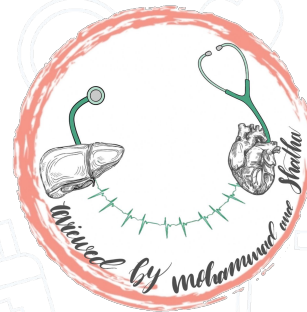


# AUTACOIDS PARACRINE MEDIATORS PART I 442

EDITING FILE



Important  
Main text  
Male slide  
Female slide  
Extra info  
Doctor notes

# Objectives

1. To describe the synthesis, receptors & function of histamine, 5-HT, eicosanoid, nitric oxide, angiotensin, & kinins
2. To study the agents which enhance or block their effects

Note: موجود فقط في سلايدات الاولاد لكن الدكتورة شرحتة بالمحاضرة

## Definition :

- They are hormone like substance
- local but can move into circulation
- autacoid produce,act,and metabolized **locally**(self remedy)

# Autacoids

med 38

## Site of synthesis

Paracrine Effect

Autocrine  
-self remedy-

## They affect

Glands  
Secretion

Nerve  
Transmitters

Smooth muscle  
Contraction  
/dilation

Platelets-aggre-  
gation  
& other tissues

## They include

Amino acids:  
1- Histamine  
2- serotonin

Fatty acid:  
3-Eicosanoids

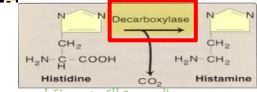
Gases:  
4-Nitric Oxide (NO)

Endogenous Peptides:  
5- Angiotensin  
6-kinins

# Histamine

## Synthesis

Histamine is synthesized from **L-Histidine**.



الصورة للتوضيح فقط  
حفظ اسم الإنزيم

## Stored

- ❑ Lung
- ❑ Basophils
- ❑ Mast cells (mainly)
- ❑ Intestinal mucosa

## Released During

- ❑ Allergic reactions
- ❑ Inflammatory reaction

## Physiological Antagonist

**Epinephrine** ( Adrenaline)-emergency-

Synthesis in the blood but during septic shock or venom it won't be enough so we give it via IV

# Histamine

These drugs that stop histamine effect-don't mistake it with epinephrine its more specific and stronger

Very important slide



**Histamine Receptor (type)**

**Major Tissue location**

**Major Biologic Effect/Actions**

**Blockers**

**Clinical Use of Blocker**

**H1**

Smooth muscle, Endothelial cells, Brain

- 1-Acute allergic response
- 2- contract smooth muscle ( Except Blood vessels)
- 3-bronchioles
- 4- uterus
- 5-Increases bowel peristalsis

**First generation**

- Diphenhydramine
- Promethazine

**Has sedating effect** -يجيب النوم-

- use to treat :
- Allergic Rhinitis
  - Urticaria
  - Motion sickness
  - Insomnia (الارق)



Urticaria

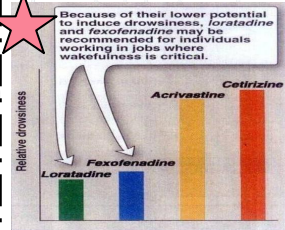
**Second generation**

- Cetirizine
- Fexofenadine

**Non-Sedating effect**

- Use to treat Allergic condition such as :
- Allergic Rhinitis (nose)
  - Conjunctivitis (eye)
  - Urticaria

البيانات خطأ لكن الفكرة جداً مهمة



يفضل أخذه في النهار

**H2**

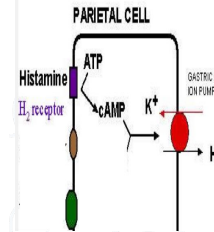
Gastric parietal cells, Cardiac muscle, mast cell, Brain

- 1-formation & secretion of HCL ( gastric acid )
- 2-increase in COP (cardiac output)

