بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 7

Adrenomimetic Drugs pt.2

Written by : Leen Alzoubi
Layan Bassam

Reviewed by : Reem Alfaqeh

In the previous lecture, we discussed the subtypes of adrenergic receptors, which include: (α1,α2,B1, B2, β3)
Some of these adrenergic receptors are found on smooth muscle, particularly vascular smooth muscle.

Adrenergic Receptors in Vascular Smooth Muscle (smooth muscles of blood vessels)
Both α and β adrenergic receptors are present in vascular smooth muscle, but their distribution and effects differ depending on the tissue supplied.

α1 receptors
- Found mainly in vascular smooth muscle of resistance blood vessels, These vessels supply:
  - Skin
  - Major blood vessels supplying the gastrointestinal (GI) system
- Activation of α1 receptors → contraction of vascular smooth muscle which result in vasoconstriction

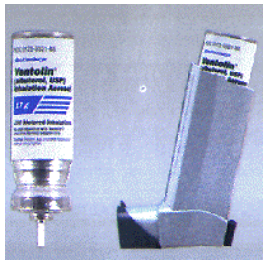
β2 receptors
- Found mainly in vascular smooth muscle of blood vessels supplying skeletal muscle
- Activation of β2 receptors → relaxation of vascular smooth muscle resulting in vasodilation

These receptors (alpha and beta) therefore have opposing (opposite) effects on vascular tone.

β2 Receptors in Skeletal Muscle
- β2 adrenergic receptors are also present in skeletal muscle fibers themselves
- Activation of these receptors enhances contraction of skeletal muscle

Autonomic Control of Smooth Muscle

Asthma inhaler



Bronchial smooth muscle has beta-2 adrenoceptors

Be careful with nonselective beta agonists!

"Because the excessive cardiac stimulation produces cardiac arrhythmias and enhanced myocardial oxygen consumption, there is no rationale for using non-beta-2 selective agonists in the treatment of asthma."

Cardiac arrhythmia refers to an imbalance or disturbance in heart rhythm, An example of arrhythmia is Tachycardia

Relax G.I. smooth muscle

- alpha and beta effects
- reduce motility
- may contract sphincters

Relax uterine smooth muscle

- beta-2 agonists delay premature labor

Relax detrusor muscle (β); contracts sphincter (α)

- urinary retention

Contract radial muscle (α)-- mydriasis

What happens to the bronchi in fight-or-flight?

- In fight-or-flight mode, the body needs more oxygen. Therefore, the bronchi must dilate and to achieve bronchodilation bronchial smooth muscle must relax

Role of Norepinephrine (NE) and Epinephrine (Epi)
Norepinephrine and epinephrine cause:

- Relaxation of bronchial smooth muscle
- This leads to bronchodilation

Application in Drug Therapy (Asthma Inhalers)

- Some drugs are designed to mimic the action of NE and epinephrine
- As shown in the picture, the drug used is an inhaler specifically used for asthma
- Asthmatic patients have trouble breathing due to:
- 1)Bronchoconstriction
- 2)Excessive bronchial secretions
- 3)Excessive inflammatory reactions

Treatment of Asthma

- To help asthmatic patients, we administer Adreno-mimetic (sympathomimetic) drugs
- Example: Albuterol

Mechanism of Action of Albuterol: Albuterol works by activating β_2-adrenergic receptors

β1 and β2 Adrenergic Receptors

- We have β1 and β2 adrenergic receptors in the body.
- When an agonist binds to β1 receptors in the heart, it causes:
  - Increase in heart rate → positive chronotropic effect
  - Increase in cardiac contractility → positive inotropic effect
  - Increase in conduction velocity → positive dromotropic effect

Non-Selective β-Agonists and Asthma Treatment

Example: Isoproterenol (Isoproterenol is a catecholamine which differs from Epinephrine and Norepinephrine in the fact that it is selective for β-adrenergic receptors also it does not differentiate between β1 and β2 receptors)

What will happen if an asthmatic patient is treated with a non-selective β-agonist such as isoproterenol:

- Bronchodilation: Occurs because the drug binds to β2 receptors in bronchial smooth muscle
- Cardiac effects (such as Tachycardia, Increased heart contractility): These occur due to β1 receptor stimulation in the heart

Clinical Problems with using Non-Selective β-Agonists

- The excessive workload on the heart can be problematic:
  - Even in a healthy patient
  - Especially in patients with ischemic heart disease (In ischemic heart disease the heart does not receive sufficient blood supply to meet the work of the heart) thus Increased workload from giving the patient a non-selective beta agonist worsens oxygen demand leading to ischemic heart attack also called Angina or myocardial infarction

Importance of the discovery of Adrenergic Receptor Subtypes

- These effects highlight the importance of the discovering of different adrenergic receptor subtypes
- Understanding receptor subtypes allows us to Develop more selective drugs that target specific receptors to reduce unwanted side effects

Effect of Sympathetic Stimulation on the GI Tract

Effect of parasympathetic stimulation on the Gastrointestinal (GI) System

- The GI system is mainly regulated by the parasympathetic nervous system (rest and digest), which is associated with Increased GI motility during resting conditions
- Therefore, when the body is at rest, we normally need active GI motility for digestion.

