Autacoids

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Histamine

Prostaglandins

Rennin-angiotensin-aldosterone

Ergot alkaloids

Serotonin (5-hydroxy tryptamine; 5HT)

…Kinin system

Histamine and its antagonists

Histamine is a biogenic amine

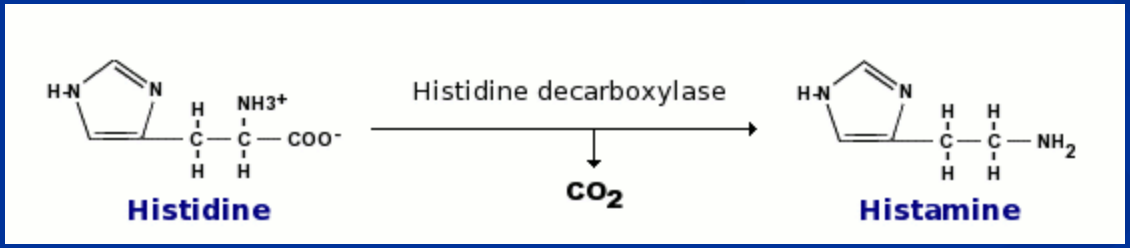
One of the best-known chemical mediators released from cells during inflammation is histamine, which triggers vasodilatation and increases vascular permeability. Histamine is stored in granules of circulating basophiles and mast cells and released immediately when these cells are injured

- In a classic study, Sir Henry Dale and his colleagues demonstrated that a local anaphylactic reaction (a type I or 'immediate hypersensitivity reaction') was caused by antigen-antibody reactions in sensitized tissue, and found that histamine mimicked this effect both in vitro and in vivo
- Later studies confirmed that histamine is present in tissues, and released (along with other mediators) during anaphylaxis

- **Synthesis:**

Histidine decarboxylase

l-Histidine → Histamine



- **Locations:**

Everywhere, intestinal mucosa, lungs, skin, mast cells, basophiles, CNS (role as a neurotransmitter)

