تفريغ ميديسينال

محاضرة: Adrenergic Part 1

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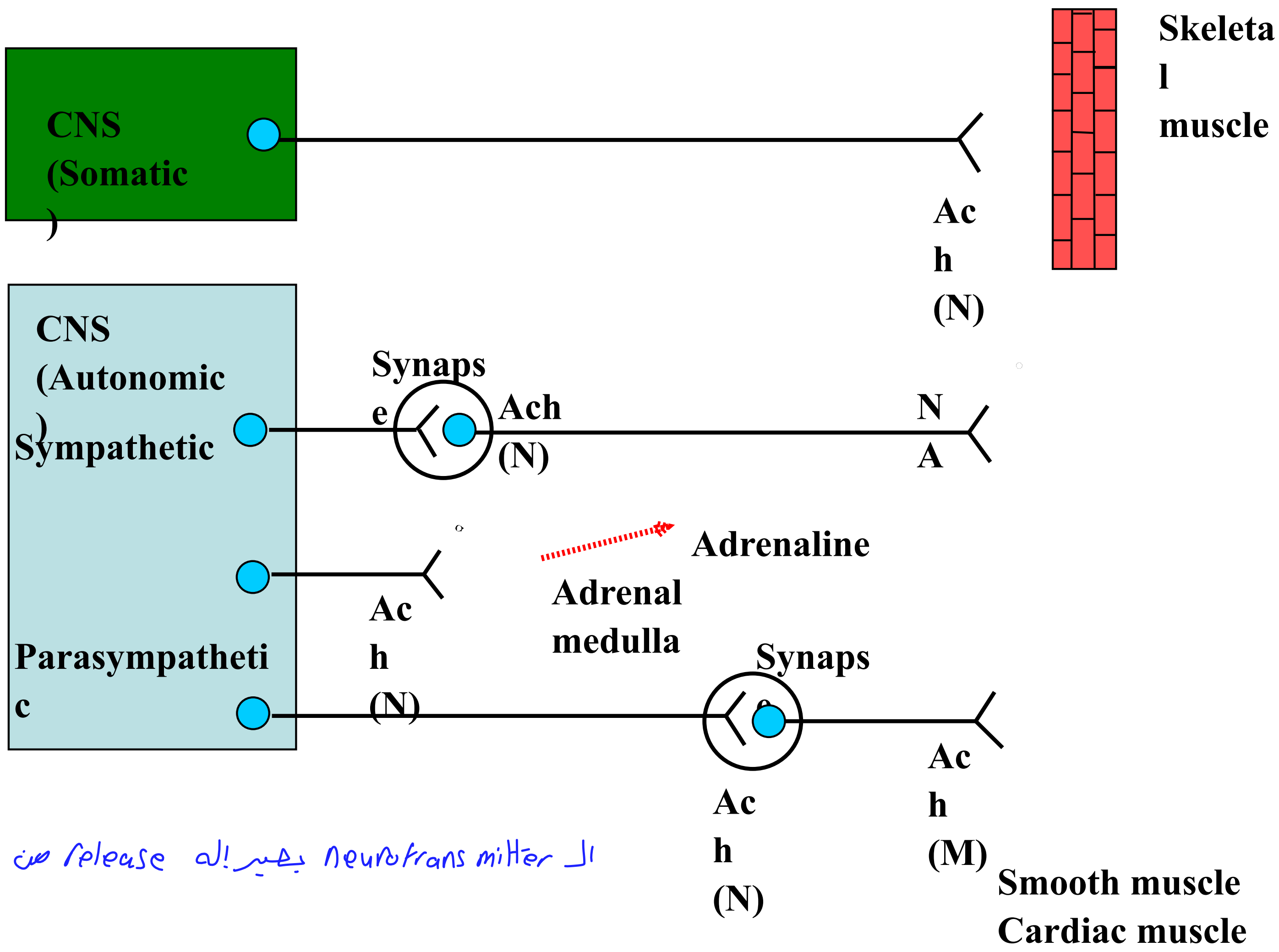
لجان الدُفعات

Soul Academy

Drugs Acting on the Adrenergic (Sympathetic) Nervous System

1. Nerve Transmission

Peripheral nervous system



AUTONOMIC

الدكتورة عملت مراجعه سريعه للـ cholinergic بس ما كتبتها عشان ما تتخربطوا بالـ Adrenergic

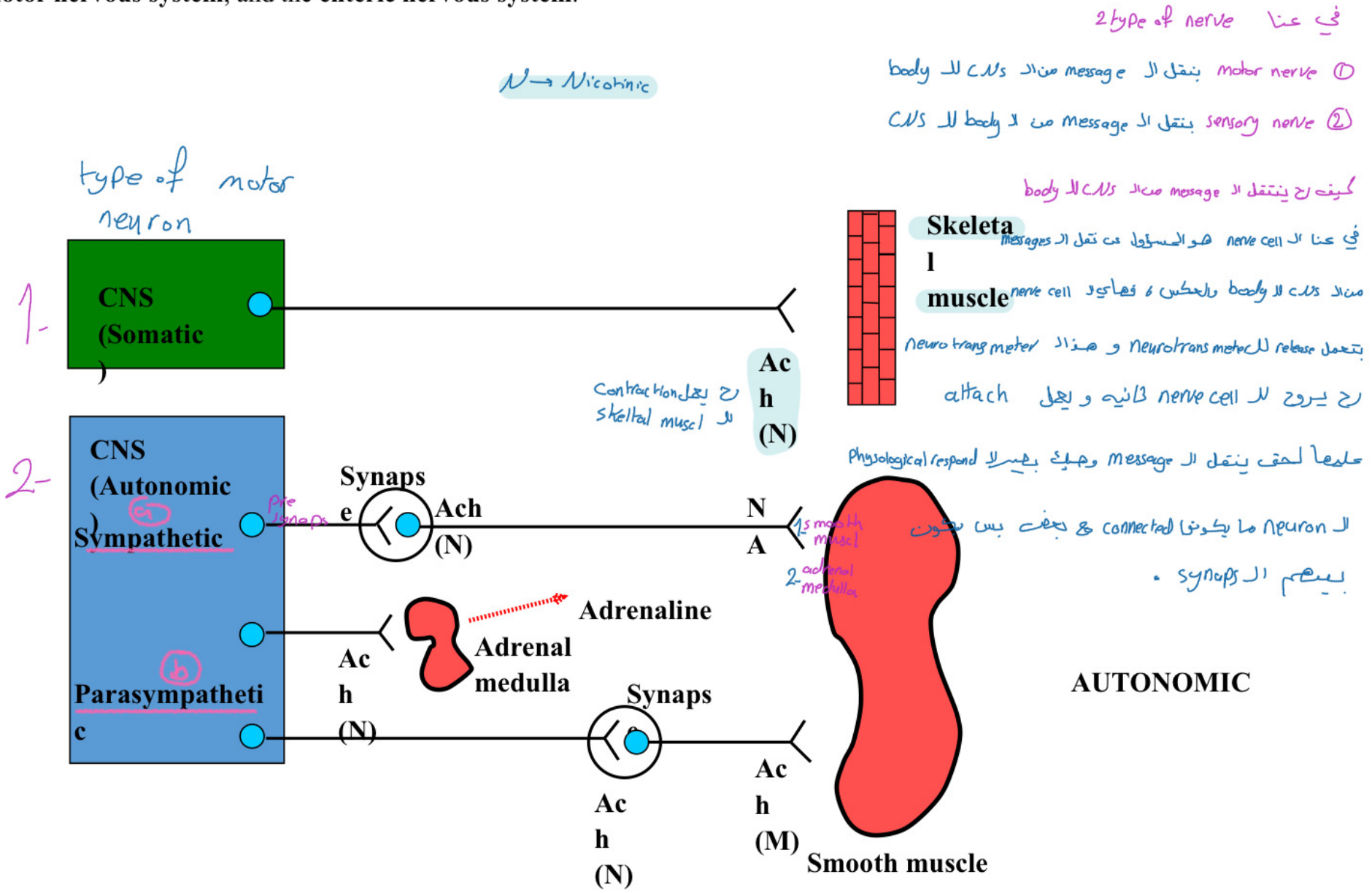
الـ neurotransmitter بصير الـ release من الـ Presynaptic

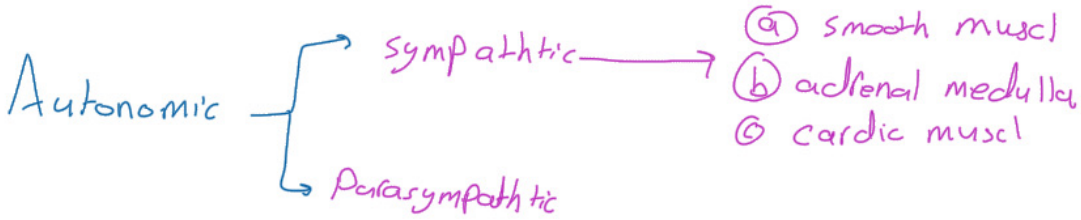
الـ nerve synaps وبعدين رح يروح للـ Postsynaptic nerve

ورح تستمر العمليه لحتى يوصل الـ target cell

1. Nerve Transmission

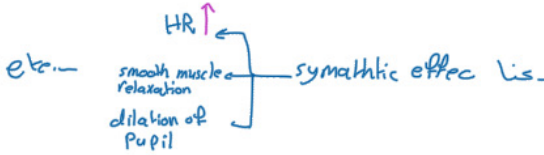
The motor nerves of the PNS have been classified into three subsystems: the **somatic motor nervous system**, the **autonomic motor nervous system**, and the **enteric nervous system**.