Effect of Sympathetic Stimulation on the GI Tract: 1) Relax GI smooth muscle 2) Reduce motility 3)may contract sphincters

Physiological Rationale (Fight-or-Flight)

- During sympathetic stimulation:
  - We do not want to focus on digesting food
  - Blood flow is redirected to more important organs, such as: Skeletal muscles, Heart, Lungs

Effects on GI Sphincters

- Sympathetic stimulation also causes contraction of sphincters
  - At the end of the stomach
  - At the end of the colon
- The reason: We do not want to worry about defecation or bowel movements during stress or danger.
- GI sphincters usually contain α_1-adrenergic receptors
- α_1 receptor activation is typically associated with smooth muscle contraction
- This explains why sphincters contract during sympathetic activation.

Effect of sympathetic stimulation on Uterine Smooth Muscle

- Uterine smooth muscle contains β2-adrenergic receptors, activation of β2 receptors causes relaxation of uterine smooth muscle.

Clinical Importance

- In a pregnant woman, if there is a risk of premature labor:
  - We can administer a β2-adrenergic agonist
  - This leads to relaxation of the uterine smooth muscle. As a result, uterine contractions decrease and premature labor is prevented or delayed. Therefore, β2 agonists can be used to prolong pregnancy when premature labor is a concern.

Effect of Sympathetic Stimulation on the Urinary System (Urinary Tract)

Effects on the Bladder

- Relaxation of the detrusor muscle (The detrusor muscle is in the wall of the urinary bladder). Relaxation allows the bladder to store urine
- Contraction of the trigone muscle and urinary sphincter: This contraction helps to prevent urine leakage and control urine flow

Effects on endocrine function

During sympathetic (fight-or-flight) activation, the body aims to liberate and mobilize all available energy sources, whether from lipids or glucose, to meet increased energy demands

Metabolic effects: stress / ”fight or flight”

- **Lipolysis (β3)**
- **Glycogenolysis (β2)**
- **Increased metabolic rate (β)**
- **Decreased insulin secretion (α2)**
- **Renin release (β1)**

Because we want to keep more glucose in the bloodstream

- β3-adrenergic receptors are found in fat cells (adipose tissue).
- Activation of β3 receptors causes lipolysis (Breakdown of stored fats) which causes the release of fatty acids into the bloodstream to be used as an energy source
- If the body needs energy, it can then use these circulating lipids.
- Currently, there are no commonly used drugs that specifically target β3 receptors. These receptors are considered a “hot area” of research. Future β3-agonist drugs may be useful in obesity management

Epinephrine

- **Stimulates all adrenoceptors (α1, α2, β1, β2).**
- **Very potent vasoconstrictor and cardiac stimulant.**
- **Positive inotropic and chronotropic actions on the heart (β1).**

Vasoconstrictor in many vascular beds (α1), and vasodilator in skeletal muscle blood vessels (β2) → increase blood flow during exercise.

Norepinephrine

Similar to epinephrine except it has no significant effect on β2 receptors.

D1 Agonists

Dopamine

- Activates D1 receptors and produce vasodilation, which is specially clinically important in renal vascular bed → increase renal blood flow.
- Activates β1 receptors in the heart.
- At high concentration, it activates vascular α receptors leading to vasoconstriction including the renal vascular bed.

• Fenoldopam

- Is a selective D1 receptor agonist causing peripheral vasodilation.
- Very useful intravenously in treating severe hypertension.

