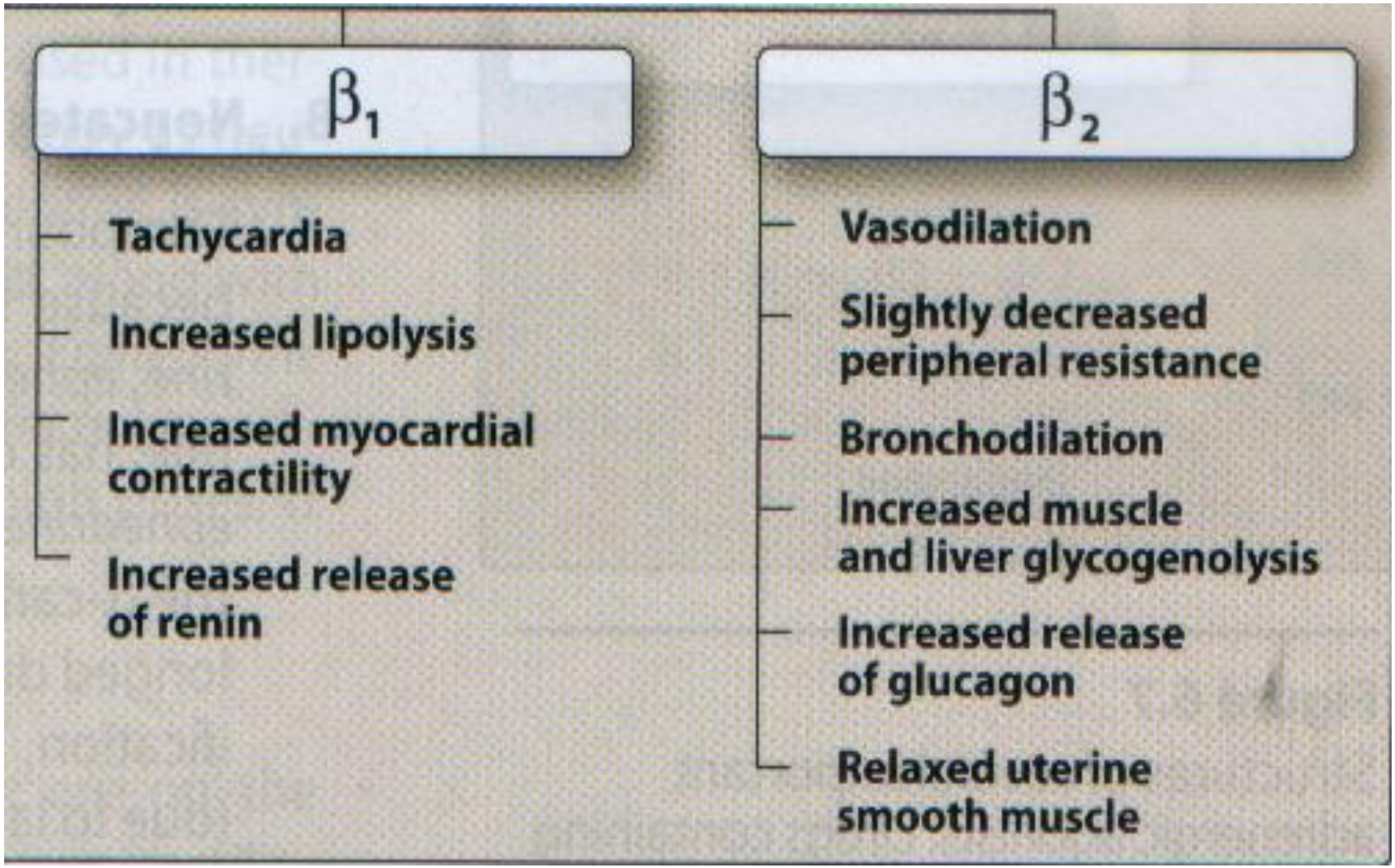
When the glucose decreases, it will cause α_2 to stop release of insulin.

- There is nothing in common between α_1 and α_2
- α_1 is stimulator while α_2 is inhibitor
- α_1 at smooth muscle causes vasoconstriction, whereas α_2 doesn't involve in vasoconstriction.

β-Adrenergic Receptors

- β receptors: β_1, β_2 and β_3
- Different locations, hence, functions
- β_1 : more predominant at Heart
- β2: more predominant smooth muscle (blood vessel and bronchi)
- B_3 and little β1 are located in adipose tissue!lipolysis
- Drugs differ in affinity to β receptors
- β1 receptors have approximately equal affinities for epinephrine and norepinephrine,
- β2 receptors have a higher affinity for epinephrine than for norepinephrine