كيف يحفز ال sympathtic ؟؟

لما يصير Ach الـ releas من الـ Pre-synaps وبرتبط بال muscrnic receptor الموجود على الـ Post-synaps رح ينقل وهاي messag



الـ messag رح تحفز الـ 2nd neuro لينتج Nor-adrenalin وهيك رح يحفز الـ sympathtic ورح يصير عنا

وممكن يصير by bass الـ 2nd neuron ويروح مباشرة الـ adrenal medulla ويعمل Simulation لحتى تفرز الـ Adrenalin

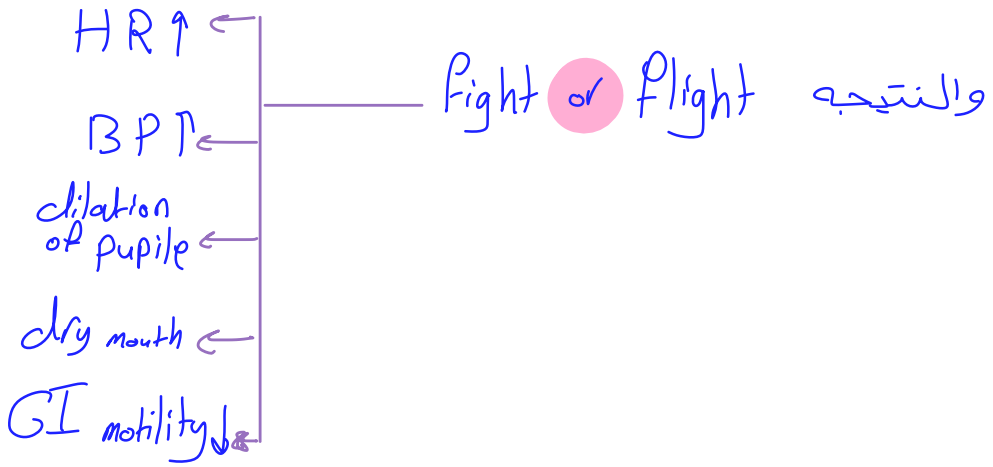
وبعمل symathtic effect

لما يصير activation الـ Adrenalin medulla ، الـ Tyrosin اللي موجود فيها رح يمر

بمجموعة Process ليوصل لمرحلة بصير الها reduction وبتحول لـ Nor-adrenalin وبعدها بصير الها

N demethylation

لما يصير release الـ N.E (neurotransmitter الـ) الي بعمل activation الـ Adrenergic system

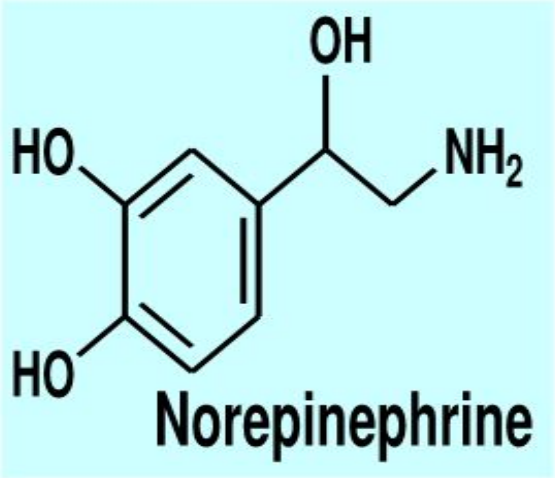


في صرموت بسمة Adrenalin بختلف عن الـ Nor-Adrenalin بوجود الـ methyl group (methyl group الـ NE الـ ما عندها الـ)

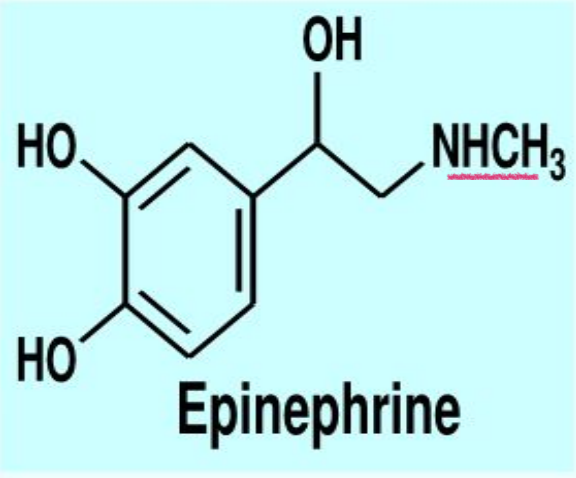
لما الـ Ach يروح لـ Adrenalin gland رح تفرز Adrenalin (هو هرمون صلي neurotransmitter)

Adrenergic Neurotransmitters

- Norepinephrine (NE) is the main adrenergic neurotransmitter.
- It is liberated from the post-ganglionic sympathetic neurons as a result of sympathetic nerve stimulation.
- Epinephrine (Adrenaline) is synthesized and stored in the adrenal medulla. Neurohormone.



Norepinephrine

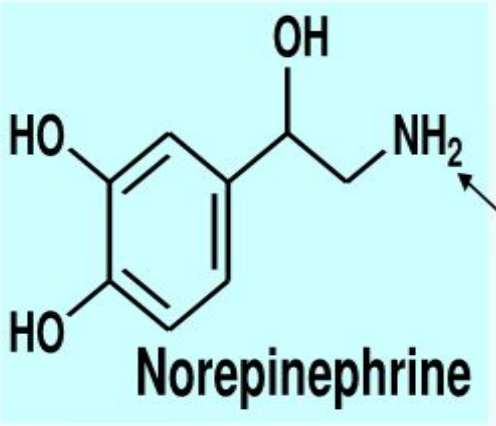


Epinephrine

Neurotransmitters

Chemical messengers

Sec. alcohol

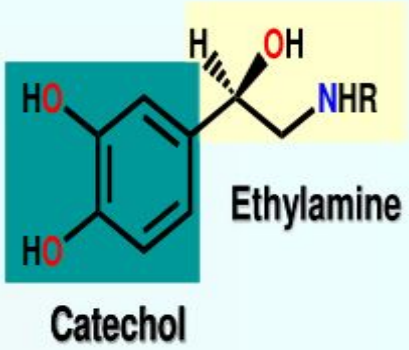


catechol

Amine

Norepinephrine

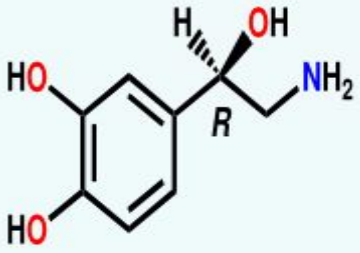
benzen (phenol ring)
+
2 hydroxyl



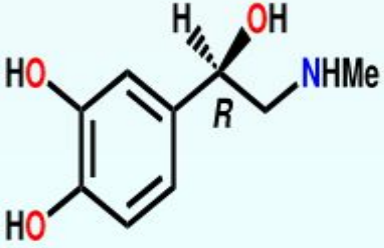
Ethylamine

Catechol

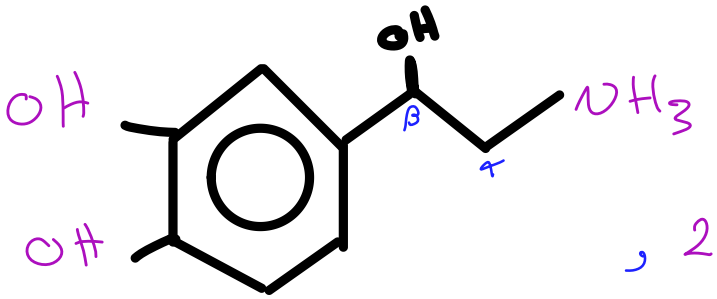
Noradrenaline – neurotransmitter



Adrenaline – hormone

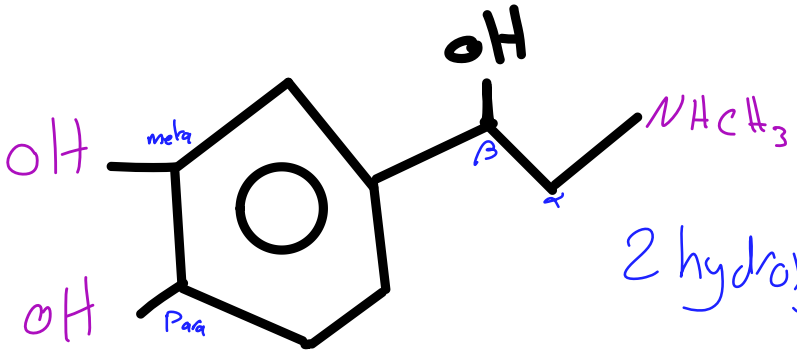


- Catecholamine derivative
- Phenylethylamine derivative



الـ structure الـ N.E عبارة عن Phenyl ring مرتبط فيها 2 hydroxyl و

ethyl-amin مرتبط فيها على الـ β position ← hydroxyl



اما الـ Epinephrine عنده الـ Phenyl groub مرتبط فيها 2 hydroxyl

ethyl ① مرتبط فيها β-hydroxy l
methyl amin ②

الـ Adrenergic الـ 2 receptor [α, β] و الـ Epinephrine رح يكون Selective لـ β و α

