

تفريغ فارما ١

اسم الموضوع: Lecture 8 part 2

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Adrenergic Agonists

→ المقصود منها الـ sympathetic

(لادوية يـي الـ effect الـها بـعد (mimicking) يعنـي يسـاـبه / يحـفز الـ sympathetic)

نرجع لفكرة انه الـ Ach يتكون بالـ neurons يعني كل خليه بتنتج الـ neurotransmitter (1) (synthesis)

يبي بتحتاجها ففيه عنا الـ neurons المسؤولين عن الـ Sympathetic Transmission فهذه بتنتج الـ norepinephrine و بتخزنوه داخل الـ vesicles (2) (storage) وبعد هيك لما يصير فيه activation يصير فيه

release الـ norepinephrine والـ norepinephrine يرتبط على الـ receptor (4) و رح يعطينا الـ effect

بعد هيك المفروض يصير (5) remove الـ norepinephrine من الـ receptor .

Adrenergic Agonists

☐ Neurotransmission at adrenergic neurons

- Norepinephrine 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

1. Synthesis of norepinephrine

main neurotransmitter
في حالة ال sympathetic

- Tyrosine entry to the adrenergic neuron via Na^+ dependent carrier Tyrosine يدخل ال Tyrosin عن طريق ال Na^+ dependent carrier و بصره hydroxylation و بصر DOPA decarboxylation
- Tyrosine hydroxylation ** RLS Dopamine hydroxylation
- DOPA decarboxylation
- Dopamine hydroxylation (inside the vesicles)

(وبعد التخليق بصره في storage داخل ال vesicles)

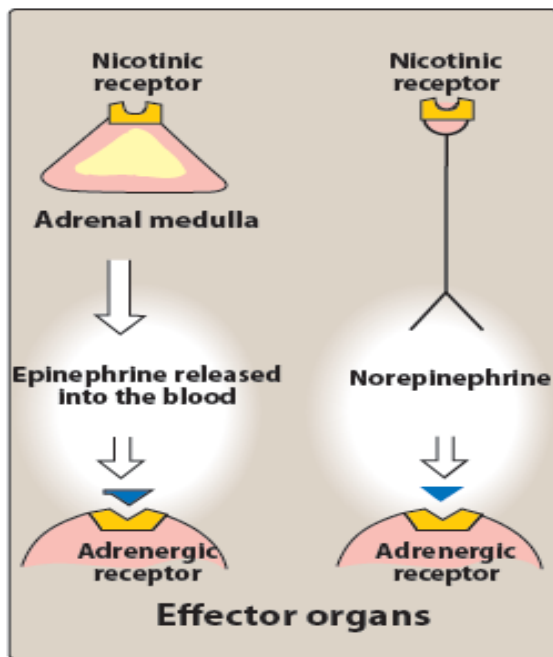


Figure 6.2
Sites of actions of adrenergic agonists.

2. Storage of norepinephrine in vesicles

precursor (مكون أولي) →

- 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 → واحد من المركبات التي لها effect (تفكيكي عنه لقدام).
- Dopamine is hydroxylated to form norepinephrine by the enzyme, dopamine b-hydroxylase
- Stored in the vesicle until released

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

• الحانيد يكون في الـ epinephrine والـ norepinephrine

الـ epinephrine بنسبة 80% .

والـ norepinephrine بنسبة 20% .

طبعاً عن طريق الـ methylation الـ norepinephrine .

