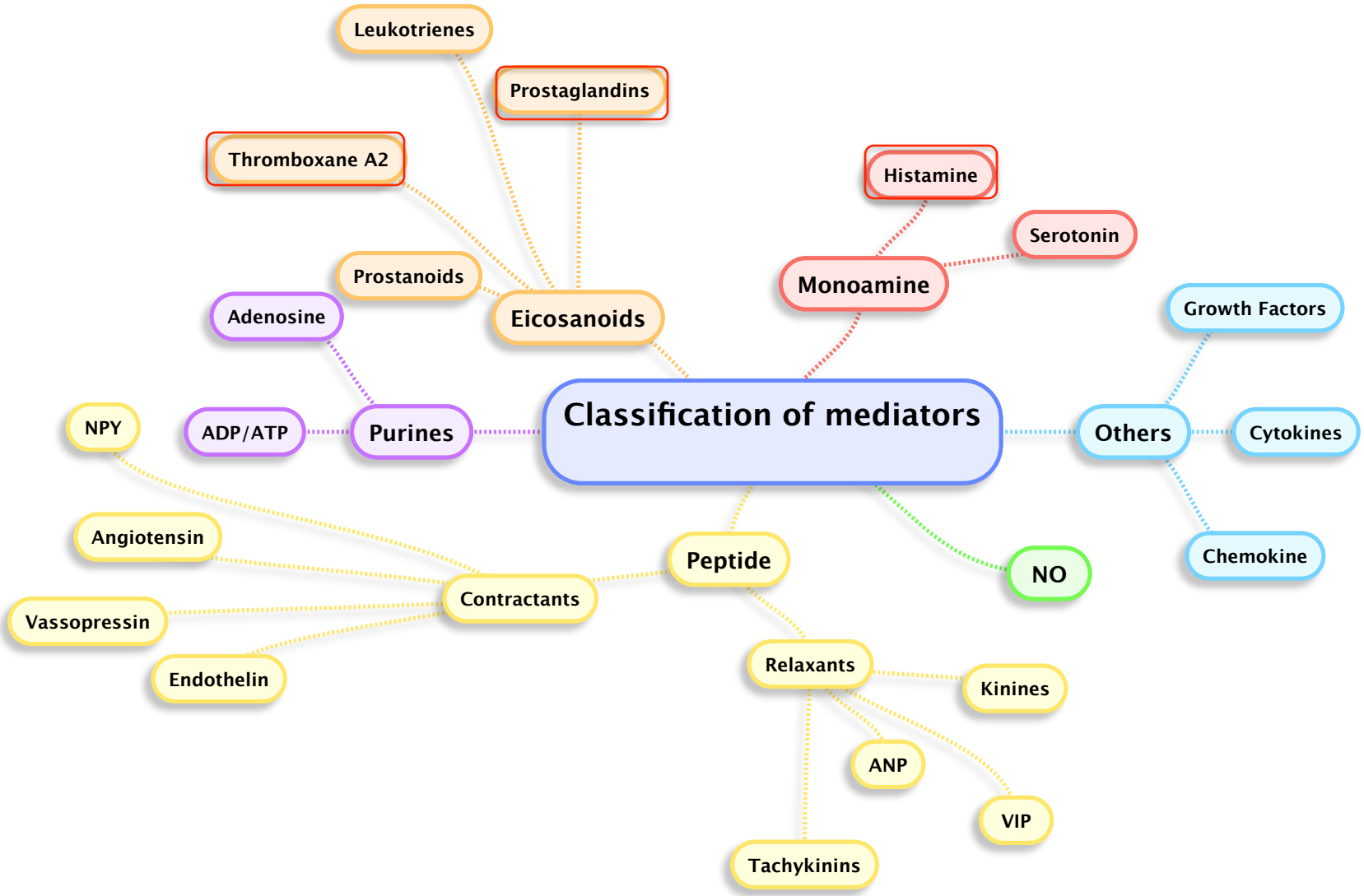
Lecture 9

Drug acting on autocrine paracrine mediators; Part II

Objectives:

1. Specify storage sites of histamine
2. Explain the synthesis, release & inactivation of histamine
3. List histamine receptors regarding: Type, major location, major biologic effects
4. Explain the clinical uses of histamine receptors antagonists.
5. Describe the synthesis of eicosanoids
6. Classify drugs that inhibit synthesis of eicosanoids
7. Enumerate the pharmacological actions of eicosanoids
8. Enumerate the clinical uses of PGs analogs