اما الـ N.E رح يكون β selective ليش؟ لانه ما عنده الـ methy groub

Van-der wal reaction وبتعمل hydrophobic pocket ans B receptor الـ

مع الـ hydrophobic groub الموجودة بالمركب فالـ Epinephrine عندة

الـ methyl groub اي رح تعمل هذا الـ reaction وهيك بكون اله

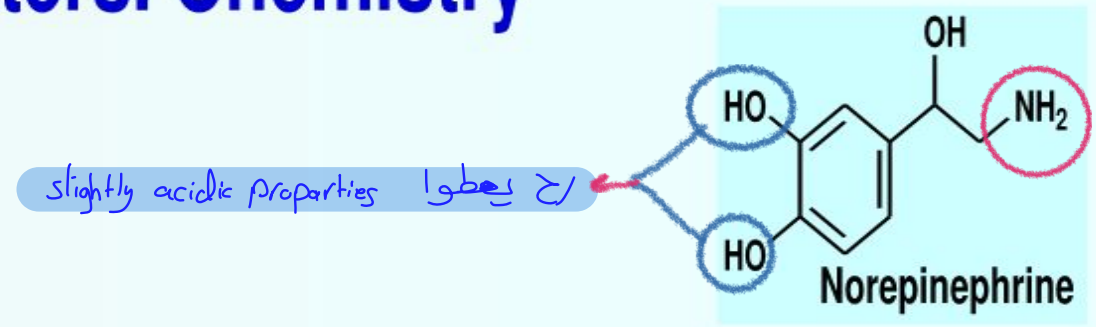
B-receptor الـ activity

الاشياء اللي لازم تكون موجوده عشان يصير ارتباط بال β Adrenergic receptor

① 2 catichol hydroxyl ② β-hydroxyl ③ amin groub

ionization يصير الها
داخل الـ receptor ورح تعمل
ionic bond

Neurotransmitters. Chemistry

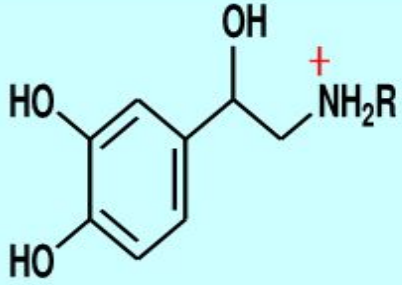


slightly acidic properties ح/ يعطوا

- Slightly acidic functional group (aromatic OHs)
- Basic functional group (aliphatic amine).

ح/ N الـ basic عتبرته ما ! الـ
Physiological pH بالـ ionize تكون ⇒ pKa < pH

- At physiological pH (7.4), NE and epinephrine exist in more than 95% in the cationic form in which the nitrogen is protonated.

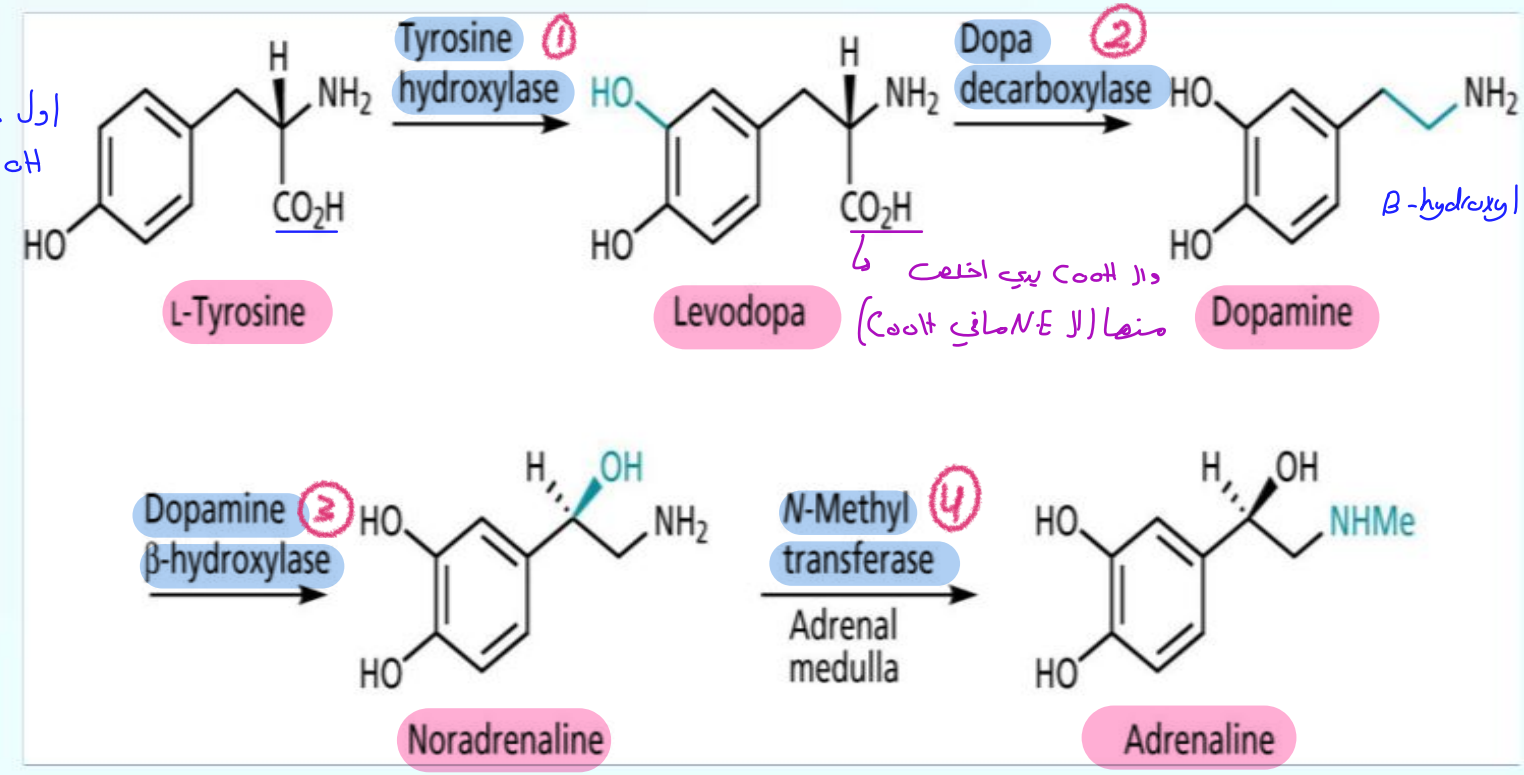


R = H or CH_3: Cationic form of Norepinephrine and Epinephrine

Neurotransmitters. Biosynthesis

الـ Tyrosin هو الـ precursor لـ N.E

From amino acid tyrosine



اول اشي بدي اضيف meta position الـ OH

لازم يكون في β-hydroxyl

والـ COOH بدي اخلص منها (COOH في الـ N.E)

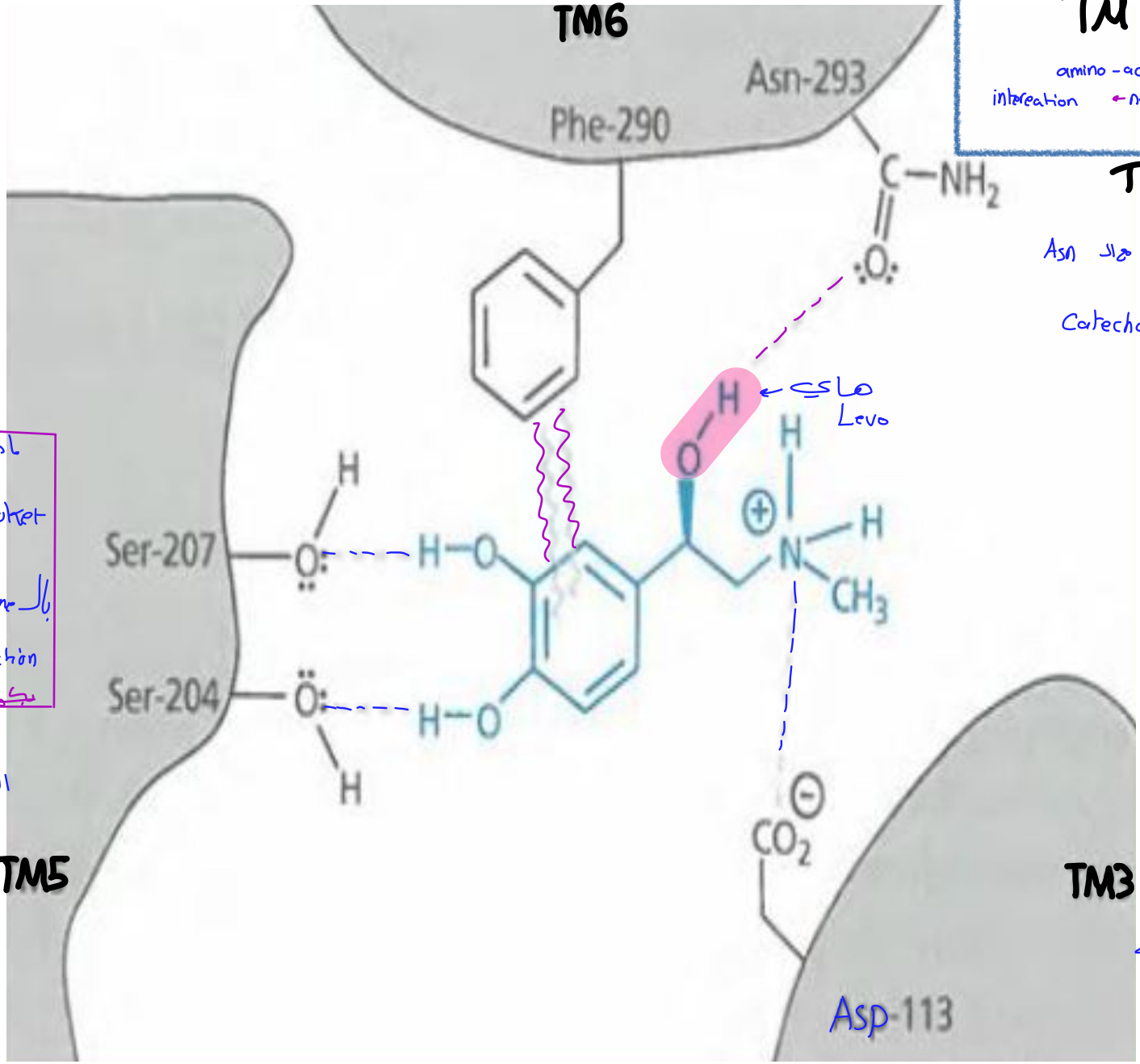
صاحب الـ process تعتبر feedback بوقف (-)