3. Release of norepinephrine

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

لها تأثير فيه
activation

release of norepinephrine

norepinephrine يرتبط مع الـ receptor

adrenergic receptor في حكاية عنهم.
post synaptic receptor

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”

بصير بـ: طريق

5. Removal of norepinephrine

Possible removal mechanisms:

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

يعني يخرج من الفجوة المشبكية ويصل إلى الدورة العامة
synaptic cleft (general circulation)

الانزيم methyl

methylation

norepinephrine

O-methylated

norepinephrine

في نهاي الخلية النوربينفرين

بطل active

When NE reenters Adrenergic neurons

neuron إلى norepinephrine (reuptake) norepinephrine oxidation في الدم

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

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

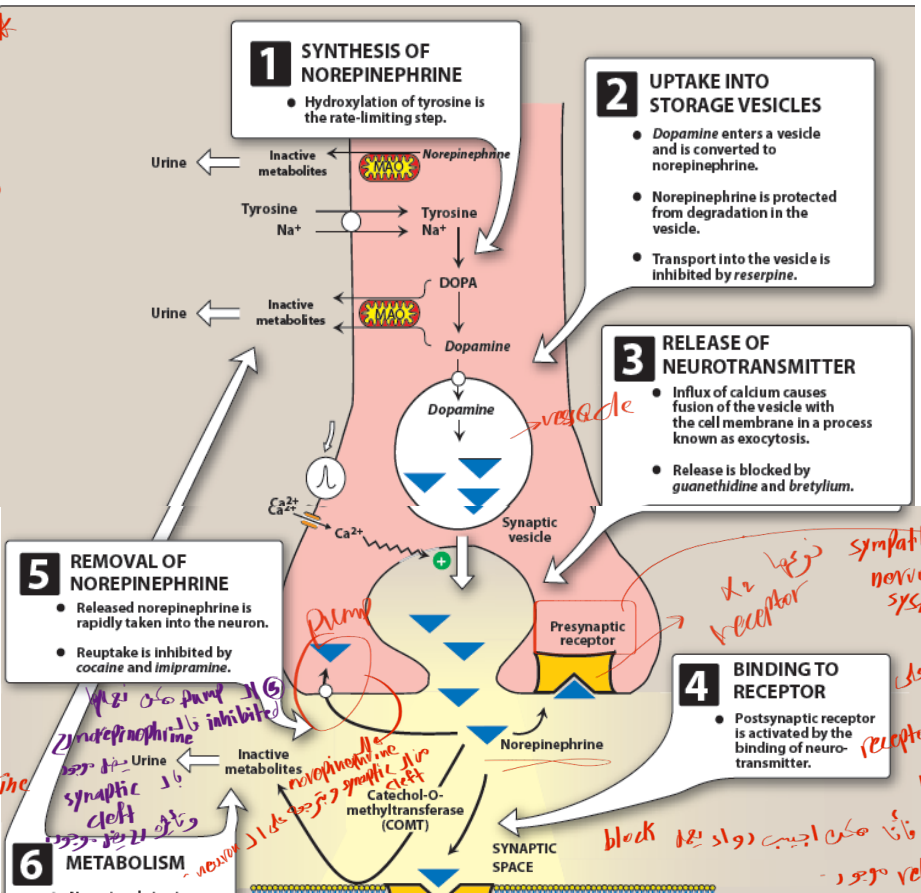
هناك ثلاث طرق من أجلnorepinephrine في مجرى الدم، إما بواسطة metabolism عن طريق COMT و MAO enzymes. يتم إنتاجها في الجسم عن طريق neuron.