- Cimetidine
  - Ranitidine
- You can take it even without description

**Inhibits** gastric acid secretion

- Use to treat :
- Gastritis
  - Peptic ulcer



# Histamine

Histamine Receptor (type)	Major Tissue location	Major Biologic Effect/Actions	These drugs that stop histamine effect <b>Blockers</b>	Clinical Use of Blocker
<b>H3</b>	Central Nervous system	Neurotransmitter	<ul style="list-style-type: none"> <li>▣ <b>Betahistine</b> (It produces dilation of blood vessel in <b>inner ear</b>)</li> </ul>	Use to treat : <ul style="list-style-type: none"> <li>▣ <b>Vertigo of Ménière's disease &amp; Other balance</b> of vestibular origin</li> </ul> Side effect: May produce headache & insomnia -because of the dilation of blood vessel in inner ear -edema-
<b>H4</b> <i>Less common</i>	Mast cells, Eosinophils, T-cell	Regulating immune response	—	—

Dr Note :You must know if they didn't mention which receptor they mean H1

# Administration of Histamine/ Action

## Rapid IV bolus injection

- ❑ Fall in blood pressure (**redness**)
- ❑ Increase in CSF pressure
- ❑ Headache due to dilation of blood vessels- **which will apply pressure on the CSF in brain-**

## Slow IV & SC

- ❑ Increase temperature
- ❑ Flushing skin ( redness:Vasodilation)
- ❑ **Increase heart rate & COP ( through increasing Ca<sup>2+</sup> influx )**
- ❑ **Edema**
- ❑ **Increase blood flow** to the periphery

## Intradermal

- ❑ Itching

 CSF=Cerebrospinal fluid

This injection is only for clinical trials to see the effect of histamine we can't treat a patient with it

# Eicosanoids

the blockers with red so important memories them-You must know everything in this slide except in chemical structure just know it has -20 carbon - peripheral COOH - four double bound

1- Arachidonic acid does not exist in the blood it's trapped in membrane phospholipids



Glucocorticoids

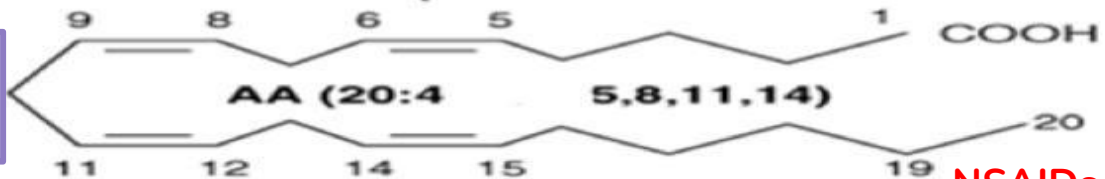
2- When there is physical -chemical inflammatory

This will activate

3 Phospholipase A<sub>2</sub>

What does it do? It will get the Arachidonic acid out in the blood

4 Arachidonic acid



Zileuton

NSAIDs

5 Lipoxygenases (LOX)

5 Cyclooxygenases (COX)

Now it is in the blood It Either become

Leukotrienes

Prostaglandins  
Prostacyclin  
Thromboxane } Prostanoids



## Important Drugs for the previous reaction

Glucocorticoids will inhibit Phospholipase A2 so it will keep the Arachidonic acid trapped in the phospholipids membrane (**the most important drug**)