- Additional Notes
- Important
- Explanation –Extra-


Classification of mediators
Eicosanoids
Leukotrienes
Prostaglandins
Thromboxane A2
Prostanoids
Monoamine
Histamine
Serotonin
Purines
Adenosine
ADP/ATP
NPY
Others
Growth Factors
Cytokines
Chemokine
NO
Peptide
Contractants
Angiotensin
Vassopressin
Endothelin
Relaxants
Kinines
ANP
VIP
Tachykinins

Histamine

✸ Histamine importance

The **importance** of histamine is its side effect it can cause to the body when its released.

- Histamine can act as a **neurotransmitter**, which play an important role in Allergic reactions.
- Inflammatory actions.-on injury it causes local vasodilation and leakage of: plasma cells, antibodies and inflammatory cells.-
- And it is responsible for the gastric acid secretion (ex. Peptic ulceration)

✸ Biosynthesis of histamine

Histidine (amino acid) → **decarboxylase** → histamine

Storage Site

(Histamine is stored everywhere in our body -widely distributed-)

- Largest amount in Mast cells
- Skin
- Lungs
- Basophiles
- Intestinal mucosa
- Stomach
- Brain

✸ Histamine inactivation

Histamine → Imidazole N-methyltransferase → Methyl histamine (Oxidation) → Diamine oxidase → Methyl imidazole acetic acid

✸ Release of histamine:

A) Primary mechanism (antigen-antibody reaction): Ex. Mosquito bite
1- **IgE antibody** interacts with **antigen** on the surface of mast cells.
2-Mast cells are degranulated and release histamine, which leads to an allergic reactions
3- its release is modulated by binding to **H3 presynaptic** receptors.

B) Enzymes as trypsin or drugs as morphine or other chemicals can liberate histamine. (Side effect of drugs)

C) Tissue injury by trauma or burn.

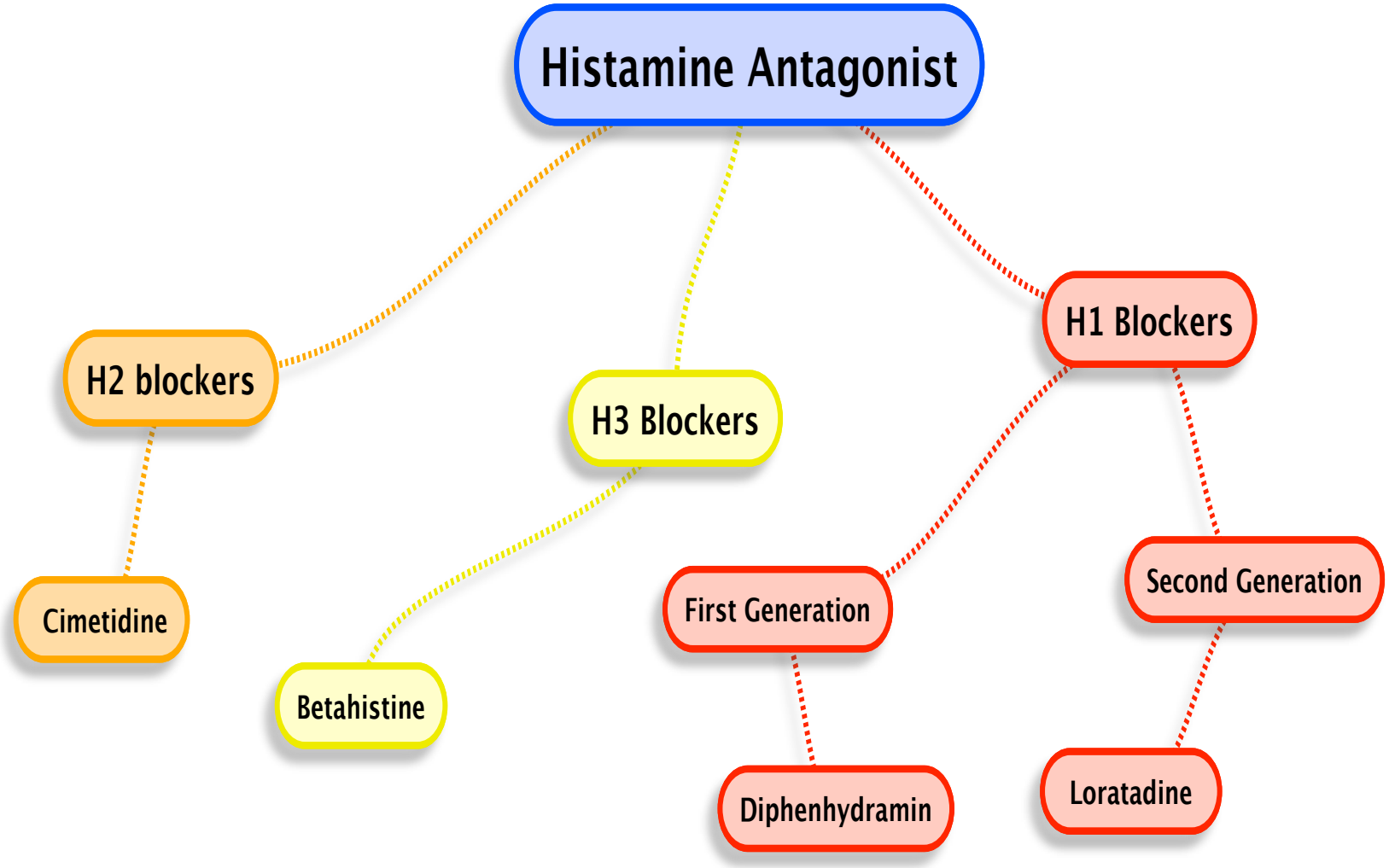
✸ Histamine receptors:

Receptor type	Major Tissue Locations	Major Biologic Effects
H_1	smooth muscle, endothelial cells	inflammation, allergic responses
H_2	parietal cells of the stoma – gastric parietal cells-	increase secretion of gastric acid
H_3	central nervous system	neurotransmission
H_4	mast cells, eosinophils, T cells	regulating immune responses

✸ Effects of histamine:

- Hypotension (due to vasodilation), tachycardia, flushing.
- Headache, visual disturbances, increase skin temperature.
- Bronchoconstriction, dyspnea, diarrhea.
- Pain ,itching, hives.
- Excessive secretion of gastric acids

✸ Histamine receptors antagonists



✸ Histamine receptors antagonists

	Diphenhydramine	Loratadine	Cimetidine	Betahistine
Receptor Type	H1 Blocker (first generation)	H1 Blocker (second generation)	H2 blocker	H3 Blocker
Sedating Effect	YES	NO	----	----
Clinical use	★ Allergic conditions as: • rhinitis • conjunctivitis ★ Insomnia ★ Motion sickness	★ Allergic conditions as: • allergic Rhinitis • Conjunctivitis • Urticarial	peptic ulcers because it is an Inhibitor of gastric acid (HCl) secretion	vertigo in middle ear : a type of balance disorder

Eicosanoids

inflammatory, chemical and physical actions will stimuli the release of phospholipase A2 enzyme, this enzyme will break down the cell membrane and you will end up with arachnoid acid. two other enzymes (lipoxygenases and cyclooxygenases) will react with arachnoid acid, this reaction will result in production of more transmitters Leukotriene(1) and Prostanoids(2)