Adrenergic Pharmacology

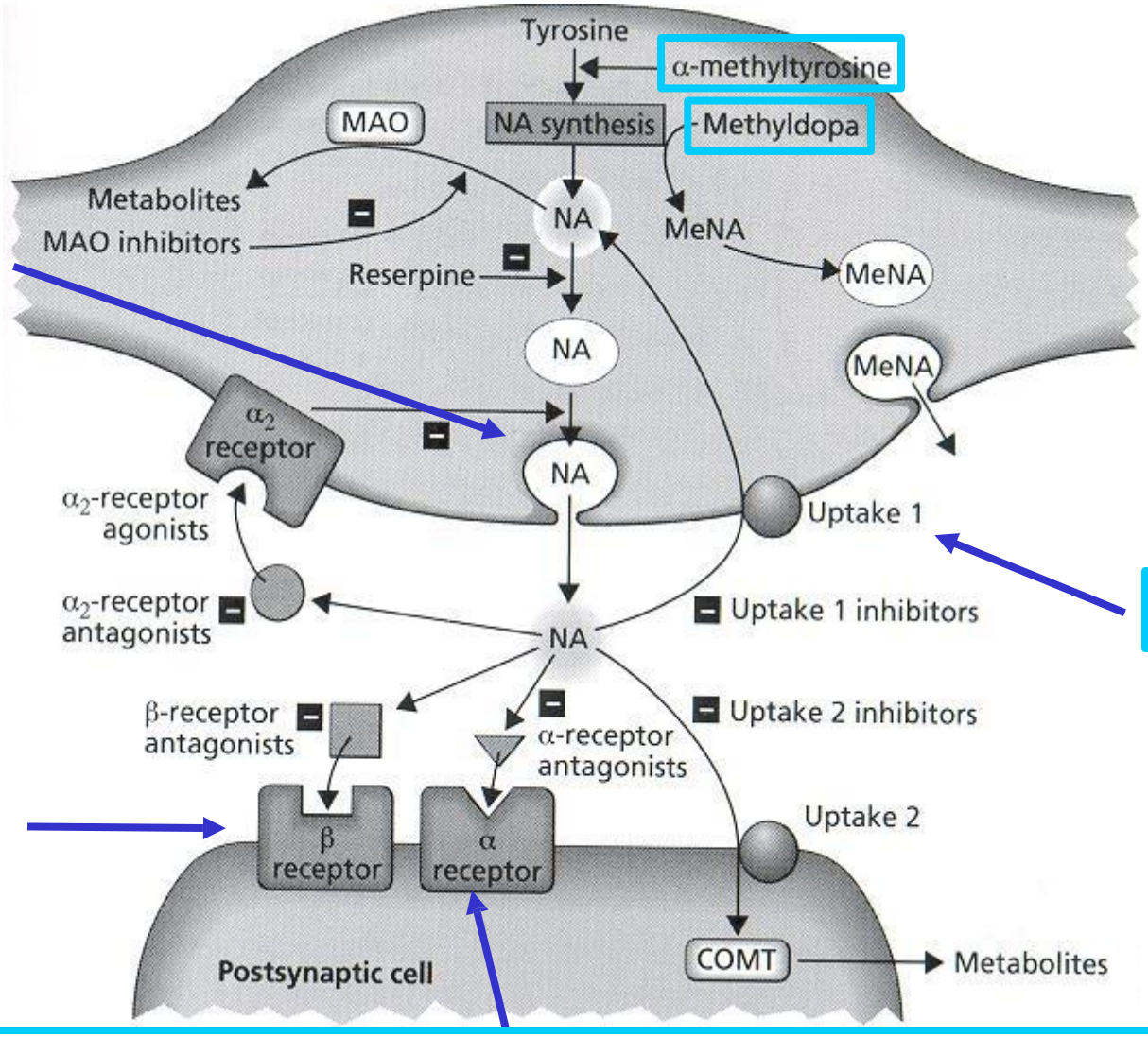
+ agonists
– antagonists

The drugs that are mentioned here are considered prototype drugs, meaning they were the earliest discovered agents in their class. Over time, many newer drugs have been developed that mimic the same actions of these prototypes but offer several advantages. These newer drugs may have fewer or different side effects and improved pharmacokinetic properties, such as longer half-lives and greater potency.

#these drug names are for memorization, memorize the agonists for now

NE release
+ amphetamine
+ ephedrine
- guanethidine
- reserpine

β-AR
+ isoproterenol
+ dobutamine
+ terbutaline
+ albuterol
- propranolol
- metoprolol



- cocaine

α-AR: +phenylephrine, +methoxamine, +clonidine
- phenoxybenzamine, - phentolamine, - prazosin

Regulation of Norepinephrine (NE) Release and Effects on the Adrenergic System

- α2-adrenergic receptors are found presynaptically on adrenergic nerve terminals.
  Their main function is regulation of norepinephrine (NE) release.
- When norepinephrine (NE) (also called noradrenaline, NA) is released into the synaptic cleft and completes its action on postsynaptic receptors, the response must be regulated to prevent excessive stimulation.
- One important regulatory mechanism is **negative feedback via α2 receptors**:
  NE binds to presynaptic α2 receptors, which signals the neuron to stop releasing more NE.
- Another key regulatory mechanism is **reuptake of the neurotransmitter:**
  - NE is taken back into the presynaptic neuron by specific transporters (not receptors).
  - After reuptake, NE is recycled and reused.
- Cocaine inhibits this reuptake mechanism, preventing NE from being removed from the synaptic cleft.

