PHARMACOLOGY
433

King Saud University
College of Medicine
Foundation Block

Drug Acting on Autocrine, Paracrine Mediators [part 2]

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Objectives :

*Explain the synthesis, release, receptors, Type, location, major biologic effects, inactivation of histamine.
*Describe the synthesis, pharmacological actions of eicosanoids.

Key Words :

First generation, Second generation, Sedating effect, Histamine, Eicosanoids, Prostaglandins, Prostaglandins Analogs.

Abbreviations :

LOX : Lipooxgenases
COX : Cyclooxgenases
TXA2 : Thromboxane
IOP : **Intraocular pressure**

Remember:

All these hormones (autocrine and paracrine) help to maintain the normal body function, but if they go beyond control they will be treated by pharmacology (drugs) to increase or decrease their activities.

Histamine

It almost occurs everywhere in the cells

It acts in the CNS as a neurotransmitter

It has a role in immunity (Allergic) and inflammatory response.

In case of a person who was bitten by an insect, the chemicals that were released from the insect (antigen) will sit in the cells. As a response of that, antibodies (immunoglobulin) will be produced from the body, forming antigen antibody reaction.

As a result of this the mast cells is broken up(degranulation) and releases histamine, it will produce an inflammatory response features (redness, swelling), It gets inactivated physiologically after doing its job.

It has a role in the stomach because it is responsible for the synthesis and release of gastric acid.

so if a person have a peptic ulcer قرحة المعدة

we can use drug to inhibit the receptors of histamine.

Biosynthesis of histamine:
from the amino acid (Histidine).

Storage Sites :

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

Knowing these receptors is important because they play a major role in inhibition of histamine; based on the wanted response from the specific area we define the blocker drug for that certain receptor.

Inactivation :

Histamine

↓ *Imidazole N-methyltransferase*

Methyl histamine (Oxidation)

↓ *Diamine oxidase*

Methyl imidazole acetic acid

(Inactivation happens in the mitochondria)

Histamine receptors

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 “headache”
H_4	mast cells, eosinophils, T cells	regulating immune responses

Release of Histamine

1) Primary mechanism, during allergic reactions [**IgE antibody** interacts with **antigen** on the surface of mast cells]. Mast cells are degranulated and releases histamine and leads to allergic reactions.
It also has some role in acute inflammation ,on injury it causes local vasodilation and leakage of plasma ,anti bodies and inflammatory cells.
Its release is modulated by binding to H3 presynaptic receptors
2) Enzymes as trypsin or drugs as morphine or other chemicals can liberate histamine. 3)Tissue injury by trauma or burn.

Effects Of Histamine

- Pain ,itching, hives.
- Hypotension, tachycardia, flushing.
- Excessive secretion of gastric acids, diarrhea.
- Bronchoconstriction, dyspnea.
- Headache, visual disturbances.
- Increase skin temperature.

Histamine receptors Antagonists

Specific receptor blockage:

Of Blocking of histamine receptors.
But in most of the cases these blockers specific in their binding and blocking activity.

Physiologic antagonists:

its effects can be reduced by physiologic antagonism such as epinephrine which acts on different receptors but produces effects opposite to histamine especially in anaphylaxis.

(Histamine is not used as a therapeutic drug. Its clinical importance lies in finding its antagonist)

*First generation H1 receptor Blockers:

Diphenhydramine, cyclizine, promathazine "has a sedating effect : causes sleepiness

*Second generation H1 receptor blockers:

Loratidine, Citrizine

1st and 2nd are both used to treat allergic reactions but:
if patient has allergy & insomnia or motion sickness ➔ 1st generation
if patient is a driver or a pilot for example and only has allergy ➔ 2nd generation

	Diphenhydramin	Loratadine
Receptor Type	H_1 antagonists	H_1 antagonists
generation	First generation	Second generation
Sedating effect	Yes	No
Clinical uses	*Insomnia (الأرق) *Motion sickness	Allergic conditions as: -allergic Rhinitis (حساسية الأنف) -Conjunctivitis (حساسية العين) -Urticaria حساسية الجلد

	Cimetidine	BETAHISTINE
Receptor Type	**H_2 antagonists**	**H_3 antagonists**
Used in the treatment of	**peptic ulcers because it is an Inhibitor of gastric acid (HCl) secretion**	**vertigo in middle ear** : a type of balance disorder (الدوار)

Sedating effect means it causes sleeping and laziness.