Zileuton will inhibit LOX enzyme so it will prevent Leukotrienes formation

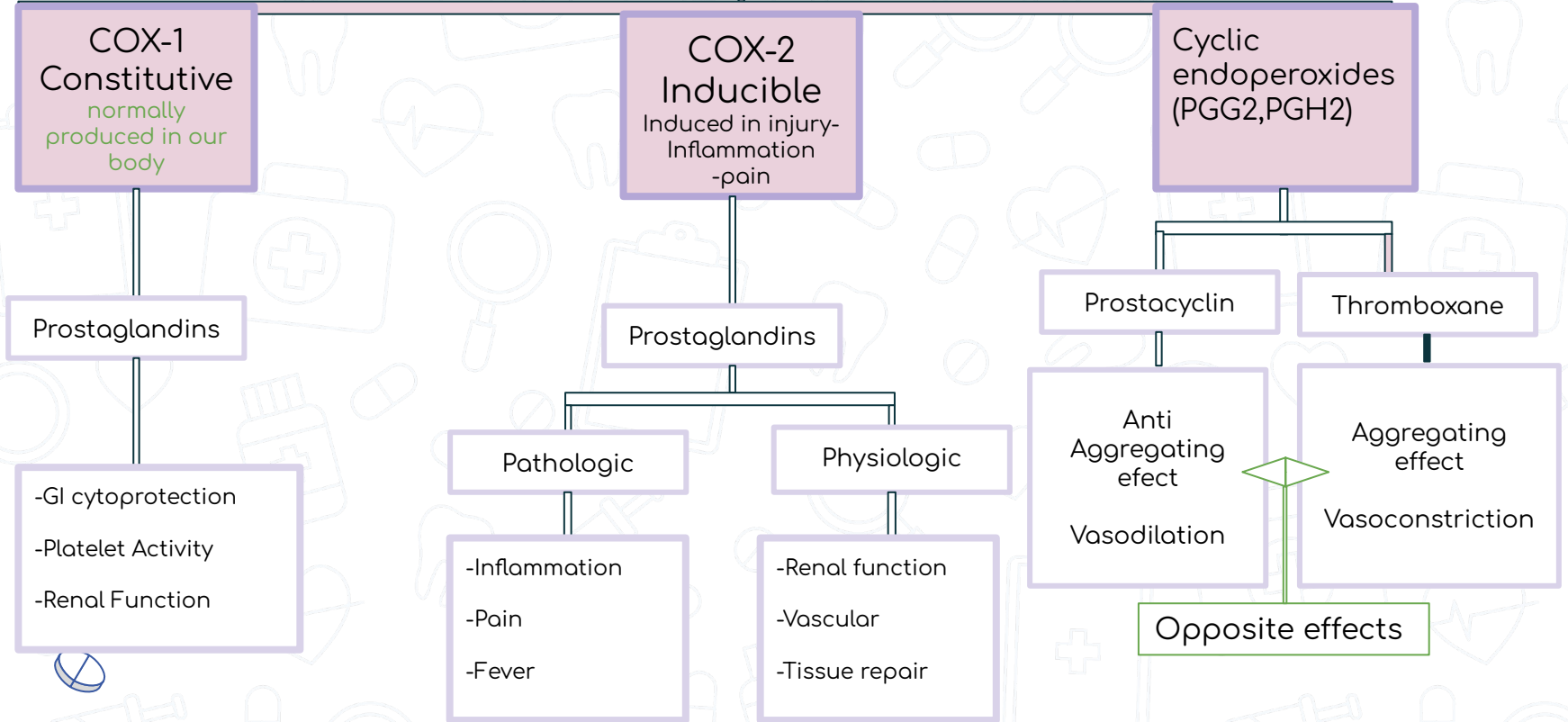
NSAIDS will inhibit COX enzyme so it will prevent Prostanoids formation

# Cox Isozymes

Note from med439

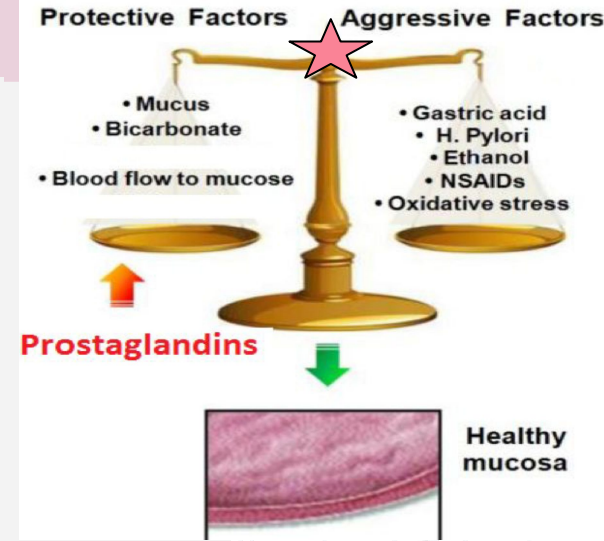
**constitutive COX** produces prostaglandins that are useful because they help maintain homeostasis ( found normally in the body), so inhibition of COX1 is undesirable

**Inducible COX** produces some prostaglandins that are not normally found in healthy individual; they are found in inflammation, so inhibition is desirable.  
Prostaglandins