Effect of Cocaine on the Adrenergic System

- Cocaine causes an increase in NE concentration in the synaptic cleft, leading to a prolonged and enhanced adrenergic (sympathetic) effect.
- This results in:
  - Increased sympathetic activity
  - Increased blood pressure (BP)
  - Constriction of important blood vessels

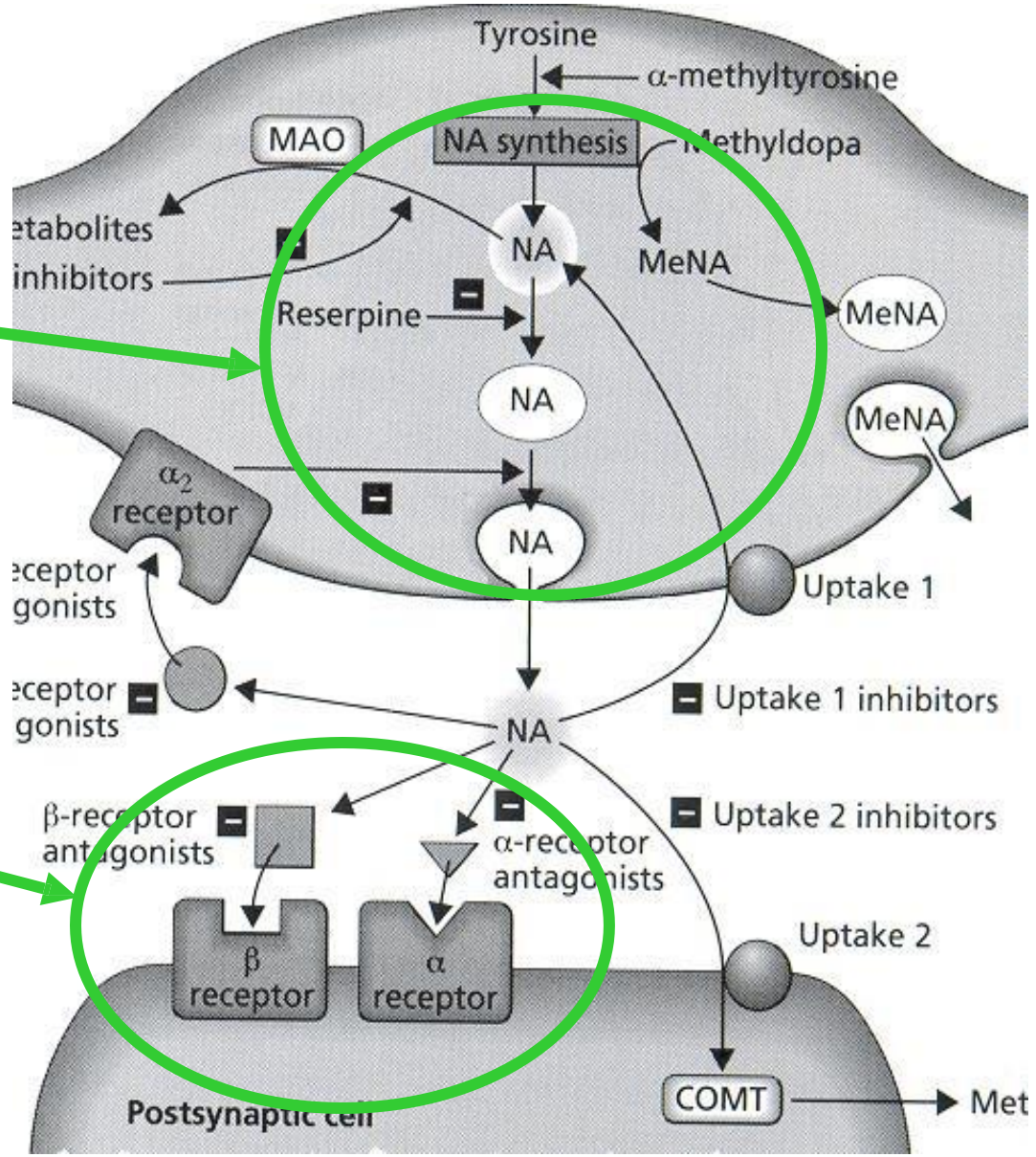
Adrenergic Agents: a dual strategy

2) **Indirect Effect**: nerve terminal

enhance / inhibit NE release

1) **Direct Effect**: adrenoceptors

mimic / antagonize effect of NE (Adrenomimetics / blockers)



Drugs that mimic the adrenergic system can act through different mechanisms.

1. Increasing Neurotransmitter Release (Indirect)

- Some drugs act at the presynaptic nerve terminal (nerve ending).
- They increase the release of neurotransmitters, mainly: Norepinephrine (NE)
- These drugs work by stimulating the nerve terminal to release more NE into the synaptic cleft.

2. Direct Action on Adrenergic Receptors

- Some drugs act directly on adrenergic receptors.
- Example:
  - β-adrenergic receptor agonists Such as isoproterenol
  - α-adrenergic receptor agonists
- These drugs bind directly to the receptor and activate it.