الادوية التي تحفز الجهاز العصبي
 sympathetic activation
 nervous system

الادوية يمكن ان تكون
 activation
 direct

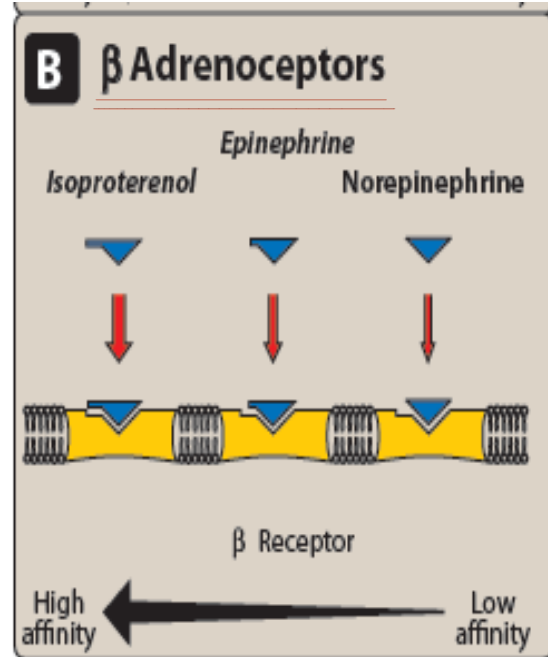
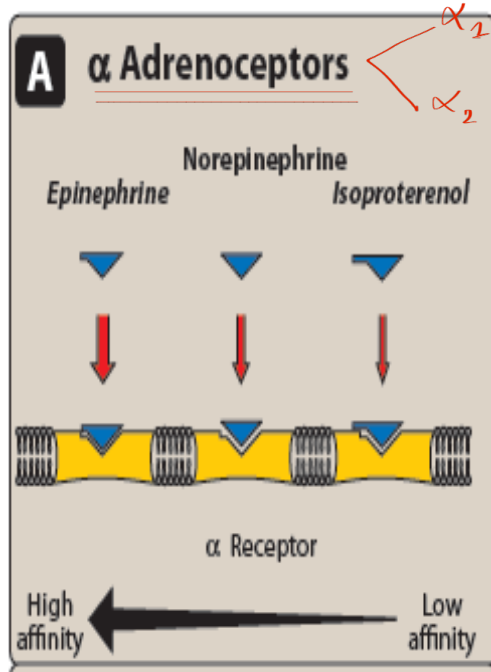
receptor (agonist)
 norepinephrine
 agonist
 direct agonist

MAO و COMT
 metabolism
 norepinephrine
 active



Presynaptic receptor
 sympathetic nervous system
 norepinephrine
 active receptor
 (auto inhibition)
 release

Adrenergic receptors (adrenoceptors)



Adrenergic receptors (adrenoceptors)

α Receptors

activation تفعيل

► $\alpha 1 :$

← postsynaptic effector organs

contraction of smooth muscles

Activation increases IP3 and DAG and Calcium release from the ER to cytoplasm

Calcium release من ال endoplasmic reticulum
فما يزيد ال calcium جدا الكمية بزيادة ال contraction

نظيرها الأساسية
(يعني انه لما يوجد ال norepinephrine
يتمسك به معين فيزي ربح inhibition
norepinephrine release

