بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 6

Adrenomimetic Drugs pt.1

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Adrenomimetic Drugs

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Quick Revision:

Adrenergic receptors are classified into two main types: alpha (α) and beta (β) receptors. Understanding the location of each receptor subtype is essential to understanding their physiological actions.

The adrenergic agonists are adrenaline and noradrenaline (epinephrine and norepinephrine).

Norepinephrine is mainly secreted from nerve terminals, whereas epinephrine is secreted from the adrenal medulla.

Both hormones activate adrenergic receptors; however, their affinity for the different receptor subtypes is not the same.

α- Adrenergic Receptors

They are sub divided into

1. **α-1 Adrenergic receptors:**

present on smooth muscle, all blood vessels (causing constriction) and the muscles that cause dilation of pupil of eye.

2. **α-2 Adrenergic receptors:**

They are mainly presynaptic are found at adrenergic and cholinergic nerve terminals.

Also, postsynaptic are found in the blood vessels and in the CNS.

α- Adrenergic Receptors

1. α-1 Adrenergic receptors:

present on smooth muscle, all blood vessels (causing constriction) and the muscles that cause dilation of pupil of eye.

Alpha-1 adrenergic receptors are present in blood vessels; therefore, during a sympathetic response, their activation leads to an increase in blood pressure. This is important in daily life because low blood pressure can cause fainting, and an adequate rise in blood pressure helps maintain alertness to an appropriate level.
When adrenaline binds to alpha-1 adrenergic receptors, it causes contraction of vascular smooth muscle cells.
These receptors are also present in the eye muscles, specifically the radial muscle of the iris. Activation of alpha-1 adrenergic receptors causes contraction of this radial muscle, leading to pupillary dilation, which improves vision and is appropriate for the "fight or flight" situation.
In addition, alpha-1 adrenergic receptors are present in the bladder sphincter, where their activation causes sphincter contraction, allowing us not to worry about bladder function at that moment.

α- Adrenergic Receptors

2. α-2 Adrenergic receptors:

They are mainly presynaptic are found at adrenergic and cholinergic nerve terminals. Also, postsynaptic are found in the blood vessels and in the CNS.

Alpha-2 adrenergic receptors are also present in blood vessels, but in very low amounts; therefore, this is not their main function. Their most important locations are the presynaptic nerve terminals and the central nervous system (CNS).

Alpha-2 receptors act as regulators of the sympathetic nervous system by providing a negative feedback mechanism. When an action potential reaches the nerve terminal, calcium enters the neuron, causing vesicles containing the neurotransmitter to fuse with the plasma membrane and release norepinephrine. Norepinephrine then exerts its effect, but this process requires regulation, as we do not want its concentration to remain high continuously.

In addition, alpha-2 adrenergic receptors function as a control mechanism by reducing sympathetic activity through inhibition of norepinephrine release. In the brain, activation of alpha-2 receptors stimulates certain nuclei responsible for regulating sympathetic activation; therefore, when norepinephrine binds to alpha-2 receptors, it inhibits the flow of sympathetic activity.

In addition to presynaptic inhibition mediated by alpha-2 adrenergic receptors, there are other mechanisms that regulate norepinephrine levels at the synapse:

- One mechanism involves enzymes, such as catechol-O-methyltransferase, which break down catecholamines, including norepinephrine.
- Another mechanism is neuronal uptake, which can be inhibited by cocaine.

β-Adrenergic Receptors

- Divided into:

1. β1 adrenergic receptors: on heart (some β2 also) increases rate and force of contraction.

2. β2 adrenergic receptors: present on smooth muscle, some blood vessels (in skeletal muscles), bronchial smooth muscles, skeletal muscles and liver

3. β3 adrenergic receptors: present in adipose tissue

β-Adrenergic Receptors

1. β1 adrenergic receptors: on heart (some β2 also) increases rate and force of contraction.

Beta-1 adrenergic receptors are mainly located in the heart. When adrenaline or noradrenaline binds to these receptors, it leads to an increase in heart rate (tachycardia), an increase in the force of contraction, and an increase in conduction rate, meaning faster conduction between the atria and ventricles.
The purpose of these effects during sympathetic activation is to make the heart work more efficiently in order to increase blood flow to muscles and organs.