إذا زاد الـ N.E الـ releas رح يصير inhibition

الـ Trysoine hydroxlase

- Pathway controlled by regulation of tyrosine hydroxylase
- Inhibited by noradrenaline - feedback control

Adrenergic Binding site: Drug-Receptor Interaction



TM : Trans-membran

كل واحد من ال TM حليه amino-acid رح تعمل مع ال neuro transmitter interaction

TM6

ال hydroxyl B جوا ال Asn رح تعمل hydrogen bond

والـTM6 فيه Phe رح يثبت ال Catechol

هاي Levo

hydrophobic اذا كان فيه

ال CH3 (B) بال Portal

بال Epinphrine رح تعمل

Levo Van-der reaction

TM5 بتكون بال

TM5

2 Catechol hydroxyl ال

ser رح تعمل مع ال

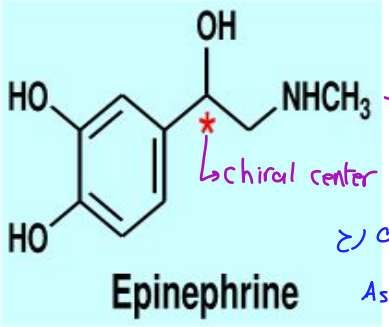
hydrogen bond

TM3

Asp → ionize at physological pH → (−) charg

رح يعمل ionic bond بواسطة ال CO2 مع ال N الموجودة بال Epinphrine/NE

Stereochemistry of NE and Epi



chiral center (Levo اصون)

لما تكون الـ OH ر ح Levo

تقدر تعمل H1 ع الـ Asn

بس اذا كانت الـ OH dextro

ر ح تكون بعيده عن الـ Asn

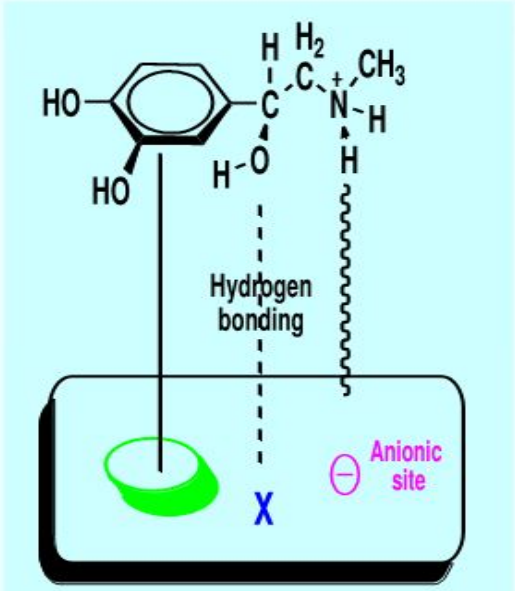
وصيك ما ر ح يكون فيه H-B bond وصيك ما في affinity

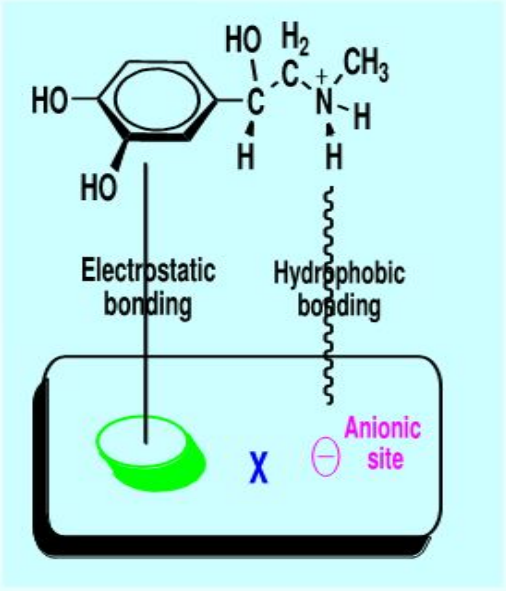
- There is a chiral carbon.
- There are two optically active isomers: (-) and (+)
- (-) Epinephrine is more active than (+) Epinephrine. Why?
- Different binding
- (-) isomer fits with receptor *via* points of interaction, more than that of (+).
- Hence, the (-) isomer has higher affinity and activity.

