PHARMACOLOGY
TEAM 439

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MED439
KING SAUD UNIVERSITY

Autacoids Paracrine Mediator (Parts I & II)

If you didn't understand any part from this lecture Click here!

- Important
- In male and female slides
- Only in male slides
- Only in female slides
- Extra information

Objectives

- To describe the synthesis, receptors, and functions of: histamine, 5-HT, eicosanoids, nitric oxide, angiotensin, kinins.
- To study the agents which enhance or block their effects.

Any Future corrections will be posted on the editing file.
make sure to check it **frequently**

Click Here

We recommend studying this lecture with the pathology "inflammation pt3" lecture :)

Definition:
Autacoids are biomaterial substances that are synthesized and metabolized locally.
From 438

Autacoids

They are either: From 438
- Paracrine 
- Autocrine 

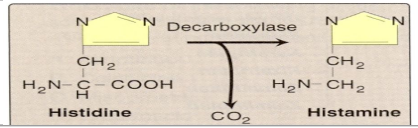
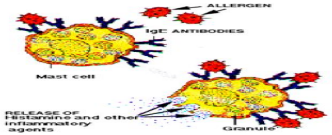
They affect: From 438
- Glands
- Nerves
- Smooth Muscles
- Platelets & other tissues

They include:

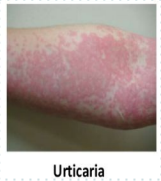
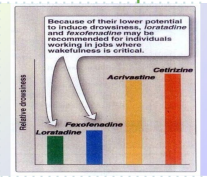
You can remember them with the mnemonic: **SHAKEN**

- Amino Acid Derivatives:
  1-Histamine
  2-Serotonin
- Fatty acids:
  3 -Eicosanoids
- Gases:
  4-Nitric Oxide (NO)
- Endogenous Peptides:
  5-Angiotensin
  6-Kinins

Histamine

Synthesis		Histamine is synthesized from **L-histidine**. 
Stored		• lungs • basophils • mast cells • intestinal mucosa
Released During		• allergic reactions • inflammatory reactions 
Actions	Rapid IV bolus injection IV = Intravenous	• fall in blood pressure (redness) • increase in CSF pressure  • headache (due to vasodilation) the headache is caused because the dilated blood vessels apply pressure on the CSF fluid in the brain
	Slow IV or SC injection IV = Intravenous , SC = Subcutaneous	• flushing of skin (redness: Vasodilation)) • increased blood flow to the periphery • Increased heart rate & COP (through increasing Ca2+ influx) • Raised temperature • Edema (increases membrane permeability)
	Intradermal injection	• itching
Physiological Antagonist		Epinephrine (adrenaline)

Histamine

Histamine Receptors (types)	Major Tissue Locations	Major Biologic Effects/Actions	Blockers Used when we don't want effects of .histamine	Clinical Use of Blocker
H_1	Smooth muscle, Endothelial cells, Brain	acute allergic responses , contract smooth muscles (bronchoconstriction, uterus , increases bowel peristalsis)	First generation: • **Diphenhydramine** • **Promethazine**	**Has sedating effect** • Allergic Rhinitis • urticaria • Motion sickness • insomnia  Urticaria
			Second generation: • **Cetirizine** • **Fexofenadine**	**Non-Sedating effect** Allergic conditions such as: • Allergic rhinitis (nose) • Conjunctivitis (eye) • Urticaria Note: read this picture 
H_2	Gastric parietal cells, Cardiac muscle , Mast cell , Brain	H2 receptors of histamine play an important role in the formation & secretion of HCl (gastric acid) & increase in COP (cardiac output)	• **Cimetidine**	**Inhibits gastric acid secretion** Used in treatment of: • Gastritis • Peptic ulcer
H_3	Central nervous system	neurotransmission	• **Betahistine** (It produces dilatation of blood vessels in inner ear)	Used in treatment of : • Vertigo of Ménière's disease & other balance disturbances of vestibular origin Side effects: May produce headache & insomnia.
H_4	Mast cells, Eosinophiles, T-cells	regulating immune responses	----	-------