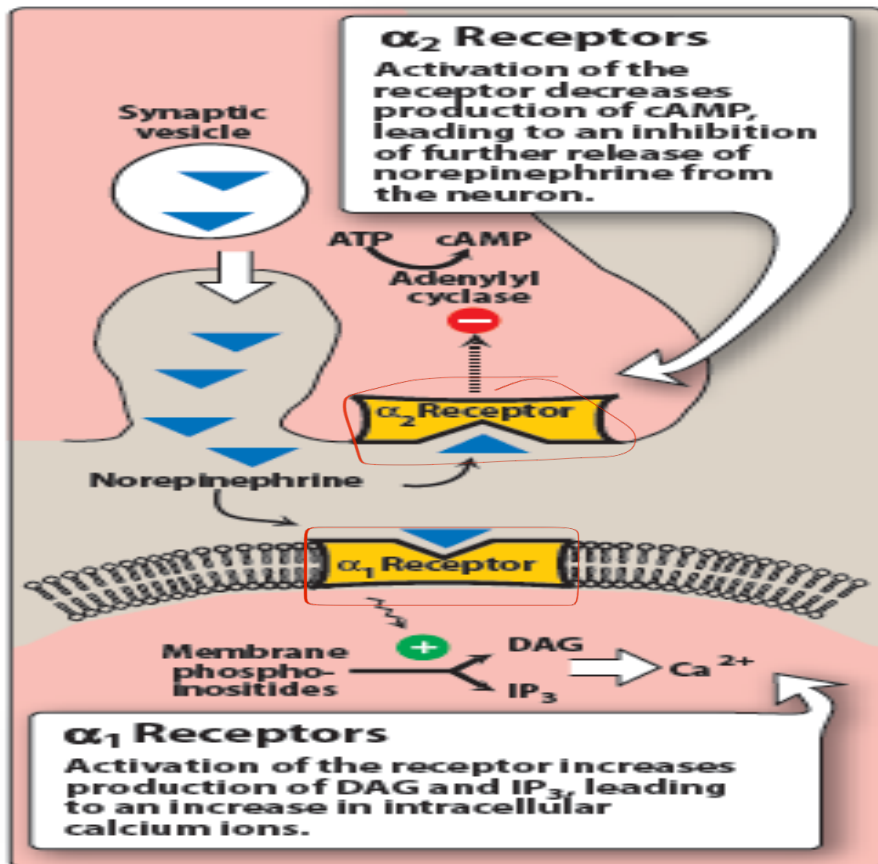
➤ $\alpha 2$: inhibition Jew

- located presynaptically → *presynaptic* موجود قبل
neuron عصبون

- Beta cell of the pancreas and on certain vascular smooth muscle cells, control adrenergic neuromediator and insulin output,

4 feedback inhibition on NE → norepinephrine release

- fall in the levels of intracellular cAMP.



✳️ receptor α_1 و α_2 أيضاً ممكن ينقسموا لـ subdivision فيها عناوين
 ↘

- The α_1 and α_2 receptors are further divided into α_{1A} , α_{1B} , α_{1C} , and α_{1D} and into α_{2A} , α_{2B} , and α_{2C} . This extended classification is necessary for understanding the selectivity of some drugs.

- For example, tamsulosin is a selective α_{1A} antagonist that is used to treat benign prostate hyperplasia. The drug is clinically useful because it targets α_{1A} receptors found primarily in the urinary tract and prostate gland.

لتنظيم غدة البروستات
 التامسولوسين
 داء علاج الوديه
 الـ هو انه نطفي
 adrenergic antagonist
 و ديك هو فقط
 و ديك رز يهد
 تا smooth muscles
 relaxation
 inhibition
 α_{1A}
 يكون عليها البروستات
 تأثير التشنج وهذا

✳️ α_{1A} موجود في smooth muscles حول الـ prostate .

لا فيه مجموعة كبيرة من الادوية الي رح ندرسها بتشغل على ال β -receptor .

β Receptors

- Strong response to **isoproterenol** rather than to epinephrine

- The β -adrenoceptors can be subdivided into three major subgroups
 - β_1 (heart, kidney)** → β_1 في ال heart يزيد ال HR و ال contractility
في ال kidney موجوده جديدا في ال juxtaglomerular cells
 - β_2 (lung, blood vessels)** → يزيد من افراز ال Renin الي يزيد من ارتفاع ضغط الدم بتزيد زلزلة ال Angiotensin II
يعمل على تضيق في الشرايين vaso constriction
 - β_3 (AD)** → Adipose tissues
له بتزيد من تكسير الدهون (lipolysis) وتحويلها ل fatty acid

[+] ال kidney تفرز ال Erythropoietin وهو هرمون ينظم انتاج خلايا الدم الحمراء

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

ADRENOCEPTORS

α_1

- Vasoconstriction
- Increased peripheral resistance
- Increased blood pressure
- Mydriasis
- Increased closure of internal sphincter of the bladder

α_2

- Inhibition of norepinephrine release
- Inhibition of acetylcholine release
- Inhibition of insulin release

β_1

- Tachycardia
- Increased lipolysis
- Increased myocardial contractility
- Increased release of renin

β_2

- Vasodilation
- Decreased peripheral resistance
- Bronchodilation
- Increased muscle and liver glycogenolysis
- Increased release of glucagon
- Relaxed uterine smooth muscle

مستقبلات α و β دو قطب دارند.