Another site where beta-1 adrenergic receptors are present is in the blood vessels of the kidneys. Certain cells, known as juxtamedullary cells, are responsible for the production of the hormones renin and angiotensin.

Activation of beta-1 adrenergic receptors on these cells leads to increased secretion of renin and angiotensin, which enhances control of blood vessel constriction and results in sodium and water retention.

These receptors therefore play an important role in hypertension and are key targets when considering how this system can be affected through beta-1 adrenergic receptor modulation.

β-Adrenergic Receptors

2. β2 adrenergic receptors: present on smooth muscle, some blood vessels (in skeletal muscles), bronchial smooth muscles, skeletal muscles and liver

Beta-2 adrenergic receptors are mainly present in the lungs, where their activation causes bronchial dilation through relaxation of bronchial smooth muscle. This is important during sympathetic activation because the body needs more energy to move and perform actions, which requires increased oxygen delivery to the entire body.

These receptors are also present in smooth muscle of blood vessels supplying skeletal muscles, where their activation causes vasodilation, increasing blood flow to skeletal muscles.

β-Adrenergic Receptors

2. β2 adrenergic receptors: present on smooth muscle, some blood vessels (in skeletal muscles), bronchial smooth muscles, skeletal muscles and liver

In addition, beta-2 receptors are present in the **liver**, where their activation increases the release of energy sources, such as glucose and fatty acids. This occurs through increased glycogenolysis and glycogenosis in the liver, and through increased lipolysis in fatty cells. All of these mechanisms help the body cope with adrenergic stimulation and the fight-or-flight response.
Beta-2 receptors are also present in **skeletal muscles**, both in the blood vessels supplying them and in the muscle tissue itself. Activation of beta-2 receptors in skeletal muscle causes muscle contraction. As a result, drugs that activate beta-2 adrenergic receptors may cause muscle tremors (رعشة في العضلات) as a side effect, such as drugs used in asthma patients, whose main action is bronchodilation. This side effect may occur when the drug is used without need.

β-Adrenergic Receptors

3. β3 adrenergic receptors: present in adipose tissue

Beta-3 adrenergic receptors are present in the wall of the bladder, which is composed of the detrusor muscle. During the fight-or-flight response, bladder emptying is not a priority; therefore, activation of beta-3 adrenergic receptors causes relaxation of the detrusor muscle, allowing the bladder to store urine.

What adrenoceptors "generally" do

Effector organ	Receptor	Response
Heart		
Sinoatrial node	β	Tachycardia
Atrioventricular node	β	Increase in conduction rate and shortening of functional refractory period
Atria and ventricles	β	Increased contractility
Blood vessels		
To skeletal muscle	α and β	Contraction or relaxation
To skin	α	Contraction
Bronchial muscle	β	Relaxation
Gastrointestinal smooth muscle		
To stomach	β	Decreased motility
To intestine	α and β	Decreased motility
Gastrointestinal sphincters		
To stomach	α	Contraction
To intestine	α	Contraction
Urinary bladder		
Detrusor	β	Relaxation
Trigone and sphincter	α	Contraction
Eye		
Radial muscle, iris	α	Contraction (mydriasis)
Ciliary muscle	β	Relaxation

We are going to talk more about this next year inshAllah

In blood vessels:
Both alpha and beta adrenergic receptors are present. In resistance blood vessels of the skin and GI tract, alpha receptors predominate, and their activation leads to vasoconstriction, resulting in an increase in blood pressure.

In contrast, the blood vessels supplying skeletal muscles mainly contain beta receptors, whose activation causes vasodilation, allowing increased blood flow to the skeletal muscles.

When a person is afraid or in danger, the skin becomes pale. This occurs because of constriction of blood vessels supplying the skin due to activation of alpha-1 adrenergic receptors, which act as vasoconstrictors.

Conversely, with some drugs that dilate blood vessels (vasodilators), the skin appears flushed or red.

Bronchial Smooth Muscle:
Bronchial smooth muscle contains beta-2 adrenergic receptors, whose activation leads to bronchodilation, thereby increasing oxygen delivery to the lungs.

Gastrointestinal Tract (GI):
The gastrointestinal tract contains both alpha and beta adrenergic receptors, with beta receptors being more predominant(in the stomach) . Beta receptors are mainly responsible for relaxation of smooth muscle throughout the body (lungs, GI, blood vessels, uterus), except in the heart.