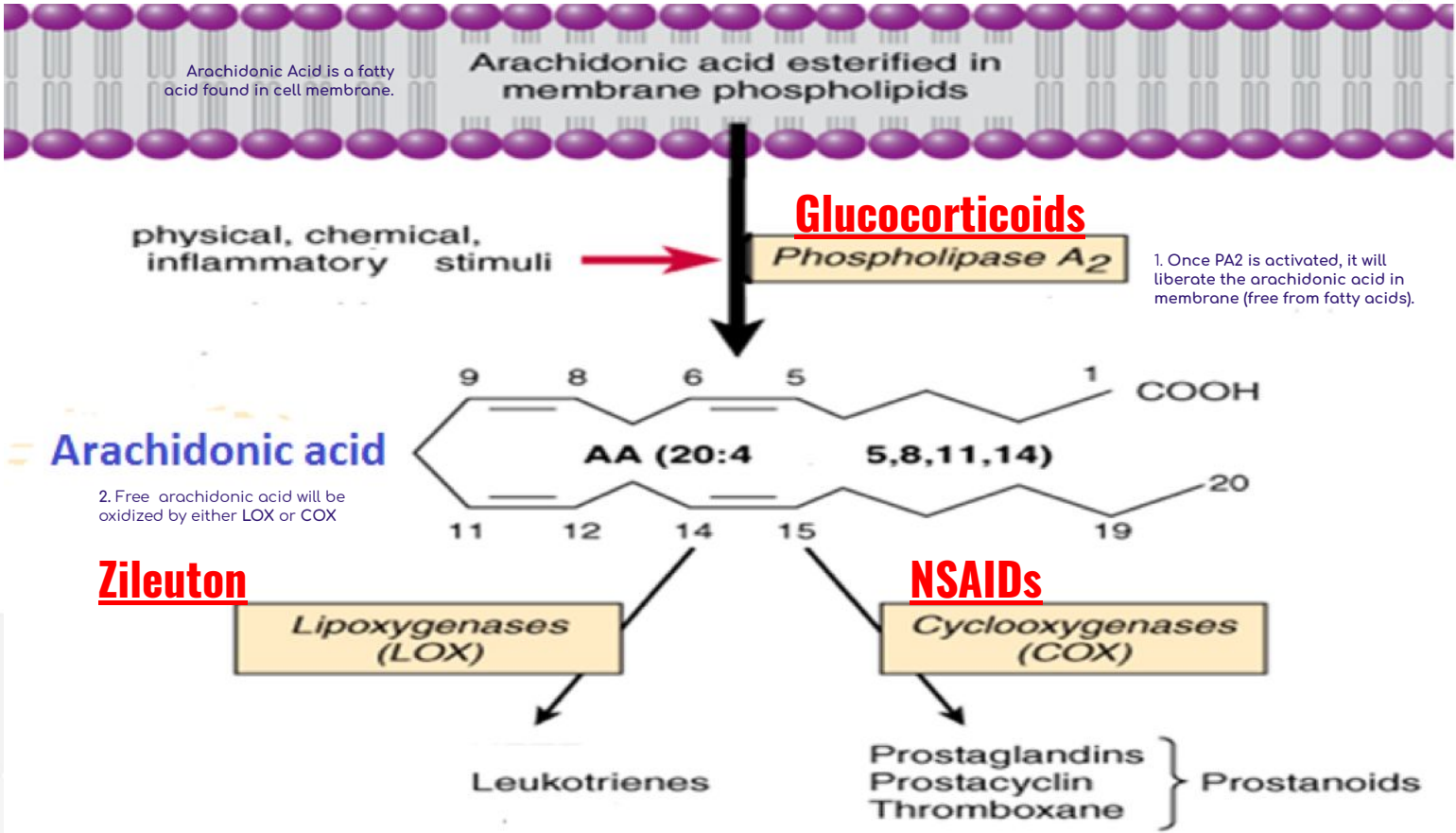
Serotonin (5-HT)

SEROTONIN "CNS neurotransmitter"	**synthesized from the amino acid L-tryptophan :** ➢ Tryptophan hydroxylized into 5-hydroxytryptophan ➢ 5-hydroxytryptophan is decarbolized into 5-hydroxytryptamine(5HT) "serotonin" 
DISTRIBUTION	1. Intestinal wall: in chromaffin cells, in neuronal cells in the myenteric plexus responsible for intestinal movements 2. Blood, in platelets: released when aggregated, in sites of tissue damage 3. CNS: a neurotransmitter in midbrain
RECEPTORS	7 receptor types that have sub types according to their distribution
ACTIONS	• Increases GIT motility • Contracts uterus, bronchiole, other smooth muscles • Contracts large blood vessels by a direct action & relaxes other vessels by releasing NO → can cause both contraction & relaxation (Relaxation is indirect) • Increases capillary pressure & permeability. • Causes aggregation, aggregated platelets release 5-HT • Neuronal terminals: 5-HT stimulates nociceptive neuron endings → pain • CNS: stimulates some neurons & inhibits others, inhibits release of other neurotransmitters.
5-HT RECEPTOR	**AGONISTS:** • **Buspirone**:- 5-HT1A agonist, effective anxiolytic ("anti anxiety") • **Cisapride**: 5-HT4 receptor agonist, used in gastroesophageal reflux & motility disorders. In gastroesophageal reflux, the gastric acid enters the esophagus through an open sphincter causing burning sensation→ patients are given antacids or prokinetic drugs (increases motility, decreasing the amount of contents in the stomach) **ANTAGONISTS:** • **Ondansetron**: Selective 5-HT3 antagonist, antiemetic action for cancer chemotherapy *chemoreceptor for this drug is in the center of the brain
CLINICAL CONDITIONS IN WHICH 5-HT IS IMPLICATED	1. **MIGRAINE:** Activation of trigeminal system leads to peptides release promoting an inflammatory reaction, which increases flow of sensory traffic through the brain stem, the thalamus & the cortex Neuropeptides release causing vasodilation and neurogenic inflammation→ Migraine, causing vasodilation only→ pain -**SUMATRIPTAN**: 5-HT 1B, 1D & 1F-receptor agonists (binds with 3 types of 5-HT) effective in acute migraine attack: It binds to 5HT1B, in cranial blood vessels causing vasoconstriction & 1D & 1F in presynaptic trigeminal nerve causing inhibition of pro- inflammatory neuropeptide release. 2. **CARCINOID SYNDROME:** malignant tumor of intestinal chromaffin cells, tumor releases 5-HT, SP (substance P responsible for inflammation and pain), PGs, kinins & histamine causing flushing, diarrhea, bronchoconstriction & hypotension → tumor will increase 5-HT -Serotonin antagonists (**cyproheptadine**, 5HT2 antagonist) could be administered to control diarrhea, flushing & malabsorption. They don't treat malignancy just control the symptoms