(-) Epinephrine

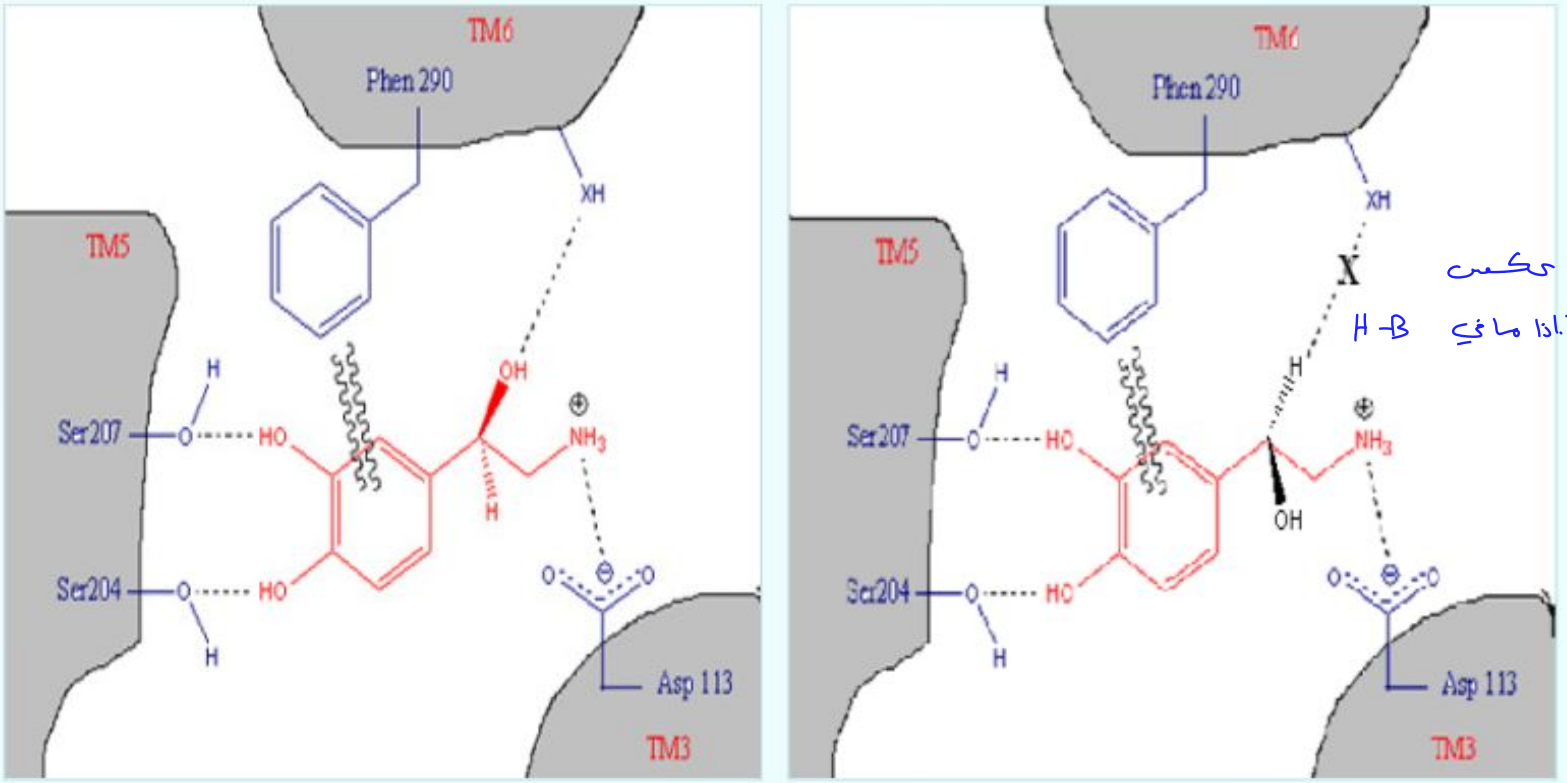
(+) Epinephrine

ل Adrenergic receptor





Binding of (-) and (+) isomers



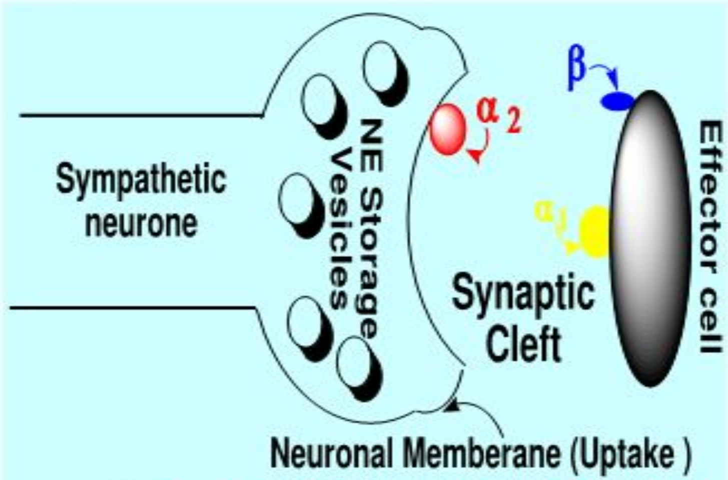
صورة اذا OH عكس
اتجاه الـ TM6 اذا مائي H-B
اذا هايي D

The (-) isomer fits with receptor *via* points of interaction, more than that of (+).

Hence, the (-) isomer has higher binding affinity.

(-) isomer is more active than (+)

Adrenergic Receptors



Postganglionic sympathetic neuron, synaptic cleft and effector cell

- Two types of adrenoceptor (α and β)
- Subtypes (α_1 and α_2; β_1, β_2 and β_3)
- Subtypes of subtypes (α_{1A} α_{1B} α_{1D} α_{2A} α_{2B} α_{2C})
- G-protein coupled receptors → الـ Adrenergic receptor إله binding site للـ NE و binding site

للـ G-protein ، فلما يرتبط الـ NE بالـ receptor رح تفتح الـ binding site الخاص

بالـ G-protein ويصير رح يصير activation لمجموعة من الـ enzyme ويصير رح يصير فيه

Signal transduction

Signal transduction

- α_1-adrenoceptor : generates inositol triphosphate and diacylglycerol
- α_2-adrenoceptor : inhibits generation of cyclic AMP
- β_1, β_2 and β_3-adrenoceptors : generate cyclic AMP

الـ Cyclic ATP مهم لأنه رح يعمل generation للـ ATP ويصير إعطاء طاقة للـ neuron

Adrenergic Receptors (adrenoceptors)

Distribution and effects

Pharmacology Class

- Receptors are distributed differently in different organs and tissues → موجودين بكل مكان
- Receptor selective drugs act selectively at different organs and tissues
- Activating α_1-adrenoreceptors generally contracts smooth muscle (except gut = relaxation of GIT smooth muscle)
- β_1- Adrenoceptors predominate in the heart HR↑, CO↑, BP↑
- Activating β_1-adrenoceptor contracts cardiac muscle
- β_2-Adrenoceptors predominate in the airways
- Activating β_2-adrenoreceptors relaxes smooth muscle → الموجودين بالـ lung bronchodilator

Receptor activation

Pharmacology Class

The receptor activation may result in:

1. α_1- Adrenergic receptors: Vasoconstriction, relaxation of GIT smooth muscle, salivary secretion and hepatic glycogenolysis. → anaphylactic shock بستخدموا
2. α_2- Adrenergic receptors (Auto-receptor): Inhibition of transmitter release including NE from autonomic nerves, platelet aggregation. → Hemorrhag بستخدموا
3. β_1- Adrenergic receptors: Increase cardiac rate and force, relaxation of GIT smooth muscle and lipolysis. → heart block بستخدموا لـ او Hypotension
4. β_2- Adrenergic receptors: Bronchodilation, vasodilatation, relaxation of visceral smooth muscle, hepatic glycogenolysis and muscle tremors. بستخدموا لـ COPD و Asthma بالتبخيرة

Inactivation of Catecholamines

الـ Adrenergic effect مابدي يفضل كل هذول
عشان هيك لازم يرجع لوضعه الطبيعي كيف؟
① Post ganglionic إلي NE لا re-uptake
② او inactivation عن طريق توعين من الـ enzym
COMT
MAO

1. Reuptake into the adrenergic nerve ending, stored into storage granules until sympathetic nerve stimulation.
2. Enzymatic metabolism: Two principle enzymes involved in Catecholamines metabolism:
   a) Monooxidase (MAO), acts via oxidative deamination of catecholamines
   b) Catechol-O-methyltransferase (COMT), methylates the meta hydroxyl group of catecholamines.

Metabolism by MAO and COMT

اذا كان الـ drug اي بدي امنعه

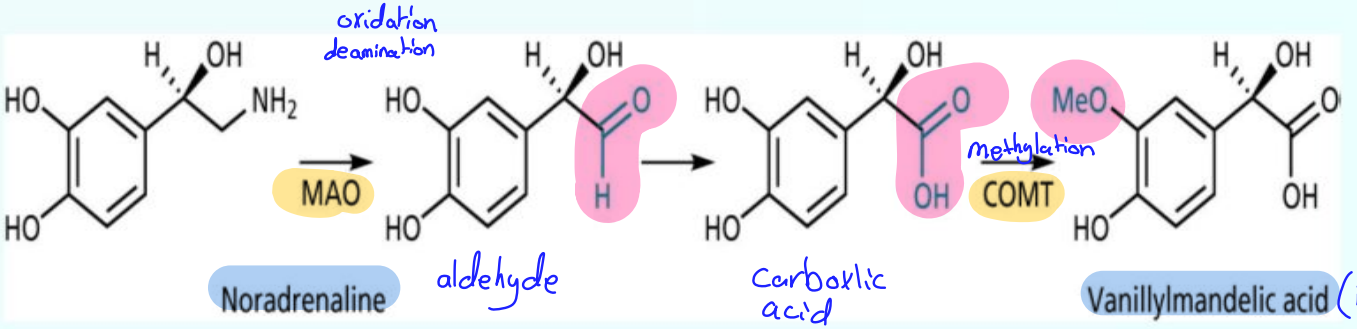
اما إذا كان الـ substrat الـ orally inavaliable رح يكون COMT

إلـ substrat الـ MAO يعني ما بصير إله

- **Effect of MAO: Oxidative deamination. i.e. Oxidation of the carbon** Short duration of action يكون إله COMT بال

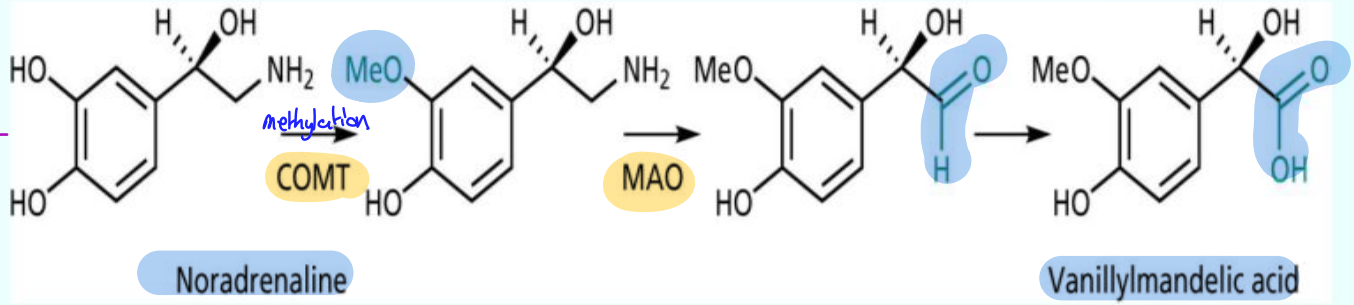
  carrying the nitrogen accompanied by loss of the nitrogen atom.

$$R\text{-}CH_2\text{-}NH_2 \longrightarrow (R - CH = NH) \longrightarrow R\text{-}CHO \longrightarrow \text{Acid or alcohol}$$



هون بلش بـ MAO بالأول بعدين COMT

(inactive metabolit)