In contrast, alpha receptors cause contraction of sphincters, such as those of the kidney and stomach. This is important during the fight-or-flight response, as the body does not prioritize urination or digestion. These processes are mainly active under parasympathetic control, which is referred to as “rest and digest.”

Urinary System:

In the urinary system, adrenergic receptors are present in the detrusor muscle, which forms the wall of the bladder, particularly in the upper region.

They are also present in the trigone, located in the lower region of the bladder, which has a triangular shape and is responsible for regulation of urination.

Eye:

In the eye, adrenergic receptors are found in the radial muscle of the iris, where activation causes pupillary dilation.

They are also present in the ciliary muscle, which is responsible for lens thickness. Relaxation of the ciliary muscle results in a thinner lens, allowing accommodation for far vision, which is important during stressful situations. In contrast, under parasympathetic activity, the lens becomes thicker, allowing accommodation for near objects.

In 1948, a pharmacologist named Raymond Ahlquist was attempting to develop a drug to treat painful menstrual cycles (dysmenorrhea). It was known that smooth muscle of the uterus contains beta adrenergic receptors, whose activation causes uterine relaxation, but at the same time leads to an increase in heart contraction.

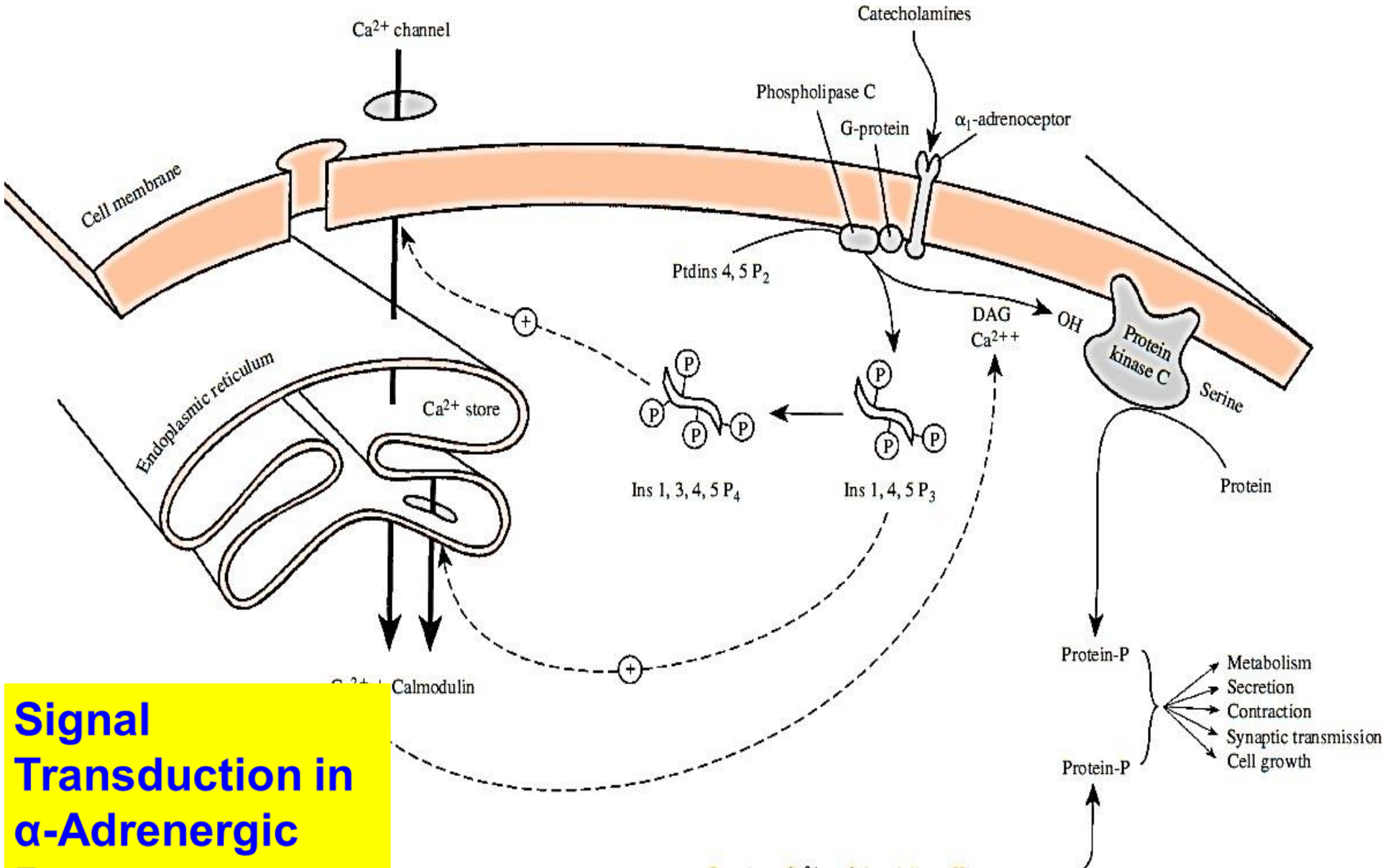
At that time, it was believed that there was only one type of receptor for the sympathetic nervous system, and that there were two different molecules:
•Sympathen E (excitatory), which was thought to bind to receptors in the heart and cause contraction, and
•Sympathen I (inhibitory), which was thought to bind to smooth muscle and cause relaxation.