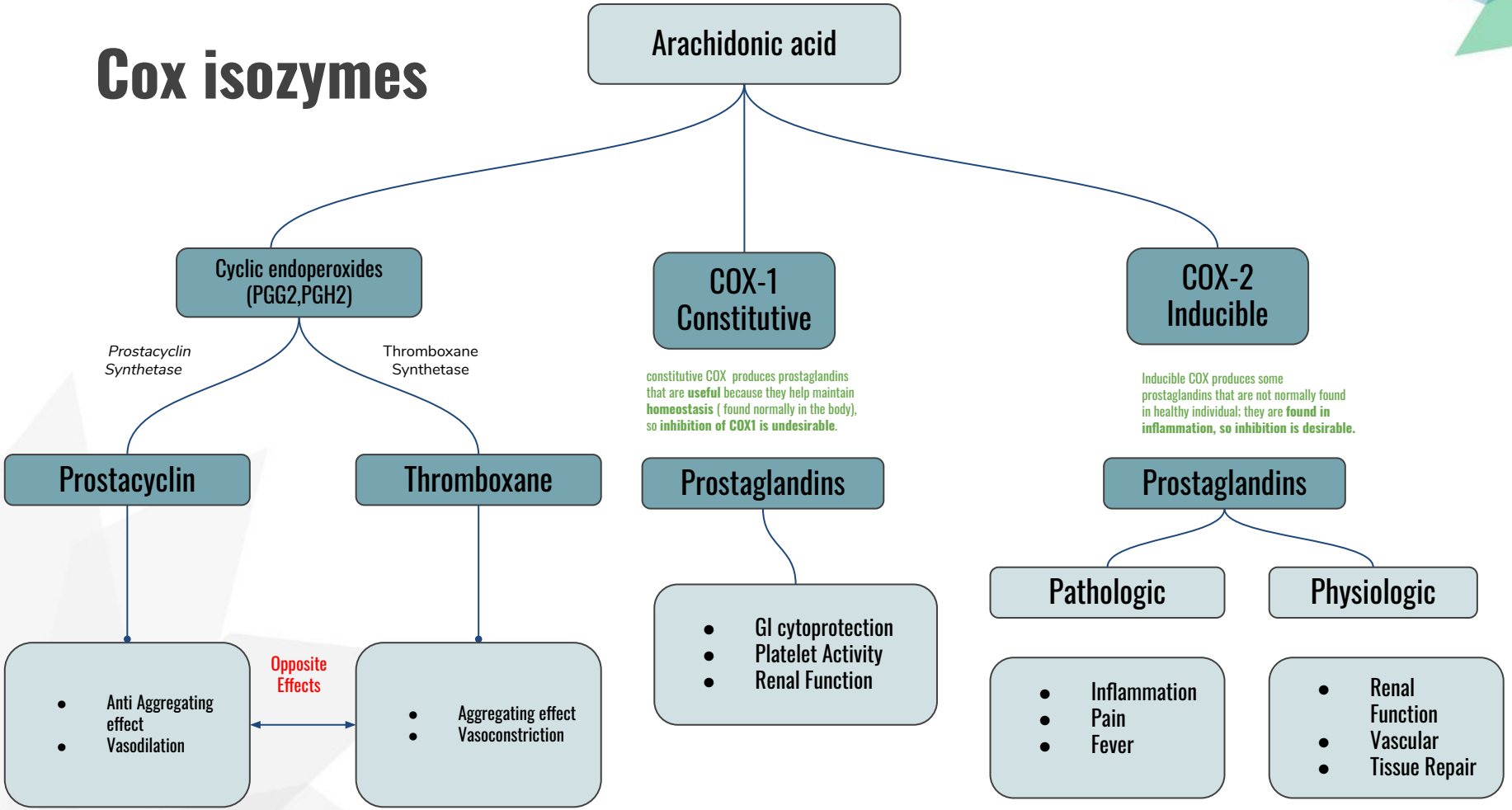
Eicosanoids Synthesis

-Eicosanoids are signaling molecules derived from arachidonic acid.
Examples:
-**Prostaglandins** (including **Prostacyclins**)
-**Thromboxanes**
-Leukotrienes

Drugs block eicosanoids by inhibiting the enzymes that produce them.
Ex of inhibitor drugs:
-Glucocorticoids (inhibits PA2)
-Zileuton (inhibit LOX)
-NSAIDS (inhibit COX)



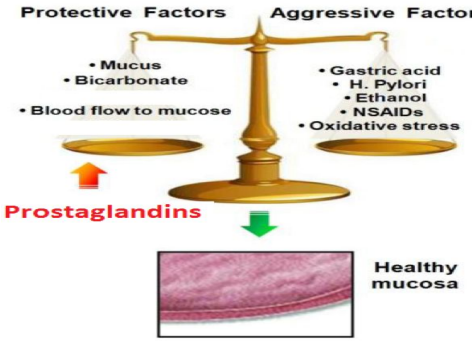
Cox isozymes



Prostaglandins

Actions of Prostaglandins

- Pro Inflammatory
- Cause vasodilation (PGI2 & PGE2)
- 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)
- Decrease intraocular pressure
- Acts on thermoregulatory hypothalamus to **increase body temperature**
- Acts on kidney to increase glomelur filtration (Vasodilation increases permeability which means more filtration)
- Acts on stomach parietal cells to protect gastric mucosa (protects stomach)



Clinical Uses of Prostaglandin Analogs

(drugs that have same effect as prostaglandins)

Analog (Drug)	Effect
Carboprost	Induces abortion in 1st trimester (by causing contractions in the smooth muscles of the uterus)
Latanoprost	Glaucoma (reduces high pressure in eye)
Misoprostol	Peptic ulcer (by inhibiting acid secretions)
Alprostadil	Erectile dysfunction (By Vasodilation)
Zileuton (lipoxygenase inhibitor) inhibits enzyme	Bronchial Asthma
Zafirlukast (leukotriene receptor blocker)	