3. Drugs with Dual Mechanism

- Some drugs have a dual function:
  - They increase neurotransmitter release
  - AND act directly on the receptor
- These drugs affect both the presynaptic and postsynaptic sides.

Adrenomimetic Amines

"mimic" the effect of NE

Direct selective adrenergic agonists:

stimulate alpha or beta adrenoceptors

alpha-1:	phenylephrine
	methoxamine
alpha-2:	clonidine
beta-1:	dobutamine
beta-2:	terbutaline
	albuterol

Alpha-1 Adrenergic Agonists

PHENYLEPHRINE

- **Alpha-1 adrenergic agonist**
- **Weak beta effects**
- **Not a substrate for COMT**
- **Primary use: vasoconstrictor**
- **Treat hypotensive states**
  - ***shock, spinal anesthesia***
- **Nasal decongestant (Neosynephrine)**
  - ***rhinitis medicamentosa or rebound***
- **Mydriasis**

Phenylephrine

- Phenylephrine is an α1-adrenergic agonist. Activation of α1 receptors causes vasoconstriction increasing the peripheral vascular resistance

Relationship to Blood Pressure

- Blood pressure (BP) is controlled by two main factors:
  - Peripheral vascular resistance
  - Cardiac output
- One group of drugs used to control BP are α1 agonists, because they increase peripheral vascular resistance through vasoconstriction and thus increasing blood pressure.

Normal Vascular Tone

- Under normal conditions, the body's blood vessels are slightly constricted at baseline.
- Although vasodilation is needed in certain situations, maintaining normal BP (around 120/80 mmHg) requires a baseline level of vasoconstriction.
- If vasoconstriction exceeds the normal limit, blood pressure rises above 120/80 mmHg, leading to hypertension.

Clinical Use of Phenylephrine

- Since phenylephrine causes vasoconstriction and increases peripheral resistance, it can be used to increase blood pressure.
- Phenylephrine is used in hypotensive states such as shocks (can be caused by excessive bleeding), and spinal anesthesia (a type of regional anesthesia)

Phenylephrine and Catecholamines

- Phenylephrine is *not* a catecholamine.
- Catecholamine drugs contain a catechol ring.
- Drugs with a catechol ring can be rapidly degraded by catechol-O-methyltransferase (COMT).
- Because of COMT metabolism, catecholamines are metabolized quickly in the body.

Examples of Catecholamines

- Adrenaline (epinephrine)
- Noradrenaline (norepinephrine)
- Isoproterenol

COMT is found outside the nerve terminal, including:

- Plasma (outside the nerve terminal)
- Liver

As a result, catecholamine drugs:

- Have a very short half-life
- Act very rapidly, but for a short duration

What Is the Problem in Hypotension?

- One of the main symptoms of hypotension is dizziness, it gets dangerous when the body attempts to compensate for the decrease in blood pressure, this compensation occurs through a reflex mechanism called the baroreceptor reflex.

Baroreceptor Reflex Mechanism

- Baroreceptors are sensors located in blood vessels.
- Their function is to detect changes in blood pressure.

When Blood Pressure Decreases (↓ BP):

- Baroreceptors detect the drop in BP.
- They activate the sympathetic nervous system centrally.
- This increases sympathetic outflow.
- Sympathetic stimulation leads to increased release of norepinephrine (NE).
- NE acts on adrenergic receptors throughout the body.

Key Effects of Norepinephrine in the Baroreceptor Reflex

On the Heart (β_1 receptors): Increased heart rate, increased cardiac output, this helps raise blood pressure

On Blood Vessels (α_1 receptors): Vasoconstriction, Increased peripheral vascular resistance, Further contributes to increasing BP

Clinical Concern: Reflex Tachycardia

- The reflex tachycardia produced by this compensatory mechanism can be problematic.
- It is especially dangerous in patients with Chronic heart disease/ Arrhythmias/ Ischemic heart disease/ History of myocardial infarction

Blood Pressure Considerations

- We do not want blood pressure (BP) to be low.
- Hypotension is not considered a disease; it is usually a symptom.
- In contrast, hypertension is a chronic disease/condition.
- Even though low BP may seem less serious, it can be dangerous because it triggers reflex tachycardia, which can stress the heart.

Phenylephrine as a Nasal Decongestant

- Another important use of phenylephrine is as a nasal decongestant.
- It acts by binding to α_1-adrenergic receptors in the blood vessels of the nasal mucosa.
- Activation of α_1 receptors causes vasoconstriction.
- During inflammation, nasal blood vessels dilate, leading to engorgement and congestion of the nasal cavity.
- By causing vasoconstriction, phenylephrine:
  - Reduces blood flow
  - Decreases swelling
  - Relieves nasal congestion

Phenylephrine as an Ophthalmic Agent

- Another use of phenylephrine is as topical eye drops.
- It is used to dilate the pupil (mydriasis).
- This dilation is needed to perform certain ophthalmologic examinations or tests.