Ahlquist realized that this concept was incorrect. He concluded that there is actually only one molecule, either adrenaline or noradrenaline, and that the difference in effect depends on the type of receptor present in the tissue, not on different molecules. Therefore, the physiological response varies according to the receptor subtype.

He also recognized that the signaling cascade of beta-1 adrenergic receptors is different from that of beta-2 adrenergic receptors. In addition, alpha-1 adrenergic receptors exist (although these subtypes had not yet been discovered at the time), and it was understood that when adrenaline or noradrenaline binds to alpha-1 receptors, it causes contraction. This occurs because alpha-1 receptors are coupled to a different type of G-protein-coupled receptor, namely Gq.

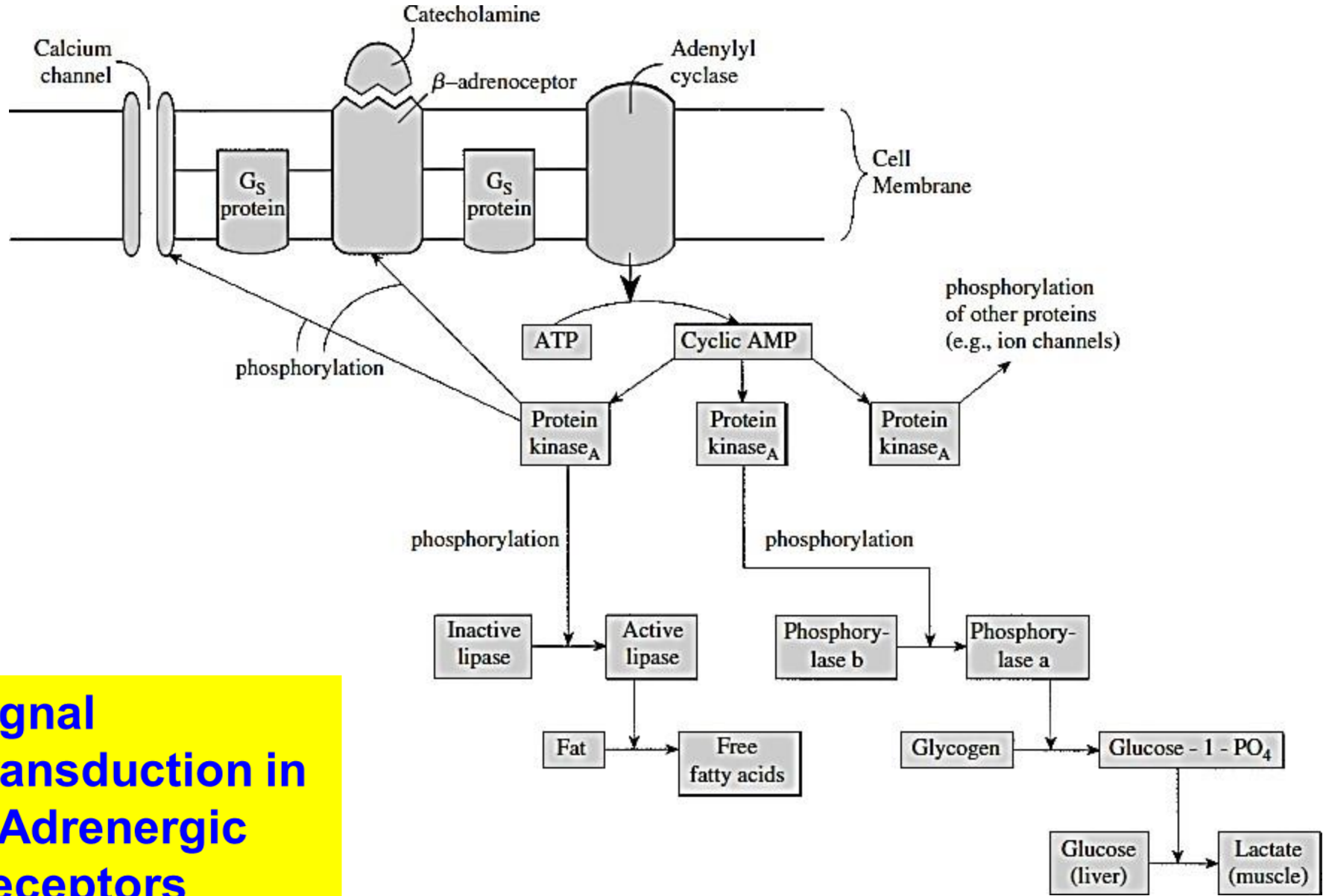
Ahlquist submitted his findings to a journal, but they were rejected by أعداء النجاح. He later submitted them to the American Journal of Physiology, where they were published. These findings caused a revolution in pharmacology and became the foundation for drug development, particularly beta blockers, which are among the main drugs used in the treatment of cardiovascular diseases. Following his discoveries, it became possible to design drugs that selectively target beta adrenergic receptors rather than alpha receptors.