# Actions of prostaglandins

- They are pro-inflammatory
- Cause vasodilation (PGI<sub>2</sub> & PGE<sub>2</sub>)
- **High PG** conc: **inhibits** of platelet aggregation
- **Low PG** conc: **increases** platelet aggregation
- Sensitize neurons to cause **pain**
- Induce labor (in last trimester to contract uterus) /induce abortion
- Decrease intraocular pressure -by stimulation secretion of aqueous humour (fluid in the eye)through anterior chamber
- Acts on thermoregulatory hypothalamus to increase body temperature
- Acts on kidney to increase glomerular filtration (Vasodilation increases permeability which means more filtration)
- Acts on stomach parietal cells to protect gastric mucosa (protects stomach)



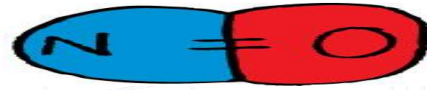
# Clinical uses of PGs analogs

You must know each one  
-name  
-use /effect

- Carboprost (PGF): Induce abortion in first trimester
- **Latanoprost (PGF): Glaucoma**
- Misoprostol (PGE1): Peptic ulcer
- Alprostadil (PGE1): Erectile dysfunction
- Zileuton (lipoxygenase inhibitor): Asthma
- Zafirlukast (leukotriene receptor blocker): Bronchial asthma.

We use analog drug because the prostaglandin has short duration and weak stability

# Nitric Oxide




Biosynthesis of  
nitric oxide:

Synthesized from L- arginine by nitric oxide synthase (NOS)

Nitric oxide  
stimulators

5-HT acetylcholine, bradykinin , histamine , serotonin

Nitric oxide  
inhibitor

Hemoglobin 

# There are 3 isoforms of the enzyme nitric oxide synthase

## Constitutive forms (physiological)

Neurons  
nitric oxide

- Neurons
- Skeletal muscle

Endothelial  
nitric oxide

- Endothelium
- Cardiac myocytes
- Osteoblasts
- Osteoclasts

## Inducible forms (pathological)

Inducible  
forms

- macrophages
- kupffer cells
- neutrophils
- fibroblasts
- vascular smooth muscle

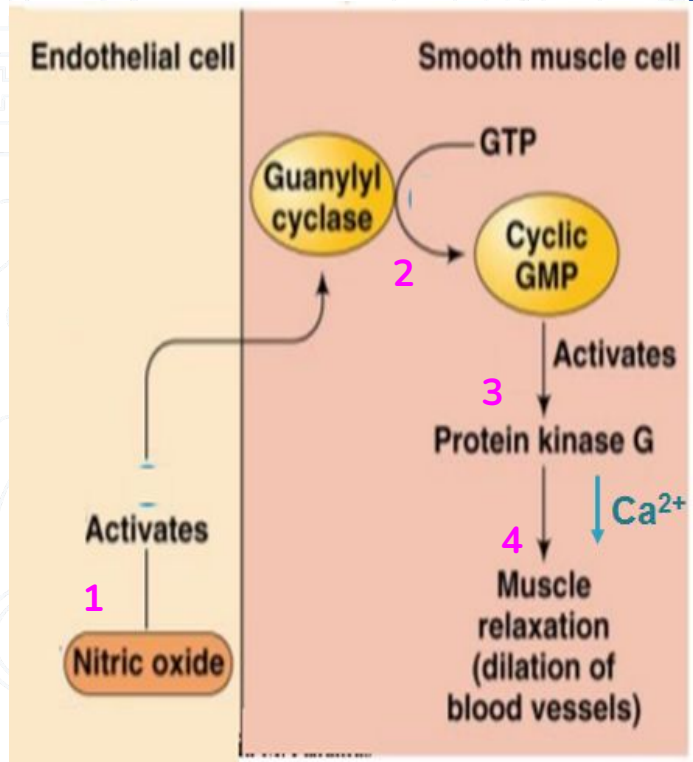
note: Kupffer cells  
is macrophages liver

# NO Mechanism of Action

- Step 1** Combining with **haem** in guanylate cyclase
- Step 2** activating the enzyme increasing cGMP
- Step 3** thereby **lowering**  $[Ca^{2+}]$