Alpha-1 Adrenergic Agonists

- METHOXAMINE Selective α1 agonist
  - ➢Alpha-1 adrenergic agonist
  - ➢Does not stimulate beta adrenoceptors
  - ➢Primary use: vasoconstrictor
  - ➢Treat hypotensive states
    - *shock, spinal anesthesia*
  - ➢Not metabolized by COMT or MAO.

Alpha-2 Adrenergic Agonists

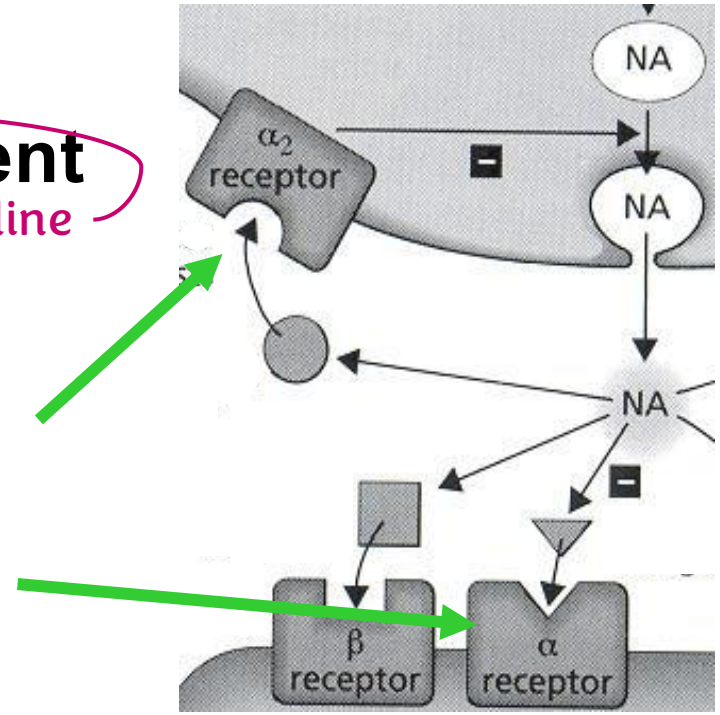
CLONIDINE (selective α_2-adrenergic agonist).

- **Alpha-2 adrenergic agonist**
- **Direct vasoconstrictor**
- **Indirect antihypertensive agent**

One of the most important clinical uses of clonidine

  - ***central suppression***

- **Rebound hypertension.**



CLONIDINE

Mechanism of action:

- α_2 receptors are present presynaptically and normally bind norepinephrine (NE).
- Activation of α_2 receptors leads to inhibition of further norepinephrine release.
- In the CNS, clonidine suppresses sympathetic outflow by activating α_2-adrenergic receptors in specific brainstem nuclei, leading to reduced norepinephrine release and decreased sympathetic activity.

Clinical effects:

ما بستخدمه لعلاج tachycardia لانه في ادوية افضل

As a result of reduced sympathetic activity, clonidine causes:

- Decreased heart rate
- Decreased cardiac output
- Reduced effects of norepinephrine on blood vessels
- Decreased vascular constriction
- Reduced peripheral vascular resistance
- Overall reduction in blood pressure

Reduced effects of norepinephrine on blood vessels, leading to less vasoconstriction.

REMEMBER :

- Epinephrine (α_1 agonist) → used to treat hypotension.
- Clonidine (α_2 agonist) → used to treat hypertension.

Peripheral α_2 receptor effects:

α_2 receptors are also present on vascular smooth muscle. If clonidine is applied directly to blood vessels (e.g., in a lab experiment), it can cause direct vasoconstriction due to α_2 receptor activation.

Effect of high doses:

- High IV doses of clonidine may:
- Activate peripheral α_2 receptors on vascular smooth muscle.
- ↑ Peripheral vascular resistance.
- Cause transient vasoconstriction.

Clinically: we do not usually use high doses.

Therapeutic doses mainly act centrally, not peripherally.

Net effect:

Despite possible peripheral vasoconstriction at high doses, the overall net clinical effect of clonidine is:

Lowering blood pressure, due to dominant central sympathetic inhibition.

General rule: Dose and selectivity

As the dose of a drug increases, receptor selectivity decreases.

At low/therapeutic doses → clonidine is mainly selective.

At high doses → peripheral effects may appear.

Rebound hypertension:

With continuous use of clonidine, rebound hypertension may occur upon abrupt withdrawal.

Continuous activation of α_2 receptors → functional changes in the receptors

When the drug is suddenly stopped:

- Loss of inhibitory control.
- Excess sympathetic activity.
- Result → rebound hypertension.

This effect is particularly noticeable with CNS-acting drugs like clonidine.