In the 1960s, another scientist developed beta blockers, relying on Ahlquist's findings.

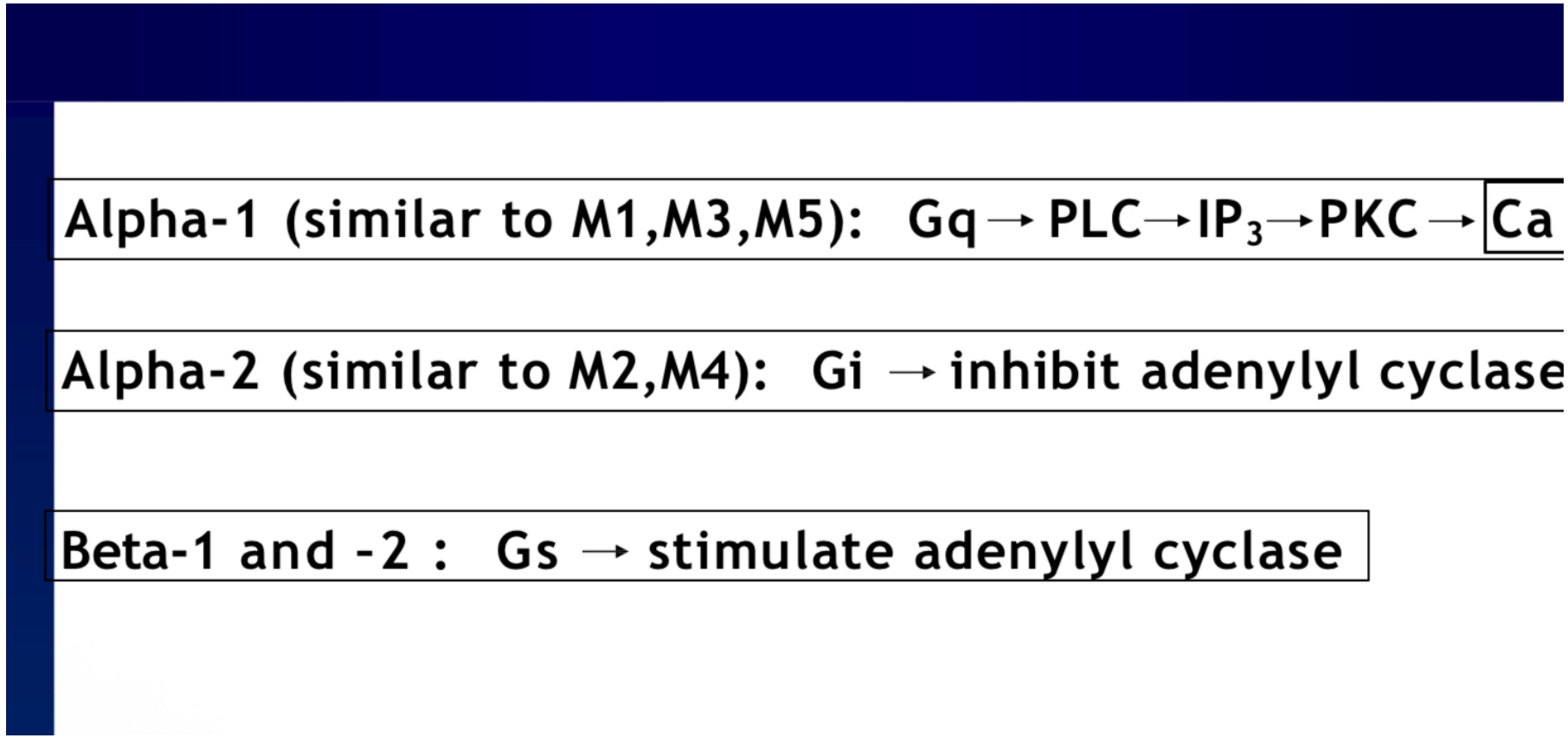


Signal Transduction in α-Adrenergic Receptors

Signal Transduction in β-Adrenergic Receptors



Adrenergic Signal Transduction



Adrenergic Receptor Signaling and G-Protein Coupling:

Alpha-1 Adrenergic Receptors:

Alpha-1 adrenergic receptors are coupled to Gq proteins, which activate the production of diacylglycerol (DAG) and inositol trisphosphate (IP3). This leads to activation of protein kinase C (PKC) and several downstream effects.

- IP3 is responsible for opening calcium channels, allowing calcium influx.
- PKC can also phosphorylate calcium channels, contributing to their opening.
- PKC affects ryanodine receptors in the endoplasmic reticulum, causing release of calcium from the ER.

The resulting increase in intracellular calcium in vascular smooth muscle causes contraction, which is the main effect of alpha-1 receptor activation.

Adrenergic Receptor Signaling and G-Protein Coupling:

Alpha-2 Adrenergic Receptors:

The main effect of alpha-2 receptors is the inhibition of norepinephrine release, primarily in nerve terminals, not in vascular smooth muscle.

- Alpha-2 receptors are coupled to Gi proteins, which inhibit adenylate cyclase, leading to decreased cAMP.
- This reduces calcium entry into the nerve terminal, inhibiting exocytosis of norepinephrine by preventing vesicle fusion with the plasma membrane.
- In the CNS, alpha-2 receptor activation stimulates certain nuclei that decrease sympathetic outflow, providing an overall inhibitory effect on the sympathetic nervous system.