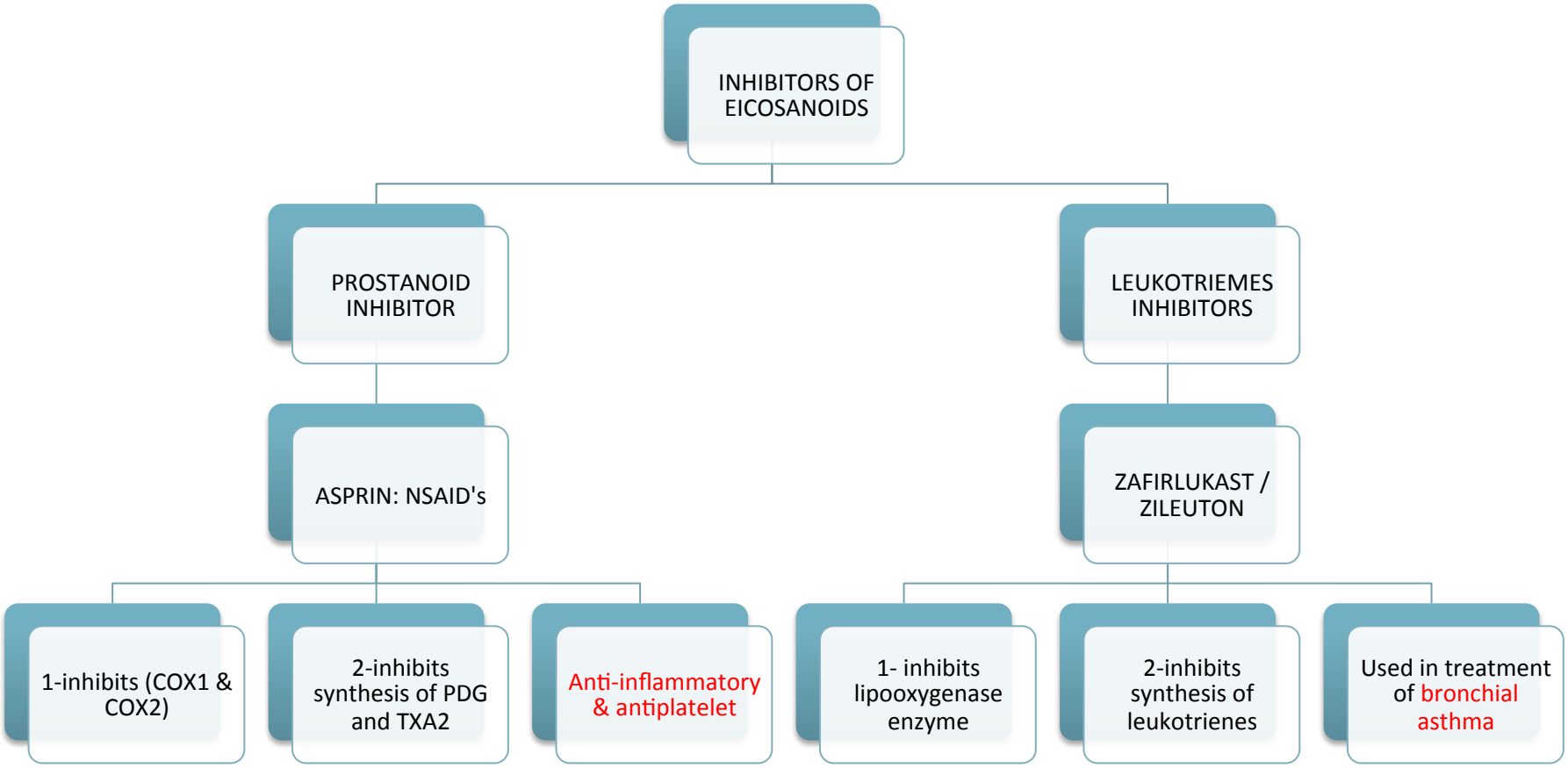
✸ INHIBITORS OF EICOSANOIDS:

For example, if u had and injury and you want to stop the reaction from happing. You take inhibitors.

A) to inhibit the release of phospholipase A2 ⟶ **Corticosteroids**
B) to inhibit the release of Cyclooxygenase ⟶ **NSAIDs** ex. aspirin
C) to inhibit the release of Lipoxygenase ⟶ **Zileuton**

(1) released by leukotriene (2) released by cyclooxygenases

✸ INHIBITORS OF EICOSANOIDS:



✸ Actions of prostaglandins -Very Important-:

- Causes vasodilatation of vascular smooth muscle cells
- Causes inhibition of platelets aggregation
- Sensitize neurons to cause pain
- Induce labor
- Decrease intraocular pressure
- Acts on thermoregulatory center of hypothalamus
- Acts on kidney to increase glomerular filtration
- Acts on parital cells of stomach to prevent gastric mucosa

✸ Comparison in actions between:-Important-

	Prostaglandins	Thromboxane A2
Vascular smooth Muscles	Potent vasodilators	Potent vasoconstrictor.
Blood	inhibit platelet aggregation	Induce platelet aggregation
Inflammation	Both play important role in inflammatory reactions	
Bronchial smooth muscle	bronchorelaxation	bronchoconstriction
Uterine smooth muscle	increase uterine contractions → Dysmenorrhea / Labor contractions(3)	-----
GIT smooth muscle	↑GIT motility	-----
GIT secretions:	↓ acid secretion ↑ Mucin secretion (4)	-----
Kidney	increase renal blood flow and diuresis.	-----
Central and peripheral nervous systems	Fever	-----