Beta-1 Adrenergic Agonist

DOBUTAMINE

Mainly

- **"Beta-1" adrenergic agonist**
- **Stimulates beta-2 and alpha adrenoceptors**
- **Inotropic agent**
- ***Vasodilation predominates***
  - ***preserves renal and G.I. blood flow***
  - ***heart failure***
- ***Tolerance may develop.***

- ❖ β_1-adrenergic receptors are primarily present in the heart. Activation of β_1 receptors in the heart leads to an increase in heart rate and myocardial contractility.
- ❖ Beta-1 receptors are also present in the vasculature. In most vascular beds, especially those supplying skeletal muscle, beta-2 receptors predominate. However, in the renal vasculature, beta-1 receptors are present and have an important role.
- ✓ Activation of beta-1 receptors in the renal vasculature causes relaxation and dilation of the afferent arteriole, which helps maintain renal blood flow. This effect allows preservation of kidney perfusion and protects the kidneys during stress conditions.
- One of the most important clinical uses of dobutamine is the treatment of cardiogenic shock .
- Cardiogenic shock is a condition in which the heart fails to pump sufficient blood to meet the metabolic demands of the body.

Why Dobutamine Is Preferred in Cardiogenic Shock ??

In cardiogenic shock, the therapeutic goal is to stimulate the heart to increase contractility and cardiac output without increasing peripheral vascular resistance or blood pressure, in order to avoid additional workload on the heart and to preserve renal perfusion.

✓ Dobutamine is preferred because it stimulates β_1 receptors, improving cardiac contractility.

✓ It has minimal α_1 receptor activation, so it does not cause significant vasoconstriction

Avoiding α_1 activation prevents:

1. Increased blood pressure
2. Increased workload on the heart and renal vasoconstriction.

Activation of α_1 receptors in renal blood vessels would cause vasoconstriction, reducing renal perfusion.

Dobutamine avoids this effect and instead:

1. Preserves renal vasodilation
2. Maintains kidney perfusion
3. Protects the kidneys during low-output states.

Beta-2 Adrenergic Agonists

أستغفر الله العظيم

وأتوب اليه

TERBUTALINE and ALBUTEROL

- **Selective beta-2 agonists (normal doses)**
- **Primary use: *broncodilator***
- **Reduced risk of cardiac stimulation**
- **May inhibit mast cell secretion**
- **Not metabolized by COMT or MAO**
  - ***long duration of action than ISO***
- **Inhalation helps limit side effects**

Terbutaline and **albuterol** are commonly used in **asthmatic patients** as **bronchodilators**.

Mast cells release histamine, which is responsible for many features of the allergic response, including bronchoconstriction. By inhibiting mast cell mediator release, these drugs provide an additional beneficial effect in the treatment of asthma.

The duration of action differs among bronchodilators.

In clinical practice, this is important because:

In acute asthma attacks, when the patient has severe difficulty breathing, we need a drug that acts rapidly to improve the condition.

At the same time, patients also require medications for daily maintenance, which usually have a longer duration of action to maintain airway dilation.

In general, when comparing selective β_2-adrenergic agonists (such as terbutaline and albuterol) with isoproterenol (a non-selective β-agonist), these agents have a longer duration of action, although the duration still varies among them:

Some have a short duration (around 2 hours).

Others have a long duration (up to about 12 hours).

Overall, their duration of action is longer than that of isoproterenol.

These drugs are commonly administered by inhalation.
Inhalation helps to reduce systemic side effects, since the drug is delivered directly to the bronchi and lungs.
However, it is important to remember that the lungs are highly vascularized organs.
Therefore, even when the drug is given by inhalation, part of it can be absorbed into the systemic circulation, which means that systemic side effects may still occur.
Although inhalation delivers the drug directly to the bronchi and causes bronchodilation, this does not completely eliminate the risk of cardiac or systemic effects, due to absorption from the pulmonary vasculature.

Indirect Adrenergic Agonists

AMPHETAMINE

- **Enhances NE release (exact mechanism)**
- **Action similar to NE**
- **Powerful CNS stimulant**
  - ***Less fatigue, increased alertness***
  - ***Better physical performance***
- One of its effects(which may sometimes be viewed as an advantage)is **Appetite suppression.** Many patients experience weight loss due to its central nervous system effects.
- **Dependency and tolerance**

Amphetamine acts **indirectly on norepinephrine**, primarily by enhancing the release of norepinephrine from nerve terminals.

Clinically, it is used in the treatment of **ADHD** and **narcolepsy**, a condition characterized by excessive and unexplained daytime sleepiness.

The major problem with amphetamine is that it can cause **addiction**.

This is mainly due to its central effects, which can produce a sense of pleasure and increased well-being.(Because of these effects, Some individuals misuse amphetamines as drugs of abuse due to their central stimulating effects while others use them to stay awake and work for prolonged hours).

For these reasons, amphetamines should be avoided unless there is a clear medical indication, and they should be used only under proper medical supervision.