EICOSANOIDS

SYNTHESIS

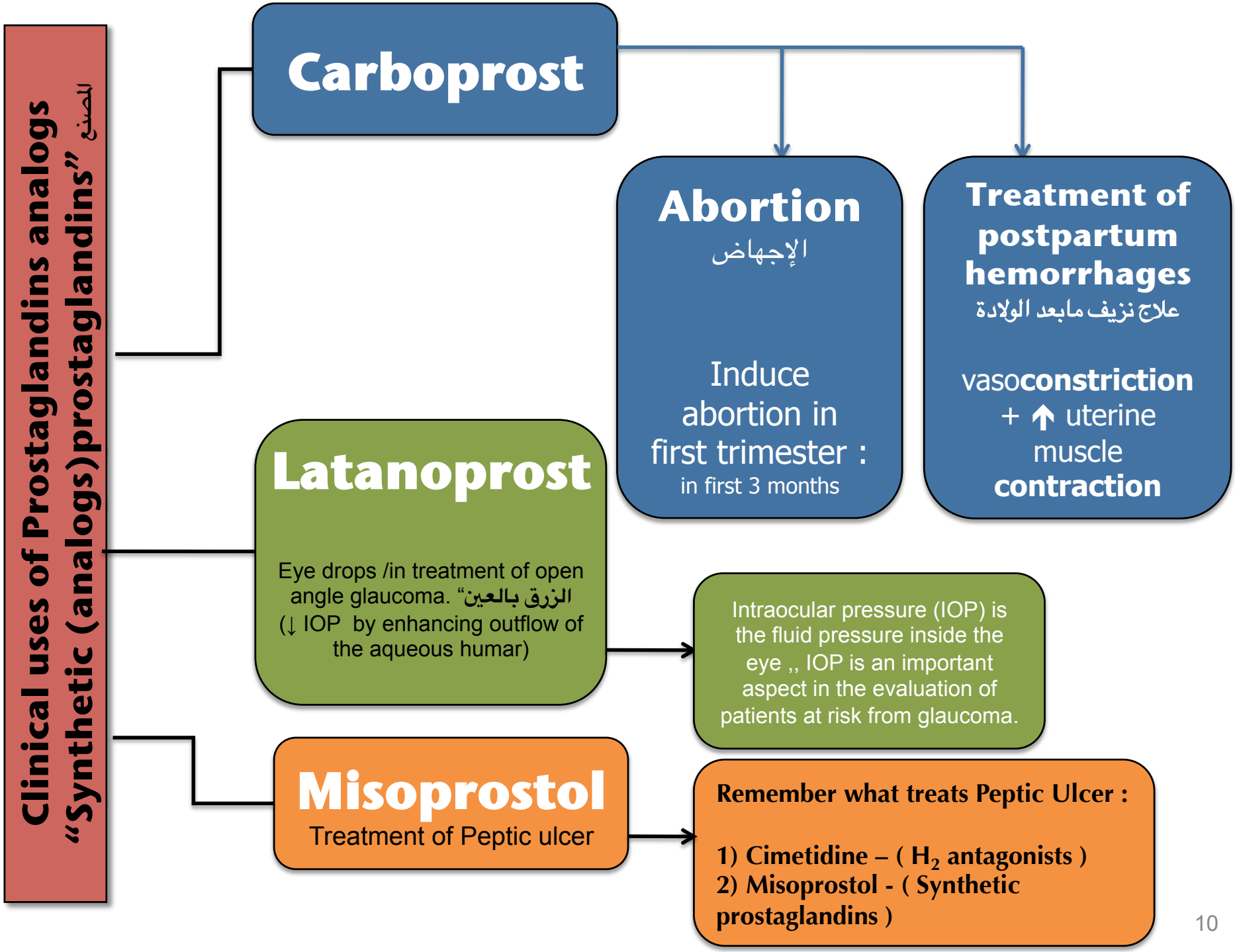
Arachidonic acid which is found in the cell membrane, when getting any external stimuli eg.
Infection → rupture of the cell membrane by Phospholipase A2
→ eicosanoids, get broke down by LOX and COX.