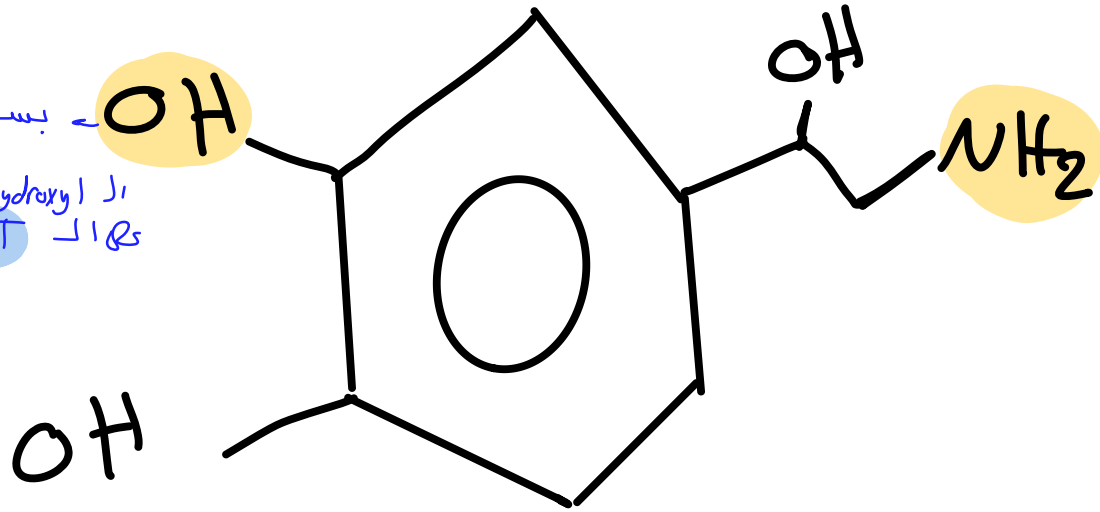


اما هون العكس بلش بـ COMT بالأول بعدين بالـ MAO

short duration of action

orally inavaliable

إذا MAO و COMT الـ substrate لـ Epinphrine و NE بما انه الـ



بسبب وجود هاي ال OH ← بسبب وجود هاي ال

ال hydroxyl رح يكون substrat

COMT ال

بسبب وجود هاي ال NH2 ←

Amin رح يكون substrate

MAO

بالنسبه للادويه اللي رح تشتغل على ال Adrenergic رح يكون الهم تأثير

enhancing

inhibtion

Adrenergic Drugs

- The drugs that act on the peripheral sites of the sympathetic nervous system are collectively named adrenergic drugs.
- They act via either enhancing or inhibiting the sympathetic activity.

Stimulating.	Inhibiting.
Sympathomimetic.	Sympatholytic.
Adrenomimetics.	antiadrenergic.
or adrenergic stimulants.	or adrenergic-blocking agents.
Agonists.	Antagonists.

Sympathomimetic Drugs

According to the mechanism of action, sympathetic drugs may be classified into :

1. **Direct acting Sympathomimetics.** → رح يرتبط مباشرة بال receptor

   (interact directly with adrenergic receptors)

2. **Indirect acting Sympathomimetics.** رح يحفز ال NE انه يطير اله release ويرتبط بال post ganglionic من ال re-uptake او يمنع ال receptor

   (initiate the release of NEpi from adrenergic nerve terminal which activate the receptor or inhibit its uptake mechanism)

3. **Mixed function adrenergic agonists**

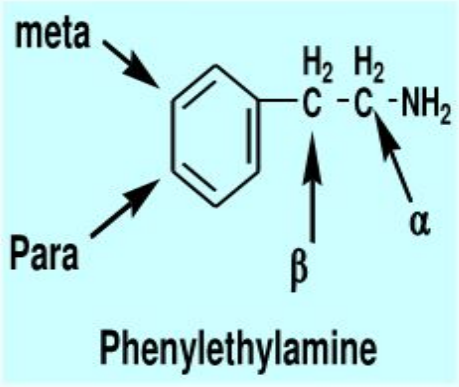
   (interact directly with the receptor and act indirectly by increasing the conc. of Nepi at the receptor site)

Direct-Acting Sympathomimetics

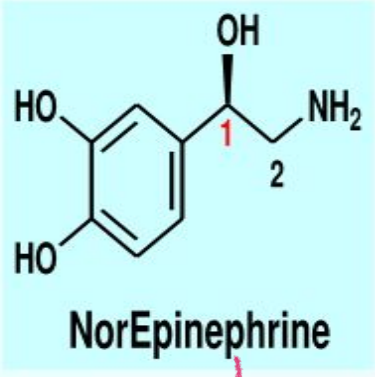
Prototype of direct-acting sympathomimetics: Norepinephrine, epinephrine and isoproterenol.

They are phenylethylamine derivatives that contain the appropriate substituents.

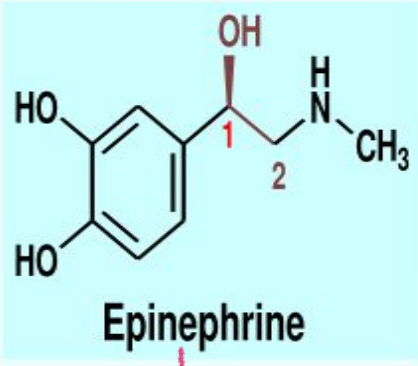
Also, they are Catecholamines.



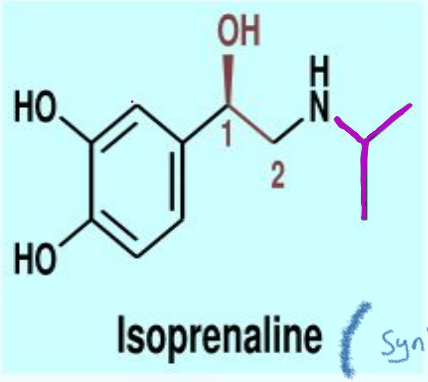
Phenylethylamine



NorEpinephrine



Epinephrine



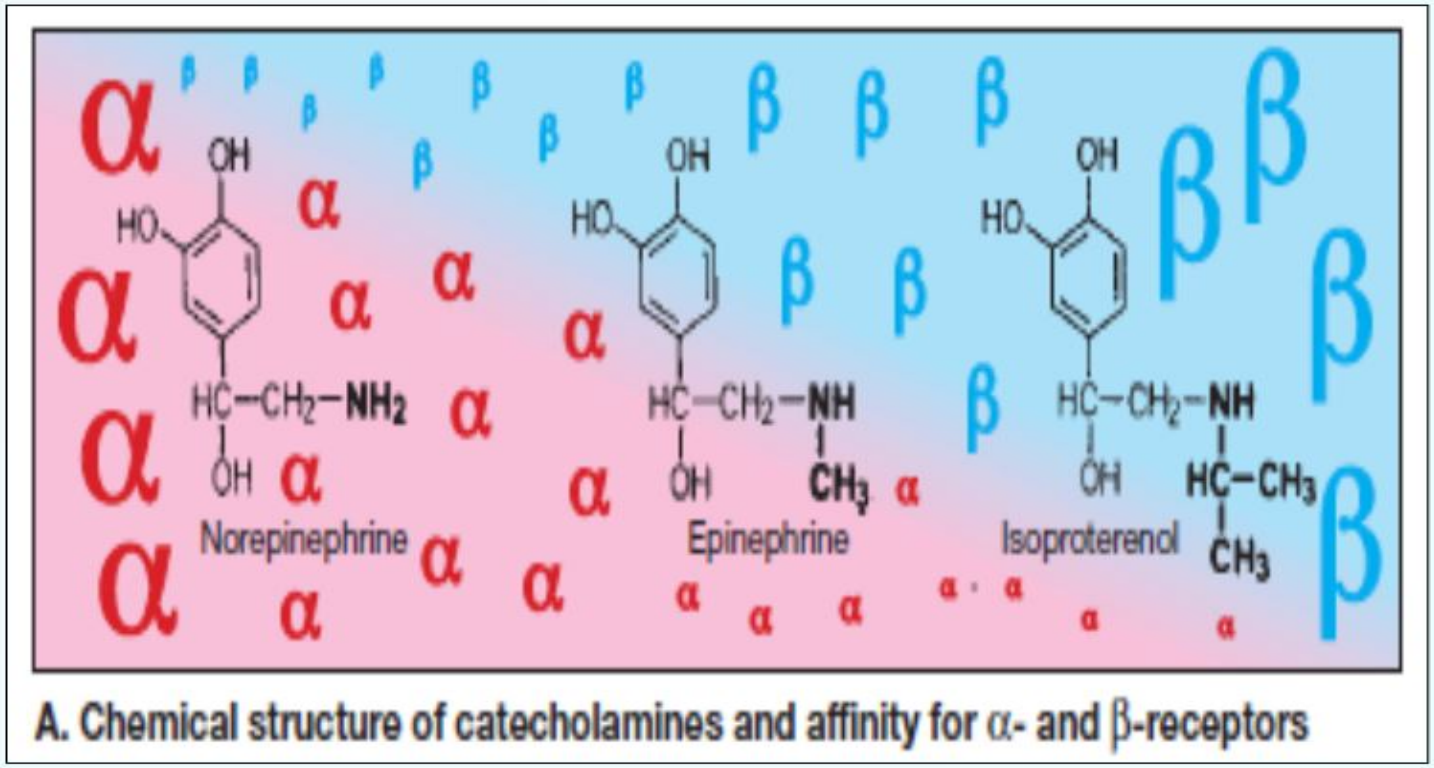
Isoprenaline (Synthtic)

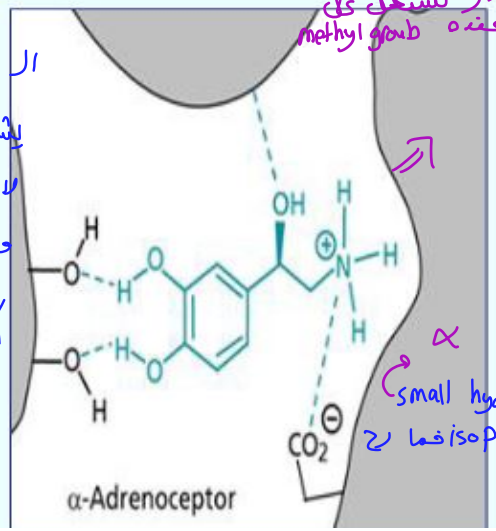
بدل ال methy فيه isopropyl او

Norepinephrine and Epi are natural neurotransmitter and neurohormone.