Mixed-Acting Adrenergic Agonist

EPHEDRINE

- **Indirect: induces NE release**
- **Direct: stimulates α and β adrenoceptors**
- **Bronchodilation due to beta effects**
  - ***replaced by beta-2 agonists***
- **Urinary incontinence** (loss of voluntary control over urination)
- **CNS stimulation**
- **Appetite suppression**
  - ***more effective combined with caffeine***
  - ***herbal preparation: Ma huang***

Ephedrine is considered a mixed-acting adrenergic agonist because it works through two mechanisms:

Indirectly, by inducing the release of norepinephrine.

Directly, by stimulating both α and β adrenoceptors.

Ephedrine can be useful because α_1 receptors are present on the urinary sphincter.

Activation of these receptors causes contraction of the sphincter muscle, which improves control over urination.

This effect is due to the direct α_1 agonist action of ephedrine.

➢ Ma huang is a natural source of ephedrine.

However, natural products should be treated like drugs in terms of dose and toxicity.

Despite being herbal, it can be dangerous because it may cause:

Tolerance

Stimulation of the sympathetic nervous system.

Increased heart rate.

Increased blood pressure.

Ephedrine increases activity, but it can have harmful effects on important organs; therefore, it should be used cautiously even though it is a natural product.

METARAMINOL

Metaraminol is a mixed-acting adrenergic agonist.
It has a direct agonist activity on α_1-adrenoceptors, with minimal β-adrenergic effects.

In addition to its direct action, metaraminol also has an indirect mechanism.
It enters the presynaptic adrenergic neuron via the norepinephrine transporter and is taken up into synaptic vesicles, where it displaces norepinephrine.

Because metaraminol utilizes the same transport and storage mechanisms as an endogenous neurotransmitter and replaces norepinephrine inside vesicles, it is referred to as a **false neurotransmitter.**

A false neurotransmitter is defined as a substance that:

- Uses the transporter of an endogenous neurotransmitter
- Is stored in synaptic vesicles in place of that neurotransmitter
- Is released instead of it upon nerve stimulation

Unlike some false neurotransmitters that replace norepinephrine without activating adrenergic receptors (and therefore reduce adrenergic tone), metaraminol does activate α_1-adrenoceptors.
Therefore, its effect is additive to the normal adrenergic activity, particularly at α_1 receptors, leading to vasoconstriction.

Due to its predominant α_1-agonist activity, metaraminol can be used in the treatment of hypotension.

Beta-3 Adrenergic Agonist

Vibegron: a selective beta-3 adrenergic receptor agonist in the detrusor muscle.

- Used for the treatment of overactive bladder.

- Side effects:
- Headache
- Urinary tract infection
- Common cold
- Diarrhea, nausea
- Upper respiratory tract infection.

Mirabegron: Similar uses and side effects

Beta-3 adrenergic receptors are present in fatty cell.

Activation of these receptors stimulates lipolysis (breakdown of fat).

This property suggests potential use in obesity management.

Beta-3 Receptors in the Bladder:

Beta-3 adrenergic receptors are also found in the detrusor muscle of the bladder and in the trigone and bladder sphincter.

When a beta-3 agonist binds to these receptors:

It causes relaxation of the detrusor muscle, helping the bladder store urine.

It may increase sphincter tone, improving bladder control.

This makes beta-3 agonists useful for treating overactive bladder.

- Some studies have reported that beta-3 agonists may increase blood pressure in
- certain patients, though the exact mechanism is not fully understood.

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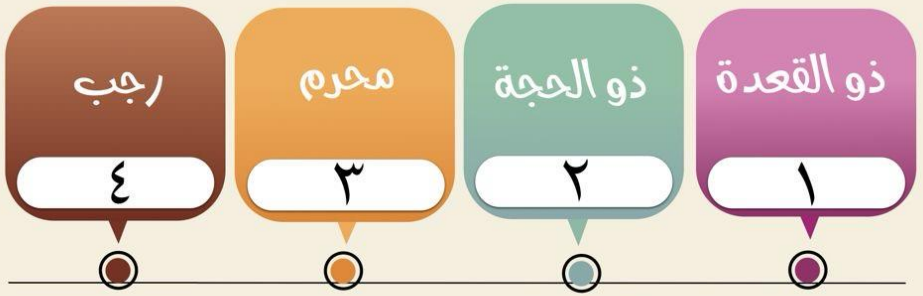

الأشهر الحرم

أتتكم الأشهر الحرم

﴿ فلا تظلموا فيهن أنفسكم ﴾

وظلم النفس فيها يكون على نوعين

١-ظلم بإرتكاب المعاصي

٢- ظلم بترك الطاعات

فالحسنات مضاعفة فليكن لك من كل طاعة سهمًا

والمعصية فيها ليست كلمعصية في غيرها بل هي عظيمة عند الله

فحرص على إجتنابها حتى لاتهبط حسناتك

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