**explanation:**

- Step 1:** nitric oxide activates the enzyme guanylyl cyclase enzyme
- Step 2:** guanylyl cyclase converts GTP to cyclic GMP
- Step 3:** cGMP activates protein kinase G
- Step 4:** protein kinase G reduces calcium level which leads to muscle **dilation**



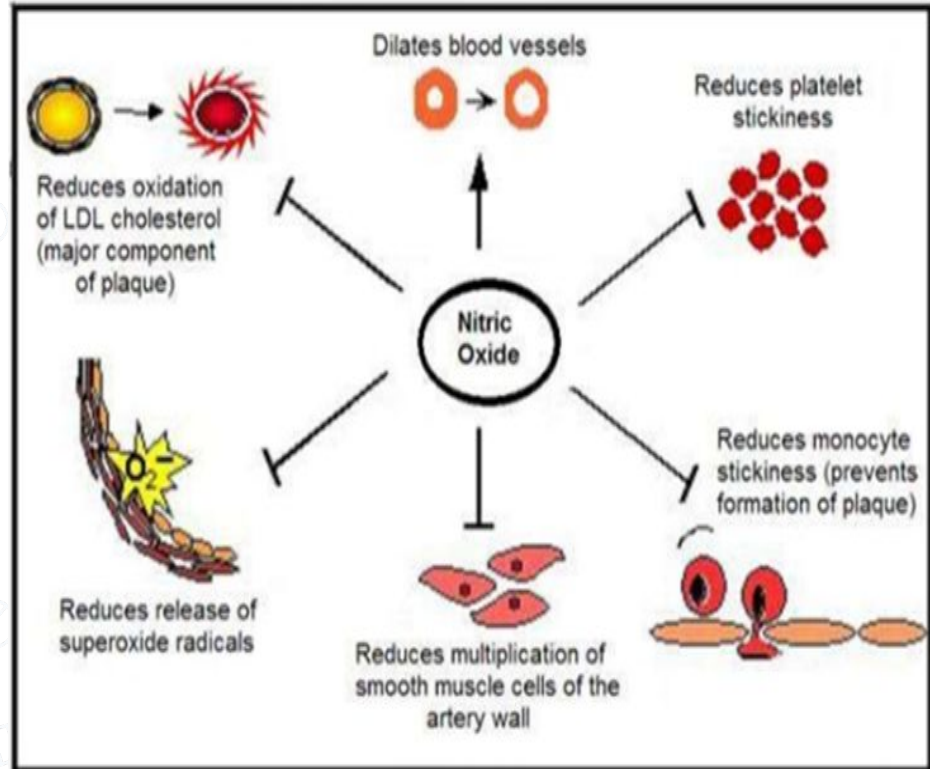
Dr note: Calcium acts on both heart and blood vessels

# Actions of NO



1. inhibition of platelets and monocytes adhesion and aggregation
2. Protection against atherogenesis
3. Inhibition of smooth muscle proliferation
4. Host defense cytotoxic effects pathogens
5. Cytoprotection
6. Synaptic effects in the peripheral and central NS

dr notes: Unlike histamine which is stored in mast cells, nitric acid is produced on demand (only when the body needs it)





# Actions of NO

## Neuronal Nitric acids(nNOS)

- long term potentiation (on nerves and nerves endings)
- Cardiac function
- peristalsis
- sexual arousal

## Endothelial Nitric acids(eNOS)

- Vascular tone(vasodilation)
- insulin secretion
- airway tone
- regulation of cardiac function and angiogenesis
  
- Embryonic heart development

## Inducible nitric acid (iNOS)

- In response to attack by parasites
- bacterial infection
- tumor growth
  
- septic shock
- autoimmune condition



★ Important Slide

# Nitric oxide in therapeutics



1

**UNDERPRODUCTION:** Endothelial NO production is *reduced* in patients with diabetes, hypertension & atherosclerosis

---

2

**OVERPRODUCTION:** of NO occurs in neurodegenerative diseases (e.g. Parkinsonism) & in septic shock

---

3

NO donors is used in critical care to **treat pulmonary hypertension** in neonates ( *inhaled by the patients in emergencies* )

---

4

NO is used in patients with right ventricular failure secondary to pulmonary embolism.

---

5

**Sildenafil(viagra)** <sup>حفظ</sup> potentiates the action of NO on corpora cavernosa smooth muscle. (It is used to treat erectile dysfunction.)