Adrenergic Receptor Signaling and G-Protein Coupling:

Beta-1 Adrenergic Receptors:

Beta-1 adrenergic receptors are mainly coupled to Gs proteins, which increase cAMP levels.

- Upon activation, Gs subunits stimulate adenylate cyclase, generating cAMP, which then activates protein kinase A (PKA).
- PKA phosphorylates target proteins, producing various effects depending on the organ:
- In adipocytes, it promotes lipolysis.
- In the liver, it promotes glycogenolysis.
- In vascular smooth muscle, it causes relaxation.
- In the heart, it increases contraction.

Thus, the same receptor can produce different effects in different tissues due to organ-specific signaling cascades.

Sympathomimetics

Type	Tissue	Actions
α_1	Most vascular smooth muscle (innervated)	Contraction
	Pupillary dilator muscle	Contraction (dilates pupil)
	Pilomotor smooth muscle	Erects hair
	Prostate	Contraction
	Heart	Increases force of contraction
α_2	Postsynaptic CNS neurons	Probably multiple
	Platelets	Aggregation
	Adrenergic and cholinergic nerve terminals	Inhibits transmitter release
	Some vascular smooth muscle	Contraction

β_1	Heart, juxtaglomerular cells	Increases force and rate of contraction; increases renin release
β_2	Respiratory, uterine, and vascular smooth muscle	Promotes smooth muscle relaxation
	Skeletal muscle	Promotes potassium uptake
	Human liver	Activates glycogenolysis
β_3	Bladder	Relaxes detrusor muscle
	Fat cells	Activates lipolysis
D_1	Smooth muscle	Dilates renal blood vessels
D_2	Nerve endings	Modulates transmitter release

In the adrenergic system, we also have dopamine receptors, specifically D1 and D2.