(3) Prostaglandins (PGE2) (4) Prostaglandins (E1)

Clinical uses of prostaglandins Analogs (Synthetic prostaglandins):

Carboprost[5]

- **1- Abortion**
  - Induce abortion in first trimester (first 3 months).
  - **2- Treatment of postpartum hemorrhages**
- (vasoconstriction + ↑uterine muscle contraction).

Latanoprost

- Eye drops in treatment of open angel glaucoma.
  - ↓ Intraocular pressure (IOP) by enhancing outflow of the aqueous humar.

Misoprostol [6]

- Treatment of peptic ulcer.
  - Given along with non-steroidal anti-inflammatory drugs to reduce the incidence of peptic ulcer and its manifestation as heartburn & gastric pain.
  - Side effect : diarrhea.

(5) analog to Prostaglandins (E2) (6) analog to Prostaglandins (E1)

✸ summary

1- Specify storage sites of histamine:

Highest amounts in **mast cells ,Basophils ,Skin ,Lung ,Intestinal mucosa ,Stomach ,Brain**

2-Explain the synthesis, release & inactivation of histamine :

- **a-Histamine** synthesized by decarboxylation of **Histidine**.
- b-Imidazole N-methyltransferase transfer **Histamine** to **Methyl histamine** (Oxidation), Diamine oxidase transfer **Methyl histamine** to **Methyl imidazole acetic acid**.
- c-Histamine released as primary mechanism during allergic reactions.

-Drugs(morphine), enzymes(trypsin), and other chemicals could liberate histamine.

-Tissue injury by trauma or burn.

3-List histamine receptors regarding :

Receptor Type	Major Tissue Locations	Major Biologic Effects
H_1	smooth muscle, endothelial cells	acute allergic responses
H_2	gastric parietal cells	secretion of gastric acid
H_3	central nervous system	neurotransmission
H_4	mast cells, eosinophils, T cells	regulating immune responses

4-Explain the clinical uses of histamine receptors antagonists:

- H1 antagonists (Blockers)

1- Diphenhydramine (First generation),has a sedation effect.

Used clinically in allergic conditions(rhinitis, conjunctivitis), insomnia, and motion sickness.

2- Loratadine(Second generation), has non-sedation effect.

Used clinically in allergic conditions (rhinitis, conjunctivitis, urticaria)

- H2 antagonists, decrease gastric secretion. Used in treating the peptic ulcers.
- H3 antagonists, BetaHistamine used in treating the vertigo in middle ear.

5- Describe the synthesis of eicosanoids:

when a cell is stimulated by inflammatory, physical, and chemical stimuli.→ **Phospholipase** released at the cell membrane.→ The **phospholipase** travels to the nuclear membrane.→ the **phospholipase** catalyzes ester hydrolysis of **phospholipid** and **diacylglycerol** to **archidonic acid** → the **archidonic acid** oxygenated by either **Lipoxygenases** to **Leukotriene's**, or by **Cyclooxygenases** to **prostanoids**(prostaglandins, prostacyclin, thromboxane)

✸ summary

6- Classify drugs that inhibit synthesis of eicosanoids:

Corticosteroids → inhibits phospholipase.

Zileuton/ Zafirlukast → inhibits Lipoxygenase enzyme. Used mainly in treatment of bronchial asthma.

NSAIDs (Aspirin) → inhibits Cyclooxygenase enzyme. Used as Anti-inflammatory & Antiplatelet.

7- Enumerate the pharmacological actions of eicosanoids:

Vascular smooth muscles:

Prostaglandins → Potent vasodilators.

Thromboxane A2 → Potent vasoconstrictor.

Blood:

Prostaglandins → inhibit platelet aggregation.

Thromboxane A2 → a potent inducer of platelet aggregation.

Inflammation : Both play important role in inflammatory reactions.

Bronchial smooth muscle:

Prostaglandins → bronchorelaxation.

Thromboxane A2 → bronchoconstriction.