Nitric Oxide (NO)

Biosynthesis

Synthesized from **L- arginine** by **nitric oxide synthase**

Stimulation/Inhibition

NO **release** is stimulated by:
-5-HT acetylcholine
-Bradykinin,
-Serotonin
-histamine

Nitric Oxide synthase is **inhibited by:**
-hemoglobin

Mechanism of Action

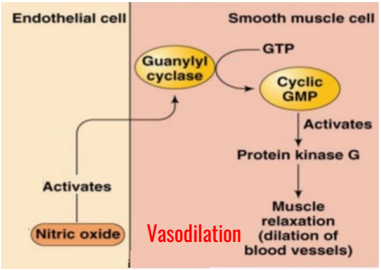
NO activates guanylate cyclase (by combining with its haem)

↓

This increases cGMP (cyclic guanosine monophosphate)

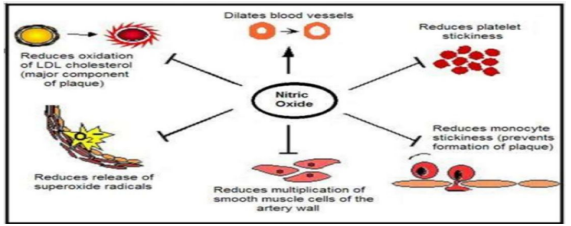
↓

Thereby lowering calcium (Ca^{2+})



Actions of NO

- Blood vessel dilator
- Inhibition of platelet/monocyte adhesion/aggregation (protection against atherogenesis= plaque formation)
- Inhibition of smooth muscle proliferation
- Host defence and cytotoxic effects on pathogens
- Cytoprotection
- Synaptic effects in the peripheral and central NS



Therapeutic Uses of NO

-Overproduction of NO occurs in: neurodegenerative diseases(e.g. Parkinsonism) and in septic shock

-Reduced endothelial NO production in: **diabetes**, **hypertension**, **angina pectoris, atherosclerosis** (NO is used to treat them):

- Used for patients with right ventricular failure secondary to pulmonary embolism
- Used in critical care to treat pulmonary hypertension in neonates

-Treatment of **erectile dysfunction** is done by **Sildenafil**(viagra) (it potentiates the action of NO on corpora cavernosa smooth muscles).