D1 receptors are mainly found in smooth muscles, and one of their important functions is dilation of renal blood vessels.

D2 receptors are primarily located at nerve endings and, similar to alpha-2 receptors, they modulate neurotransmitter release, providing a regulatory function.

Alpha agonists	
Phenylephrine, methoxamine	$\alpha_1 > \alpha_2 >>>>> \beta$
Clonidine, methylnorepinephrine	$\alpha_2 > \alpha_1 >>>>> \beta$
Mixed alpha and beta agonists	
Norepinephrine	$\alpha_1 = \alpha_2; \beta_1 >> \beta_2$
Epinephrine	$\alpha_1 = \alpha_2; \beta_1 = \beta_2$
Beta agonists	
Dobutamine[1]	$\beta_1 > \beta_2 >>>> \alpha$
Isoproterenol	$\beta_1 = \beta_2 >>>> \alpha$
Albuterol, terbutaline, metaproterenol, ritodrine	$\beta_2 >> \beta_1 >>>> \alpha$
Dopamine agonists	
Dopamine	$D_1 = D_2 >> \beta >> \alpha$
Fenoldopam	$D_1 >> D_2$

By understanding the pharmacology of a receptor, we can predict the effects of a drug as well as anticipate its potential side effects.

Alpha agonists	
Phenylephrine, methoxamine	$\alpha_1 > \alpha_2 >>>>> \beta$
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Mixed alpha and beta agonists	
Norepinephrine	$\alpha_1 = \alpha_2; \beta_1 >> \beta_2$
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Dopamine agonists	
Dopamine	$D_1 = D_2 >> \beta >> \alpha$
Fenoldopam	$D_1 >> D_2$

Alpha-1 Adrenergic Receptor Agonists:

Two drugs, Phenylephrine and Methoxamine, are used to treat hypotension (low blood pressure).

Blood pressure is controlled by two main factors:
Blood pressure = Cardiac output * Peripheral vascular resistance

To maintain an ideal energy state, blood vessels should be more constricted than dilated. Dilated blood vessels lead to low blood pressure (hypotension). Therefore, Phenylephrine and Methoxamine, which are alpha-1 agonists, are used to increase blood pressure in such cases.

Another use of Phenylephrine is in nasal sprays for colds, such as Otrivin, which contains a drug similar to Phenylephrine. Why is it used here? During illness, histamine release causes edema and dilation of nasal blood vessels, leading to nasal congestion. Spraying an alpha-1 agonist constricts the blood vessels, creating more space for airflow and improving breathing.

NOTE: Phenylephrine can act slightly on alpha-2 receptors, but it is mainly alpha-1 selective and has no effect on beta receptors.

Alpha-1 Adrenergic Receptor Antagonist:

An antagonist of alpha-1 receptors is Prazosin.

- Prazosin blocks the binding of norepinephrine to alpha-1 receptors in vascular smooth muscle cells, causing relaxation of the blood vessels.
- This leads to a decrease in blood pressure, making it useful for treating hypertension.
- If used in a person with normal blood pressure, Prazosin can cause hypotension.

Alpha-2 Adrenergic Receptor Agonists:
Clonidine and Methylnorepinephrine are alpha-2 agonists. They also have very weak activity on alpha-1 receptors and do not significantly affect beta receptors.

Mixed Alpha and Beta Agonists:
Norepinephrine and epinephrine, although primarily neurotransmitters, can be used as drugs in certain clinical situations.

Beta-2 Adrenergic Receptor Agonists:
Dobutamine primarily activates beta-1 receptors, with minor effects on beta-2 and very low activity on alpha receptors.
•A common clinical use of Dobutamine is in cardiogenic shock, a condition in which the heart suddenly fails to pump sufficient blood.
•In such cases, Dobutamine is administered intravenously to increase cardiac output.
Isoproterenol is another beta agonist.

Regarding Raymond Ahlquist, it was discovered that these drugs can be selective for specific receptor subtypes. However, adrenaline and noradrenaline do not strongly distinguish between receptors, which was a key finding of Ahlquist. Adrenaline activates alpha, beta-1, and beta-2 receptors, allowing us to take advantage of the variety of receptor subtypes when designing drugs that selectively activate alpha-1, alpha-2, beta-1, or beta-2 receptors.