Uterine smooth muscle:

Prostaglandins → derived from membrane lipid in the endometrium increase uterine contractions (Dysmenorrhea, Labor contractions).

GIT smooth muscle: Prostaglandin increases GIT motility, decrease acid secretion in the stomach, increases mucin secretion.

Kidneys: prostaglandins increases renal blood flow and diuresis.

Central and peripheral nervous systems: causes fever.

8-Enumerate the clinical uses of PGs analogs:

Synthetic prostaglandins:

Carboprost → Induce medical abortion in first trimester(Abortion), and Treatment of postpartum hemorrhage (vasoconstriction, increases uterine muscle contraction).

Latanoprost → eye drops /in treatment of open angle glaucoma(decreases Intraocular pressure(IOP) by enhancing outflow of the aqueous fluids).

Misoprostol(analog PGE1) → Given along with non-steroidal anti-inflammatory drugs to reduce the incidence of peptic ulcer and its manifestation as heartburn & gastric pain.

Check your understanding here ! –MCQ's

For part 1:

http://www.onlinequizcreator.com/drugs-acting-on-autocrine-paracrine-mediators-part-1/quiz-49422

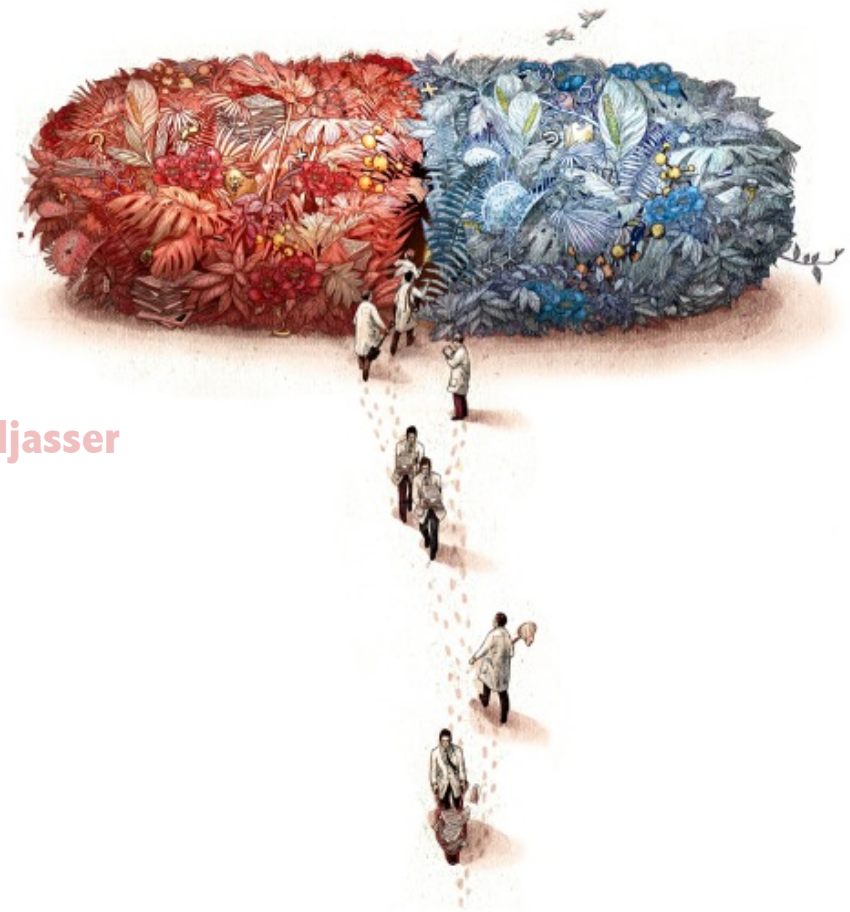
For part 2:

http://www.onlinequizcreator.com/drugs-acting-on-autocrine-paracrine-mediators-part-2/quiz-49429

Good luck!

Done by Pharmacology team 434

Moneera Aldraihem
Amal Afrah
Rawa alohali
Ahad alsubai
Noha AlGwaiz
Nora AlHelali
Lama alwallan
Sarah Mohammad aljasser
Manal alhamdan
Sara albqami
Rasha bassas
Nouf almasoud
Lamyaa Althawadi
Dhahera aljohani
Sara alsalman
Razan alsubhi



For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology434@gmail.com