Nitric Oxide (NO)

Isoforms
of **Nitric Oxide Synthase (NOS)**
(the enzyme that makes NO)

Nature of NOS isoform	**Form** of NOS	**Location** of NOS isoform	**Action** of NOS isoform
1.Neuronal NOS (nNOS)	Constitutive Form (Physiological)	-Neurons -Skeletal muscle	- long-term potentiation (synaptic effects in the peripheral and central NS) - cardiac function - peristalsis - sexual arousal
2.Endothelial NOS (eNOS)		-Endothelium -Cardiac myocytes -Osteoblasts -osteoclasts	- vascular tone (vasodilation) - airway tone (bronchodilation) - regulation of cardiac function and angiogenesis - insulin secretion -embryonic heart development
3.Inducible NOS (iNOS)	Pathological	-Macrophages -Neutrophils -Fibroblasts -Kupffer cells(specialized macrophages in the liver) -Vascular smooth muscle	-in response to attack by parasites, bacteria,and tumor growth -causes septic shock and autoimmune conditions

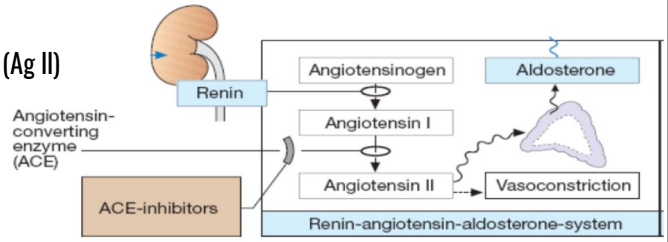
Angiotensin

Biosynthesis

Angiotensinogen —(Renin)→ Angiotensin I (Ag I) —(ACE*)→ Angiotensin II (Ag II)

(from the liver) (inactive form)

Renin(released from kidney) converts angiotensinogen to Ag I
ACE converts Ag I to Ag II
***ACE:** Angiotensin Converting Enzyme



Action

-Promotes **vasoconstriction** (-directly or indirectly- by releasing NA and AD) (noradrenaline, adrenaline)
-Increases force of contraction of the heart by promoting calcium influx
-water and sodium retention by increasing the aldosterone release

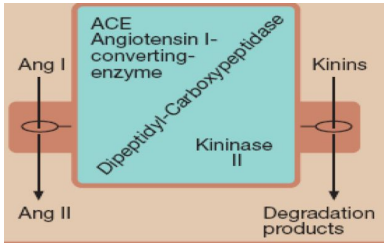
-Disadvantages:
Causes **hypertrophy of vascular and cardiac cells**
Increases synthesis and deposition of collagen by cardiac fibroblast (remodeling) Ex. heart enlarging with age

ACE Inhibitors

Note: ACE inhibition is coupled with increased kinins

Cause a fall in blood pressure in hypertensive patients
(especially those with high renin levels)
Examples: **Captopril**, **Enalapril**

Clinical uses:
hypertension, cardiac failure(reduce heart hypertrophy),& after myocardial infarction

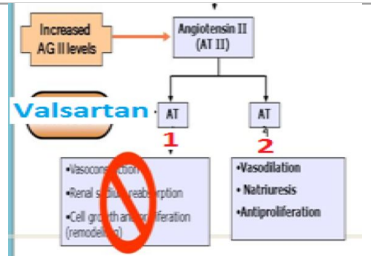


Angiotensin receptor blockers (ARBs)

-AT 1 receptors predominate in vascular smooth muscle,
mediate most of the known actions of ANG, coupled to G proteins & DAG

-Angiotensin receptor(AT_1 and AT_2) blockers:
Losartan, **valsartan**

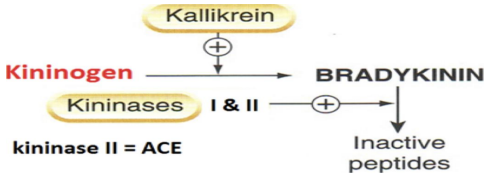
-The therapeutic uses are similar to ACE inhibitors



Kinins

Synthesis

Bradykinin is formed by proteolytic cleavage of kininogens (circulating proteins)



Types

Bradykinin and Kallidin

Actions

-Potent(strong) **vasodilator, reduces** blood pressure
-Local injection will **dilate arterioles** (by generation of PGI and releasing NO and increasing the permeability of capillary venules)
-**Contracts most smooth muscles** -SLOW and LAST LONG- (intestine, uterus, bronchiole)
-**Stimulation** of epithelial **ion transport and fluid secretion** in airways and GIT
-**Causes pain,** this effect is potentiated by prostaglandins
-**Has a role in inflammation**