When studying selectivity between alpha and beta receptors, comparisons were made between epinephrine, norepinephrine, and isoproterenol:

- Epinephrine and norepinephrine act on both alpha and beta receptors, with epinephrine being more potent.

Epinephrine is particularly important in life-threatening allergic reactions, such as anaphylactic shock, where blood pressure drops dramatically and swelling occurs due to histamine release in areas like the lips or larynx, causing airway obstruction. Similarly, severe reactions to snake or scorpion bites involve high histamine release, leading to hypotension, bronchial constriction, and swelling of the lips, tongue, and throat, which can be fatal.

In these situations, epinephrine (EpiPen, adrenaline) is the drug of choice, as it acts on all relevant receptor subtypes and can rapidly reverse the life-threatening effects, saving the patient's life.

Catecholamine Effects

Cardiovascular system:

Blood vessels:

- **Catecholamines are important in the regulation of peripheral vascular resistance and venous capacitance.**
- **Skin and splanchnic vessels have predominantly α-receptors → constriction.**
- **Skeletal muscle blood vessels have predominantly β-receptors → dilation.**
- **Dopamine D1 receptors promote vasodilation of renal resistance vessels (arterioles).**
- **Vasoconstriction reduces blood flow, while vasodilation increases blood flow.**

Catecholamine Effects

Cardiovascular system:

Heart:

- **Effects on the heart are predominantly mediated through β1 receptors.**
- **Increase pacemaker activity → increase heart rate = "positive chronotropic effect".**
- **Conduction velocity in the atrioventricular (AV) node is increased "positive dromotropic effect".**
- **AV node refractory period is decreased.**

Catecholamine Effects

Cardiovascular system:

B. Heart:

Myocardial contractility is increased = "positive inotropic effect".

Sympathomimetic that stimulate β1-receptors in the heart, increase cardiac output and thus, systolic blood pressure.

Cardiac output is also increased by an increase in venous return to the heart.

Catecholamine Effects

Cardiovascular system:

Blood Pressure :

- **Diastolic blood pressure is related to systemic vascular resistance and is increased by vasoconstrictors and reduced by vasodilators.**

- **α-agonists increase peripheral arterial resistance → rise in diastolic blood pressure.**

- **β2-agonists decrease peripheral vascular resistance and thus diastolic blood pressure.**

Types of Antagonism:

1. Physiological Antagonism:
This occurs when a drug produces an effect that opposes the action of a substance in the body.
•Example: In anaphylactic shock, histamine release causes dangerous symptoms. Instead of using an antihistamine, which acts slowly, adrenaline is administered to counteract the effects of histamine immediately. This is an example of physiological antagonism.

2. Pharmacological Antagonism:
This occurs when a drug directly blocks a receptor or pathway.
•Example: Antihistamines, which block histamine receptors to prevent its effects.

3. Chemical Antagonism:
This occurs when a drug directly neutralizes a substance chemically.
•Example: Antacids, which neutralize stomach acid through a chemical reaction.

رسالة من الفريق العلمي:

قال ابنُ الجَوزِيّ رَحِمَهُ اللّٰهُ :

" جلستُ يومًا، فرأيتُ حَوْلي أكثرَ من عشرةِ آلافٍ، ما فيهم إلّا مَن قد رقَّ قلبُه، أو دمعت عينُه، فقلتُ لنفسي: كيف بِكِ إن نَجَوْا وهلكتِ؟! فصِحتُ بلسانِ وَجدي: إلـٰهي وسيّدي! إن قَضَيتَ عليَّ بالعذابِ غدًا، فلا تُعلِمْهم بعذابي، صيانةً لكرمِكَ، لا لأجلي، لئلَّا يقولوا: عذَّبَ مَن دلَّ عليهِ..
إلـٰهي! قد قيل لنبيّكَ صلَّى اللّٰهُ عليه وسلَّمَ: اقتُل ابنَ أُبَيٍّ المُنافقَ، فقال: "لا يتحدَّث النَّاسُ أن مُحَمَّدًا يقتلُ أصحابَهُ. "

- صَيْدُ الخاطِرِ

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			