ADRENOCEPTORS



TISSUE	RECEPTOR TYPE	ACTION	OPPOSING ACTIONS
Heart			
• Sinus and AV	β_1	↑ Automaticity	Cholinergic receptors
• Conduction pathway	β_1	↑ Conduction velocity, automaticity	Cholinergic receptors
• Myofibrils	β_1	↑ Contractility, automaticity	
Vascular smooth muscle	β_2	Vasodilation	α-Adrenergic receptors
Bronchial smooth muscle	β_2	Bronchodilation	Cholinergic receptors
Kidneys	β_1	↑ Renin release	α_1-Adrenergic receptors
Liver	β_2	↑ Glucose metabolism, lipolysis	α_1-Adrenergic receptors
Adipose tissue	β_3	↑ Lipolysis	α_2-Adrenergic receptors

Skeletal muscle	β_2	↑ Potassium uptake, glycogenolysis Dilates arteries to skeletal muscle	—
Eye-ciliary muscle	β_2	Relaxation	Cholinergic receptors
GI tract	β_2	↓ Motility	Cholinergic receptors
Gall bladder	β_2	Relaxation	Cholinergic receptors
Urinary bladder detrusor muscle	β_2	Relaxation	Cholinergic receptors
Uterus	β_2	Relaxation	Oxytocin

- β_1 is on the heart, by sympathetic stimulation it will cause increase the contraction (intropic) and increase the heart rate (chronotropic)

اذا عندي مريض وبدي أزيد ال **heart rate** وأعطيه دواء يزيد شغل ال **β1** شو هذا المرض؟

Bradychardia= we call it cardiac arrest (not cardiogenic shock)

Sock means hypotension and hypovolemia

لما بيجي واحد ضغطه أقل من 60 بعطيه β_1

- β_2 is more predominant in the lung, when I give agonist it causes bronchodilation
- All asthma's drugs are β_2 agonist
- β_3 has a little action, but mainly in lipolysis and some insulin secretion

- β_1 agonist cause:

1) (+) chronotropic
2) (+) intropic
3) (+) increase lipolysis, sometimes needed but in certain situations, maybe considered as side effect
4) (+) increase release of renin

هذا موجود عند α كمان, ولكن ما رح يشتغلوا مع بعض واحد بزيد افراز وواحد بقلل افراز حسب حاجتي

- All above are used in bradycardia hypotension

- β_2 actions:
- β_1 causes vasoconstriction, while β_2 causes vasodilation
- Glucagon: cause glycogenolysis= degradation of glycogen to glucose, so increase the glucose
- Glucagon is the opposite of insulin

Adrenergic Agonists (Sympathomimetic)

- **They are classified according to their structure:**

A. Catecholamines

- such as **epinephrine, norepinephrine, isoproterenol, and dopamine**
- show highest potency in activating α or β receptors.
- Rapid inactivation: metabolized by COMT and MAO
- Short t1/2
- Poor penetration into the CNS: polar
- Only parenterally (not effective orally)

Adrenergic Agonists Sympathomimetic

- **They are classified according to their structure:**

B. Noncatecholamines

- include **phenylephrine, ephedrine, and amphetamine**
- Low potency
- have longer half-lives, because they are not inactivated by COMT.
- Greater access to the CNS.
- Oral and parenterally

- What is the neurotransmitter that act on sympathetic?

There is two types of neurotransmitters act on sympathetic, and can be divided according to their structure

- Epinephrine, norepinephrine, isoprotenol, and dopamine → have the same structure, they have catecholamine
- These 4 neurotransmitters are inside my body, and I can make drugs from them
- ولكن عندهم مساوئ:

they have higher potency, because they are similar to my body, and they have similar activity, but they are inactivated by COMT and Mao, they are targets for these enzymes, so the terminate the action very fast, so short half life

- The half life of epinephrine is short, so there is no orally epinephrine, it's only parenteral, because I don't want it to last too much

لما عملوا non-catecholamine يلي بختلف من حيث التركيب, وجدوا انهم أفضل

Because they don't penetrate the CNS

- Non-catecholamine: have structure difference, and they have a longer onset of action

- Ex: Amphetamine(ceptagon)
- Increase stimulation of epinephrine

المريض لما يوخذه بتنبه زيادة زي ال block , مثل العضلة لما تعمل انقباض ويصيرلها paralysis

- Pseudoephedrine and phenylephrine are drugs for decongestant
- Ortivin:

ممنوع ينعطى لأكثر من ٣ أيام حتى لو كان asprey للdecongestant لانه بصير tolerance وبالتالي زيادة الجرعة ممكن تعمل rebound nasal

كيف بتعمل rebound؟

معناها لما الواحد يوخذ دواء منوم ويوقف عنه فترة طويلة, اذا وقف فجأة بعمله rebound anxiety يعني برجعله ال anxiety بزيادة

فإذا طول على ال decongestant بعمله reborn decongestant مرة ثانية وبطول عنده الحالة لحتى تشفى, فممنوع استخدمه لأكثر من ٣ أيام

- Non-catecholamine, the aren't metabolized by COMT and Mao, so have longer duration of action, but they are given orally, nasal, drop, or parentally

ما عندي مشكلة فيهم ولكن they can cross CNS ولهيك بنعسوا شوي

مركز ال amphetamine هو الدماغ, فكل هذول الأدوية can cross the BBB

So, they cause sedation or tolerance or addiction