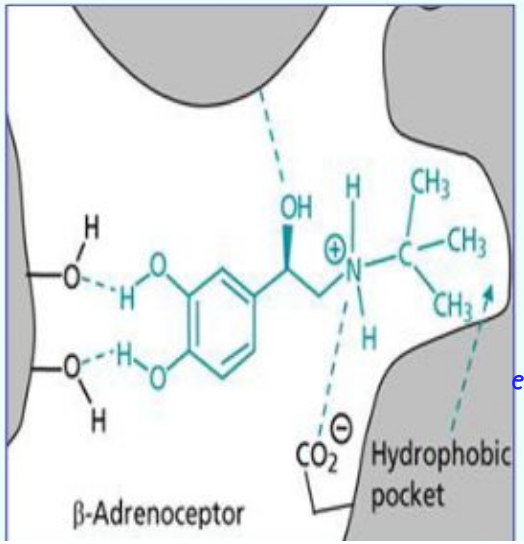
Isoproterenol is a synthetic compound.

Catecholamines





Chemistry explains the differences. isopropyl is β-directing



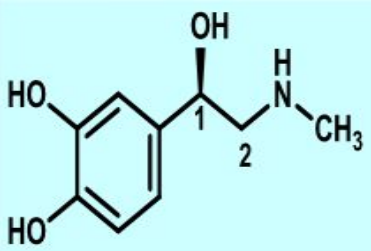
الـ Epinphrine بقدر يشتغل عالـ α و الـ β لانه عنده methyl groub وايضا صغيره كثير رح بقدر تدخل بالـ Pocket الموجود بالـ α و الـ β

الـ NE بقدر يشتغل على الـ α لانه ما عنده methyl groub

α small hydrophobic pocket لهاد رح يشتغل عليه isoproterenol

β Larg hydrophobic pocket هون فيه isoproterenol عنده isopropyl groub لهاد رح يعمل Larg hydrophobic effect و رح يعطي Van der waal rxn فبيكون الـ β selective

Epinephrine (Adrenaline)



Epinephrine (Adrenaline)

- Prototype.
- Direct adrenergic agonist, due to the presence of the catechol OHs, the β-OH and a secondary amine group.

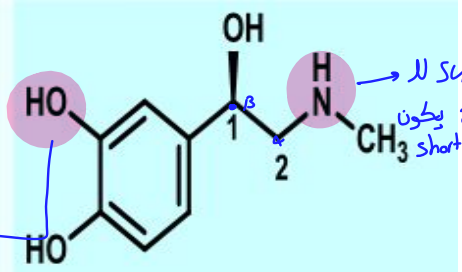
- The (N) atom is a secondary amine with a methyl substituent, which provides non selective adrenergic activity: both α- and β- activities.
- Epinephrine has both α and β-effects. No selectivity (α and β)
- The amine function is affected by MAO.
- Short duration of action

Structural features

بسبب وجود ال 2catchol hydroxyl وال β hydroxyl وال amin رح يكون Direct Acting

رح تكون substrate لل MAO إذاً رح يكون short duration of action الـ

رح تكون substrat لل COMT ← oral inavaliable



Epinephrine (Adrenaline)

- Because of the catechol nucleus, it is metabolically vulnerable; rapidly affected by COMT.
- Short duration of action and oral inactivity.
- Highly polar molecule: decreased penetration into the eye.

غالباً ال Epinphrine بستخدمه لقطرات العين glucoma لانه رح يتكسر بال MAO وال COMT بس مع هيك في اشياء ما بتخلي افضله بالإستخدام كقطرة للعين

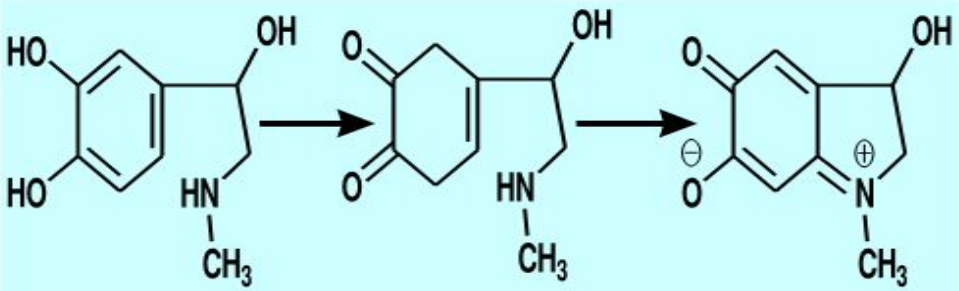
① ال N رح تصير ionize وما رح يصير الها penetration بالعين

② ال 2 hydroxyl رح يعمل irritation بالعين

- Because of the catechol nucleus, it is oxidized easily and darkens slowly on exposure to air (chemical instability) due to formation of inactive quinone.

رح يعطي Pigment (غامقة red)

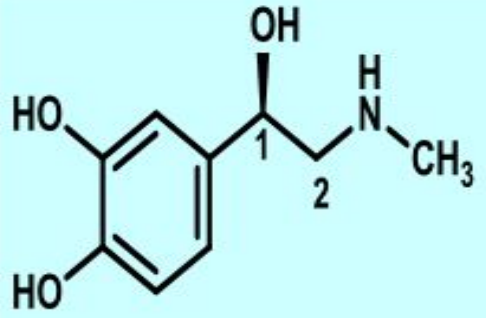
عشان هيك بعطي الـ Epinphrine مع antioxidant



Red pigment, Adrenochrome

Thus, solutions are stabilized by adding reducing agents as ascorbic acid.

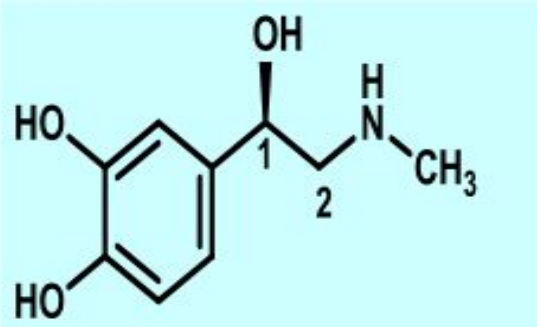
Structural features



Epinephrine (Adrenaline)

- There is a chiral carbon
- There are 2 isomers
- The *levorotatory* isomer of epinephrine is more active than other isomer.
- So, the drug should be prepared as R(-) isomer.

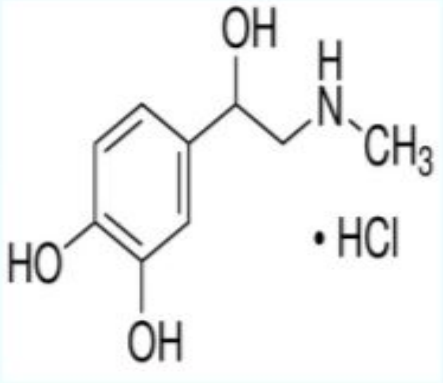
Structural features

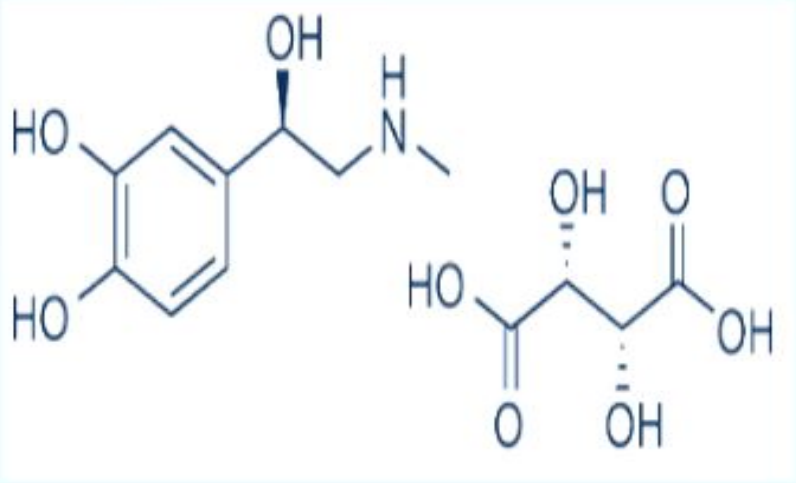


Epinephrine (Adrenaline)

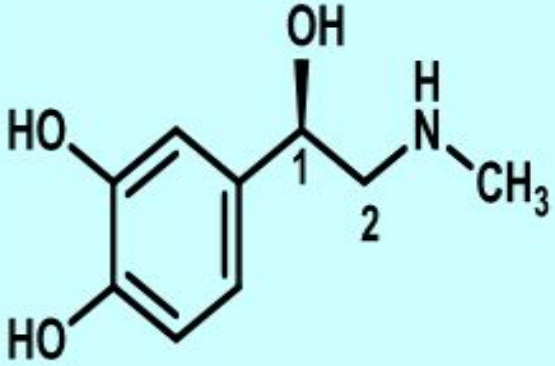
stabilizing يضيفم لاعل للمركب

- As a drug, epinephrine is available as HCl and bitartarate salts.
- Salts are of high degree of water solubility. → absorption حشان احسن ال
  more stable
- Bitartarate salt shows increased *in vitro* stability against alkaline media.
  لانه ال Hcl ما رح يقدر يعمل Salt مع ال Adrenaline