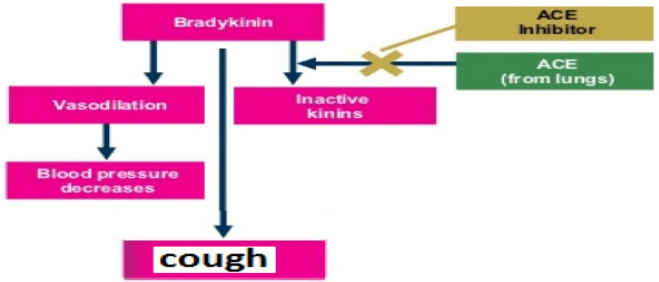
Receptors and their Actions (Both receptors are G protein-coupled receptors)

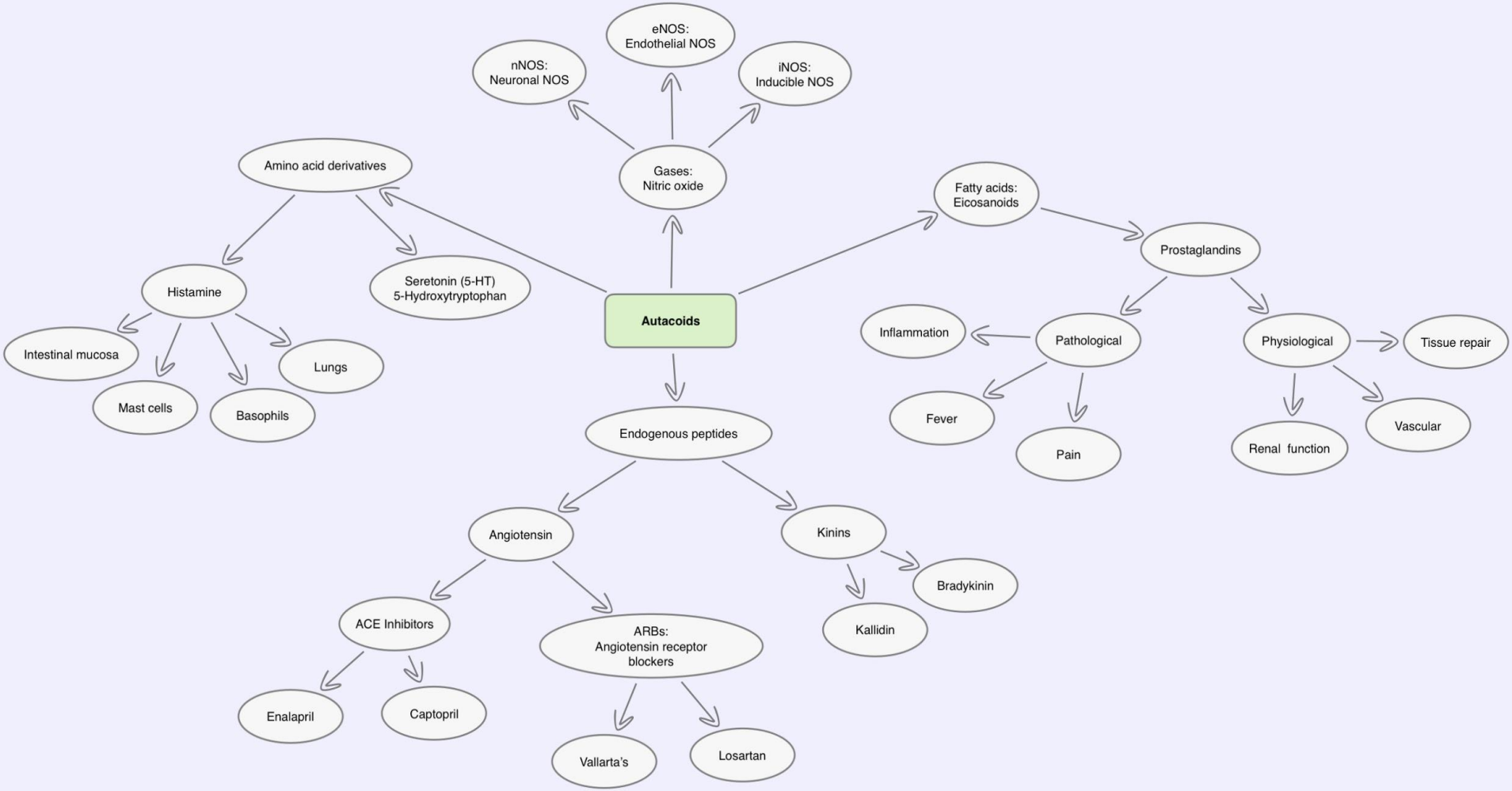
B_1	B_2
-**Inducible** under **inflammation** -**Low affinity** to bradykinin -Plays a significant role in inflammation and hyperalgesia	-**Constitutive** -**High affinity** to bradykinin and mediates the majority of its effects