---

6

NO donors have well established therapeutic uses e.g. in hypertension & angina pectoris

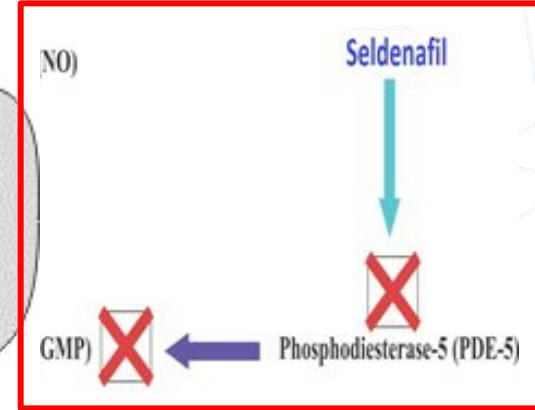
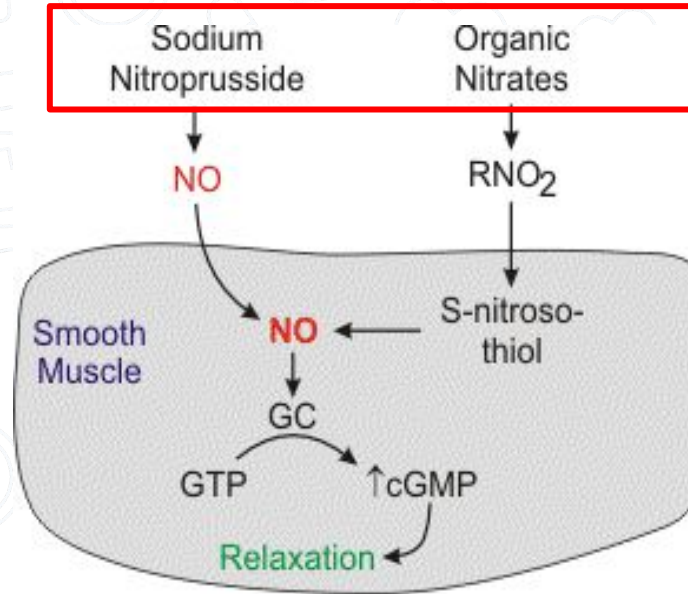


# mechanism of Sildenafil:

We know that nitric oxide works as an activator of cGMP right? However in this case there's an enzyme called **PDE-5** which destroys the cGMP **preventing** the nitric acid from activating it and performing its function.

**Sildenafil** inhibits the **PDE-5** enzyme so the cGMP is ready to be activated by the Nitric oxide

## Nitric acids donors



It is something like block the blocker

Corpus smooth muscles relaxation

Penile erection

# MCQ

Q-1 what kind of receptor blockers has non-sedating effect?from Dr

A)H1 first generation. B) H2. C)H4. D)H1 second generation

Q-2 what is Eicosanoids blocker?

A) H1 B) Glucocorticoids C) PGF D)H2

Q-3 UNDERPRODUCTION Endothelial NO production is *reduced* in patients with?

A) Hypertension B). Ulcer C).kidney failure

Q-4 in Clinical uses of PGs analogs Zileuton (lipoxxygenase inhibitor) for?

A) Asthma B). Heart failure C). I don't know

Q-5 Sildenafil inhibits the ?

A) H1 B) PDE-5 C) PG1 D) I don't know

1-D

2-B

3-A

4-A

5-B

SAQ

Q-1 if a patient that works as a truck driver took diphenhydramine from a pharmacy and complained to the doctor that he felt sleepy what should you prescribe instead and why?

### Answers

1-cetirizine and fexofenadine  
Because it doesn't have a sedating effect

due to it being less lipophilic meaning it will not cross blood brain barrier or it doesn't block histamine receptor .



# SAQ

Q-2 Where does the histamine synthesis from? from the Dr

## Answers

2- L-Histidine

3- slide 18

Q-3 list 3 isoforms of the enzyme nitric oxide synthase

You GOT  
THIS!

## DONE BY THE AMAZING TEAM

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Kadi aldossari  
Hend Almogary  
Razan Almohanna  
razan almanjomi  
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