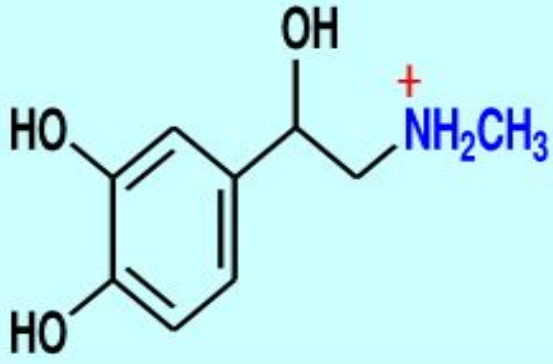


Structural features

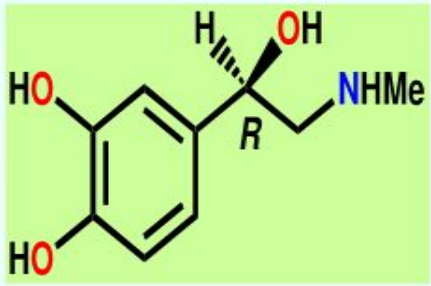


Epinephrine (Adrenaline)

- At physiological pH (7.4), NE and Epi are found to exist in more than 95% in the cationic form in which nitrogen is protonated.
- Henderson–Hasselbalch equation
- pKa of epinephrine = 8.55



Adrenaline. Uses



حساسية

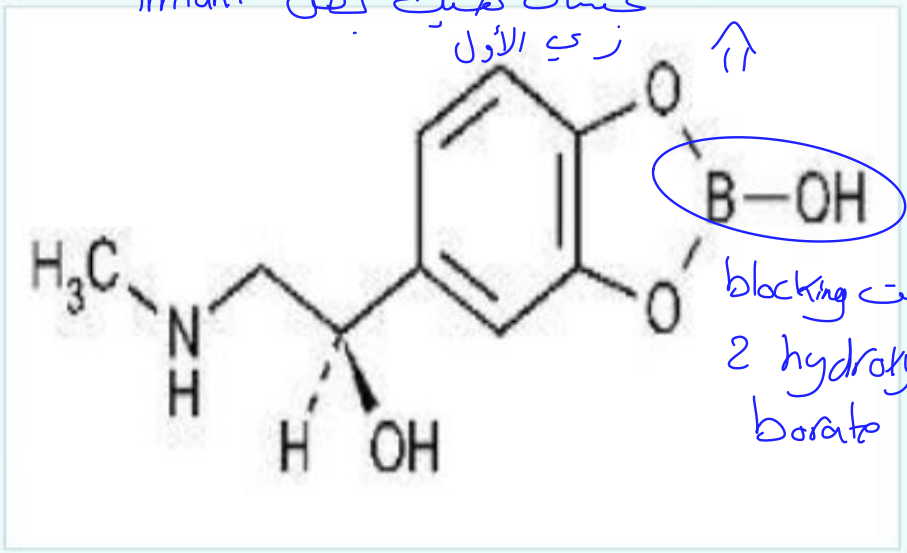
- Adrenaline used for severe anaphylactic shock
- Vasoconstrictor in patient with hemorrhage.
  - fast acting, but short acting
  - unsuitable for long term medication
  - cardiovascular side effects → لانه بشتغل على ال قلب
- Vasoconstrictor in nasal decongestion.
- Increase the activity of local anesthetics.
- a limited use in case of bronchial asthma and heart block → لانه non-selective فمثلاً اذا اعطيته لل asthma يأثر على القلب

Disadvantages

- Short duration. (rapid metabolism)
- Not taken orally

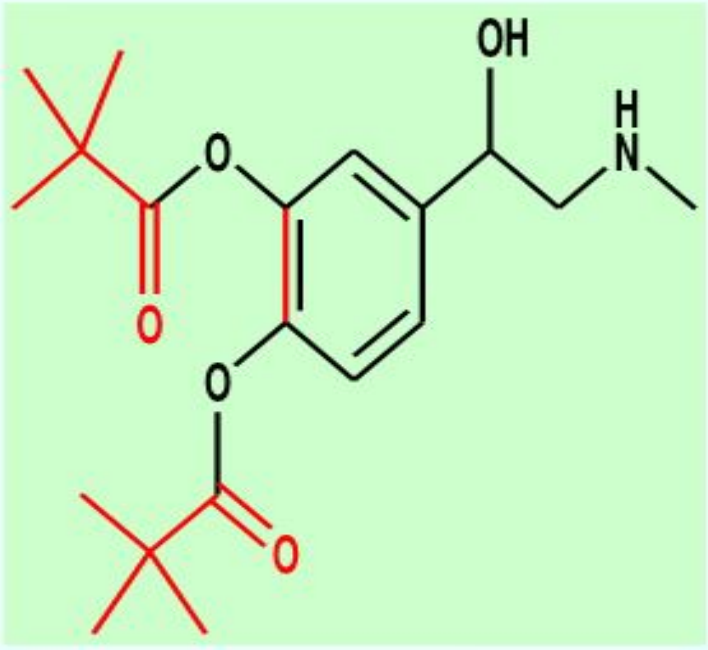
Modified structures of Epinephrine

2 hydroxyl ل blocking حطت
irritant عشان هيك بطل
زي الأول



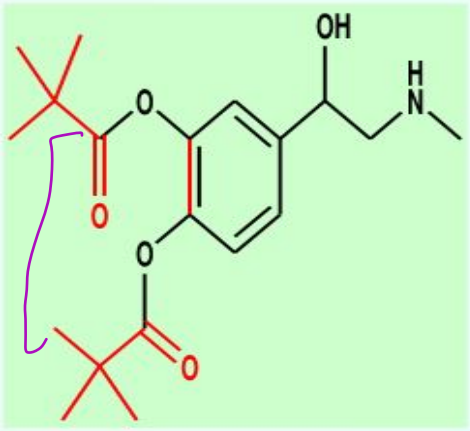
blocking حطت
2 hydroxyl لل
borate بال

- **Epinephryl borate**
- It is used in the treatment of primary open angle glaucoma.
- Less irritant than epinephrine.

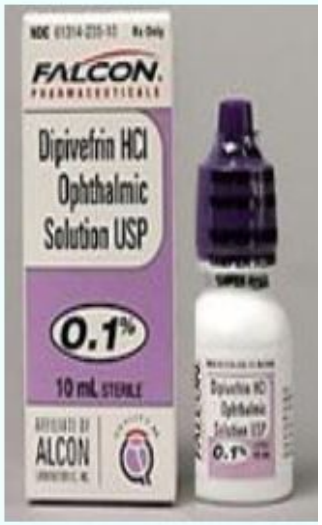


- **Dipivefrin**
- **Ophthalmic for Glaucoma**
- Less irritant than epinephrine

Dipivefrin



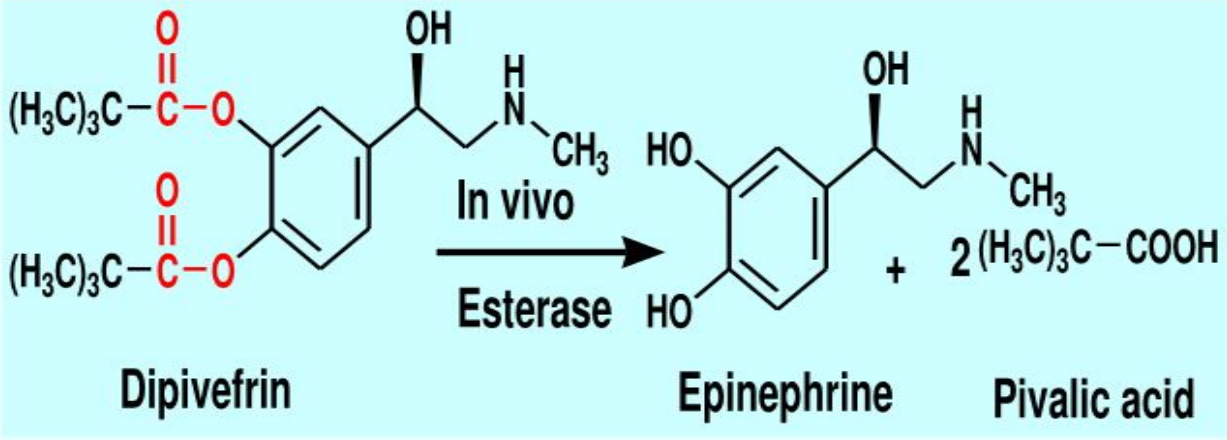
Pivalic acid بال blocking OH صار لل
وهيك زادت ال lipophilicity للمركب
(لانه المركب اي صفته lipophilic)
وهيك بقدر يصير له Penetration
بالعين



- It is the pivalic acid **prodrug of epinephrine**, with higher **lipophillic** character so with better ocular penetration when used in glaucoma

بستخدمه topical

- Less irritant than epinephrine.
- **A Prodrug.** It is converted to epinephrine by **esterases** in in the cornea and anterior chamber.



لا تنسوا زميلنا ايهم من دعائكم