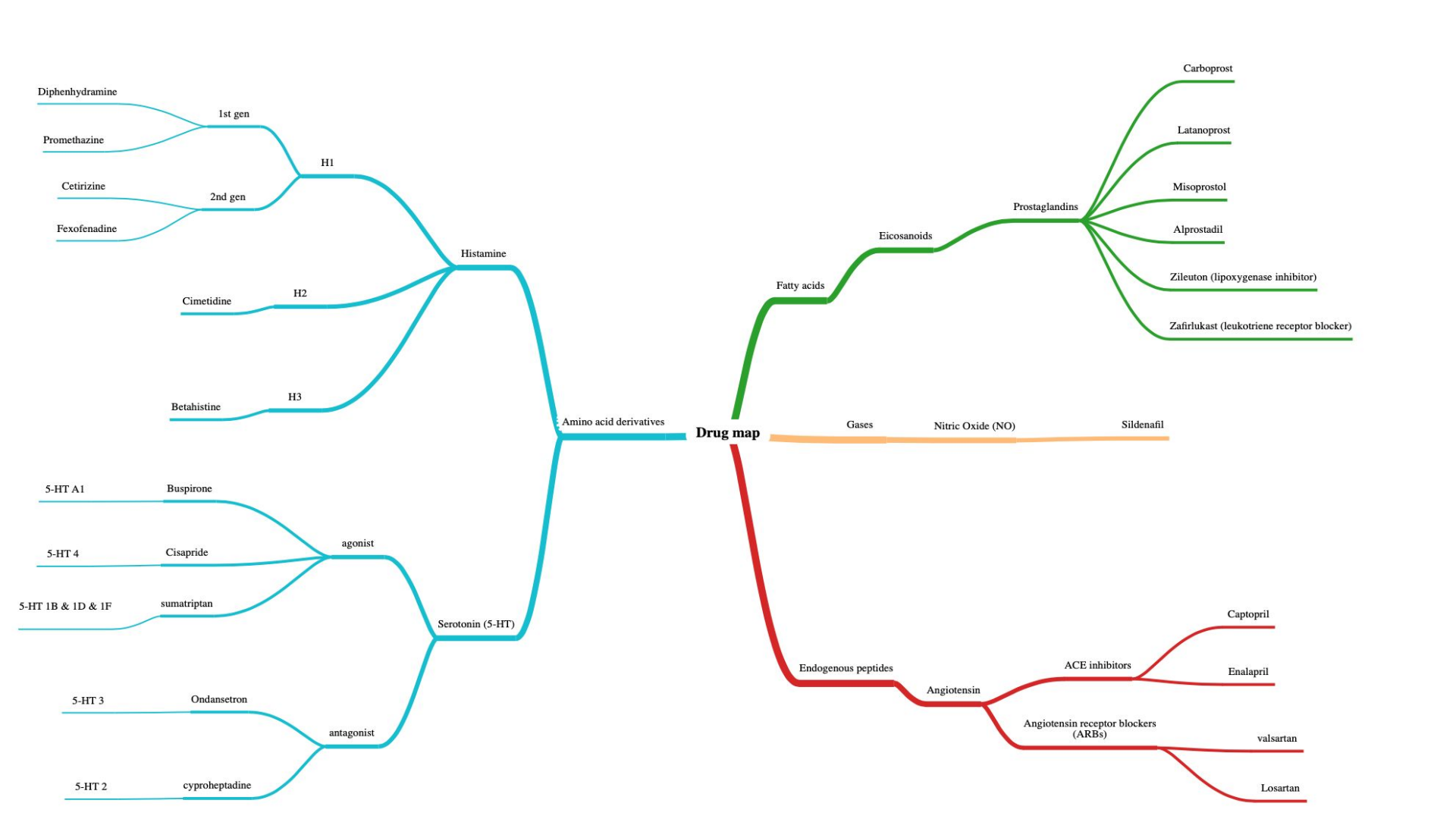
Therapeutic uses

-No current therapeutic use of bradykinin

ACE inhibitors Increase bradykinin resulting in cough




eNOS:
Endothelial NOS
nNOS:
Neuronal NOS
iNOS:
Inducible NOS
Gases:
Nitric oxide
Amino acid derivatives
Fatty acids:
Eicosanoids
Prostaglandins
Histamine
Seretonin (5-HT)
5-Hydroxytryptophan
Autacoids
Intestinal mucosa
Mast cells
Basophils
Lungs
Inflammation
Pathological
Physiological
Tissue repair
Fever
Pain
Renal function
Vascular
Endogenous peptides
Angiotensin
Kinins
Bradykinin
Kallidin
ACE Inhibitors
ARBs:
Angiotensin receptor
blockers
Enalapril
Captopril
Vallarta's
Losartan