INHIBITORS OF EICOSANOIDS (DRUGS)

Corticosteroids
Zileuton
NSIDs

Comparison in Actions

	Prostaglandins	Thromboxane A2
Vascular smooth muscles	Potent vaso**dilators**	Potent vaso**constrictor**
Platelets	Inhibit platelet aggregation	a potent inducer of platelet aggregation.
Inflammation	Both play important role in inflammatory reactions.	
Bronchial smooth muscle	Broncho**relaxation**	Broncho**constriction**
Uterine smooth muscle	Increase uterine contractions → Menstruation/ Dysmenorrhea/ Labor contractions	
GIT smooth muscle	↑GIT motility	
GIT secretions	↓Acid secretion ↑ Mucin secretion	
Kideny	Increase renal blood flow and diuresis.	
CNS & PNC	Fever	


Clinical uses of Prostaglandins analogs
"Synthetic (analogs)prostaglandins" المصنع
Carboprost
Abortion
الإجهاض
Induce abortion in first trimester :
in first 3 months
Treatment of postpartum hemorrhages
علاج نزيف مابعد الولادة
vasoconstriction + ↑ uterine muscle contraction
Latanoprost
Eye drops /in treatment of open angle glaucoma. "الزرق بالعين
(↓ IOP by enhancing outflow of the aqueous humar)
Intraocular pressure (IOP) is the fluid pressure inside the eye ,, IOP is an important aspect in the evaluation of patients at risk from glaucoma.
Misoprostol
Treatment of Peptic ulcer
Remember what treats Peptic Ulcer :
1) Cimetidine – (H_2 antagonists)
2) Misoprostol - (Synthetic prostaglandins)

SUMMARY

•**Storage sites of Histamine** : Mast cell (Highest amount) , Basophils , Skin , Lung , Intestinal mucosa , Stomach , Brain.

•**Histamine receptors are** : H1 which is located in smooth muscles and endothelial cells and it's biologic effect in acute allergic responses , H2 which located in the gastric parietal cells and it's biologic effect is secretion of gastric acid , H3 which is located in the CNS and it's act as neurotransmission , H4 which located in the mast cells and eosinophils and T cells and its biologic effect to regulate the Immune responses .

•**We Use the Histamine receptor antagonists to :**avoid the Histamine effect on our body as hypotension, flushing … ect .

•**Some of the Clinical uses of Prostaglandins analogs are** :Carboblast :for abortion or treatment of postpartum hemorrhages, Misoprostol: treatment of peptic ulcer, Latanoprostal : treatment of open angle glaucoma .

MCQs

1. **The drug that inhibit cyclooxygenase is :**
   - A-Corticosteroids
   - B- Betahistine
   - C-Zileuton
   - D-NSAIDs

2. **Someone has a Motion sickness, the doctors will give him:**
   - A-Diphenhydramin
   - B-H_1 antagonists (first generation)
   - C-BETAHISTINE
   - D- both A&B

3. **..... Induce abortion in first trimester, and used in Treatment of postpartum haemorrhage**
   - A- Misoprostol
   - B-Latanoprost
   - C-Zileuton
   - D- Carboprost

4. **Thromboxane inhibit platelet aggregation, but Prostaglandins a potent inducer of platelet aggregation.**
   - A- True
   - B- False

5. **Latanoprost used in treatment of :**
   - A-open angle glaucoma
   - B-postpartum haemorrhage
   - C-peptic ulcers
   - D-vertigo in middle ear

6. **A girl has Insomnia and allergic condition, the doctor will give her :**
   - A- H_3 antagonists
   - B- H_1 antagonists (first generation)
   - C- H_2 antagonists
   - D- H_1 antagonists (second generation)

7. **The drug BETAHISTINE works as antagonist on .....receptor , and Used in treatment of .....**
   - A-H2 , vertigo in middle ear .
   - B-H3 , vertigo in middle ear .
   - C-H3 , peptic ulcers .
   - D- H1, peptic ulcers .

8. **..... Has no-sedating effect and use in allergic condition:**
   - A-Latanoprost
   - B-Diphenhydramin
   - C-Loratadine
   - D- both B&C

9. **Prostaglandins increase uterine contractions,and increase Mucin secretion and decrease acid secretion :**
   - A-True
   - B-False

1-D 4-B 7-B
2-A 5-A 8-C
3-D 6-B 9-A

We hope we made this lecture easier for you.!
Contact us for any questions or comments
Good Luck !

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Histamine
(http://www.youtube.com/watch?v=ke3YyYQUJuw)

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