Drug map
Amino acid derivatives
Histamine
H1
1st gen
Diphenhydramine
Promethazine
2nd gen
Cetirizine
Fexofenadine
H2
Cimetidine
H3
Betahistine
Serotonin (5-HT)
agonist
5-HT A1
Buspirone
5-HT 4
Cisapride
5-HT 1B & 1D & 1F
sumatriptan
antagonist
5-HT 3
Ondansetron
5-HT 2
cyproheptadine
Fatty acids
Eicosanoids
Prostaglandins
Carboprost
Latanoprost
Misoprostol
Alprostadil
Zileuton (lipoxygenase inhibitor)
Zafirlukast (leukotriene receptor blocker)
Gases
Nitric Oxide (NO)
Sildenafil
Endogenous peptides
Angiotensin
ACE inhibitors
Captopril
Enalapril
Angiotensin receptor blockers (ARBs)
valsartan
Losartan

MCQ

1) H_2 receptor blockers used to treat :			
A) Gastritis	B) insomnia	C) headache	D) conjuntivitis

2) Histamine stored in :			
A) Mast cells	B) basophils	C) lung	D) all of them

3) which of the following increases bowel peristalsis:			
A) H_2	B) H_3	C) H_1	D) H_4

4) Which of the following causes a hypertrophy in the cardiac cells			
A) NO	B) bradykinin	C) angiotensin	D) kallidin

ANSWERS

1	A
2	D
3	C
4	C

MCQ

5) Captopril is an example of			
A) ACE inhibitor	B) ACE activator	C) Angiotensin receptor blocker	D) Renin inhibitor

6) Which of the following receptors have High affinity to bradykinin			
A) B_1	B) B_2	C) AT I	D) AT II

7) Nitrous Oxide synthase is inhibited by			
A) Glucocorticoids	B) Zileuton	C) Bradykinin	D) Hemoglobin

8) Which of the following drugs is used to treat bronchial asthma by inhibiting lipoxygenase			
A) Zafirlukast	B) Latanoprost	C) Zileuton	D) Carboprost

ANSWERS

5	A
6	B
7	D
8	C

MCQ

9) Which is NOT an action of Nitric Oxide			
A) Vasoconstriction	B) Cytoprotection	C) Host defenses and cytotoxic effects	D) Inhibition of smooth muscle proliferation

10) Serotonin is synthesized from the amino acid:			
A) 5-hydroxytryptophan	B) L-Tryptophan	C) 5-hydroxytryptamine	D) cyproheptadine

11) Sumatriptan is used for:			
A) anxiety	B) CARCINOID SYNDROME	C) acute migraine attacks	D) gastroesophageal reflux

12) Ondansetron is a selective antagonist for 5-HT receptor			
A) 5-HT4	B) 5-HT1A	C) 5-HT3	D) 5HT2

ANSWERS

9	A
10	B
11	C
12	C

Saq

1) what's the difference between drugs that prevent the effects of histamine and drugs the prevent the effect of of eicosanoids?

2) what are types of H receptor blocker ? Give example

3) what is the major biological effect of H_3 ?

4) What are the examples of Angiotensin receptors blockers -2 examples-

5) List 3 examples of nNOS actions

6) Give 2 examples of Prostaglandin analogs and their uses

ANSWERS

A1) drugs the prevent histamine effect are receptor blockers whereas drugs that prevent eicosanoid effect are enzyme inhibitors

A2) First generation: Diphenhydramine - Second generation : Fexofenadine

A3) neurotransmission

A4) Losartan and valsartan

A5) Cardiac function, Peristalsis, Long term potentiation

A6) 1-Latanoprost:Glaucoma 2-Misoprostol:Peptic Ulcers

Saq

7)What is the function of Renin and from where is it released?

8) What will a local injection of bradykinin cause?

9) 5-HT implications cause which clinical conditions?

10) What is Serotonin's action on blood vessels?

11) Give examples of the two types of drugs that work on 5-HT receptors

12) List 2 differences between Thromboxane and Prostacyclin

ANSWERS

A7) convert angiotensinogen to angiotensin I, and it's released from the kidney

A8) dilates arterioles

A9) Migraine and carcinoid syndrome

A10) Contracts large blood vessels by a direct action & relaxes other vessels by releasing NO

A11) agonists: Buspirone and Cisapride , antagonist: Ondansetron

A12) Thromboxane has an aggregating effect and causes vasoconstriction, while prostacyclin has an anti aggregating effect and causes vasodilation

GOOD LUCK!

this lecture was done by :

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نورة المسعد
وسام آل حويس
رانيا المطيري
نورة الدخيل
اسيل الشهري
الجوهرة البنيان
شادن العبيد
سديم آل زايد
روان باقادر
ميس العجمي
نورة السالم
نوف السبيعي
ندى بابللي
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باسل فقيها
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حمد الموسى
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