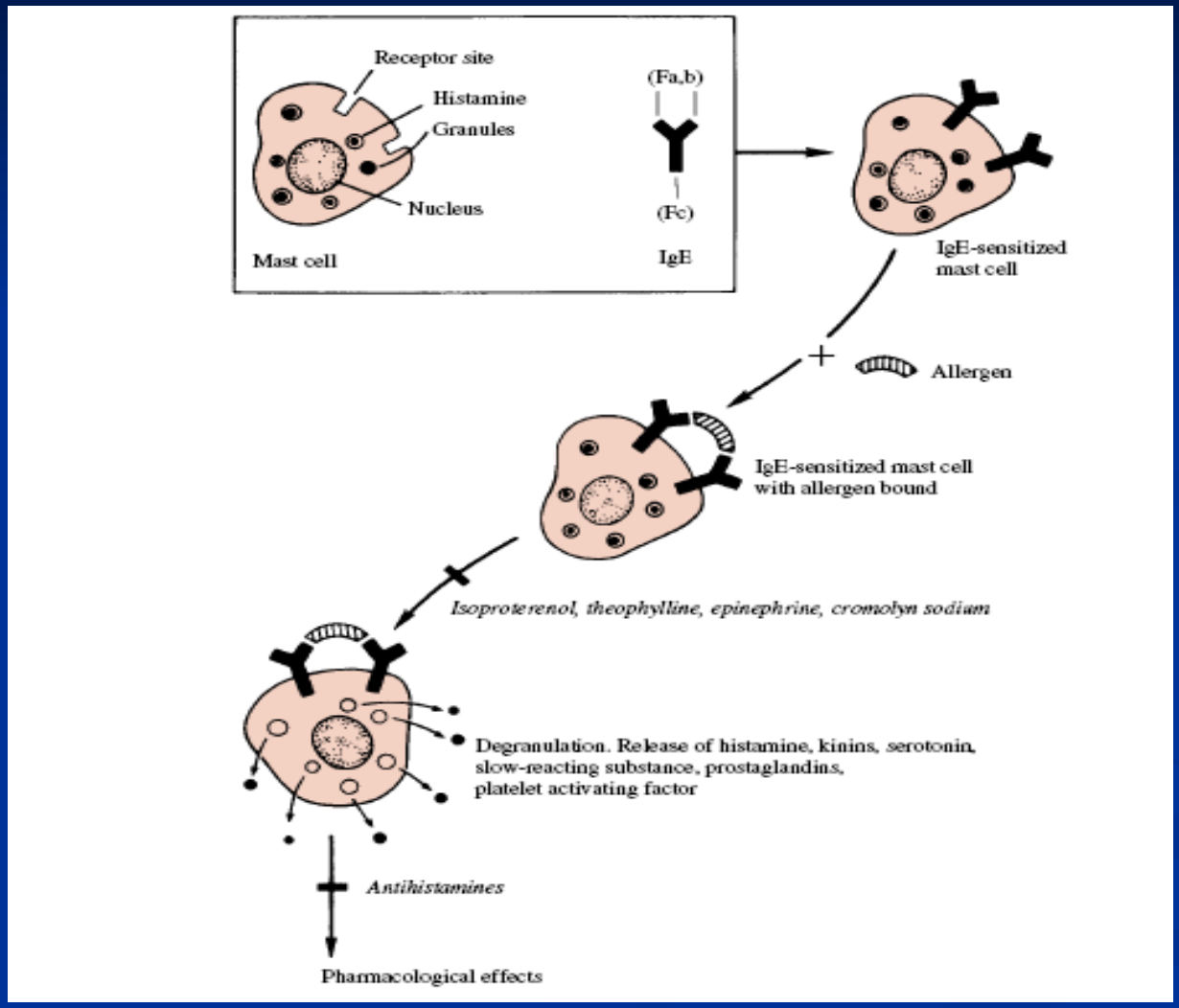
- **Release:**

- Specific (antigen-mediated)

Ag-Ab → mast cell degranulation

- Non-specific (non-antigen-mediated)

Drugs (antibiotics, anticancerous agents, compound 48/80…etc), dyes, venoms, mechanical or thermal stress


Receptor site
Histamine
Granules
Nucleus
Mast cell
(Fa,b)
(Fc)
IgE
IgE-sensitized mast cell
Allergen
IgE-sensitized mast cell with allergen bound
Isoproterenol, theophylline, epinephrine, cromolyn sodium
Degranulation. Release of histamine, kinins, serotonin, slow-reacting substance, prostaglandins, platelet activating factor
Antihistamines
Pharmacological effects

- **Histamine actions:**

  Mediated through interaction of histamine with mainly 2 types of receptors H_1 & H_2 (H_3 receptors are present in CNS = inhibitory in nature inhibit HA & NE release)

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	modulating neurotransmission
H_4	mast cells, eosinophils, T cells, dentritic cells	regulating immune responses

- **H_1 receptors:**

  Intestine, smooth muscles (blood vessels, bronchi), brain, and endothelium
- **H_2 receptors**

  Stomach, atria, brain, smooth muscles

  ↑ cAMP
- **H_1 receptor agonists**

  Histamine

  Compound 48/80
- **H_1 receptor antagonists**

  Classical antihistamines

- H_2 receptor agonists
  - Histamine
  - Compound 48/80
  - Apromidine
- H_2 receptor antagonists
  - Cimetidine
  - Ranitidine
  - Famotidine…

- **H_3 receptor agonists**

  Histamine

  Compound 48/80

  Betahistine (partial agonist)
- **H_3receptor antagonists**

  Betahistine (effective in Meniere's disease, obesity and atypical depression)

- **Responses to histamine:**

  - Lewis triple response (hypersensitivity reaction; H_1 & H_2)

    Dilatation of capillaries → red spot (flush)

    Dilatation of arterioles → flare

    Increased capillary permeability → whitish swelling (wheal)

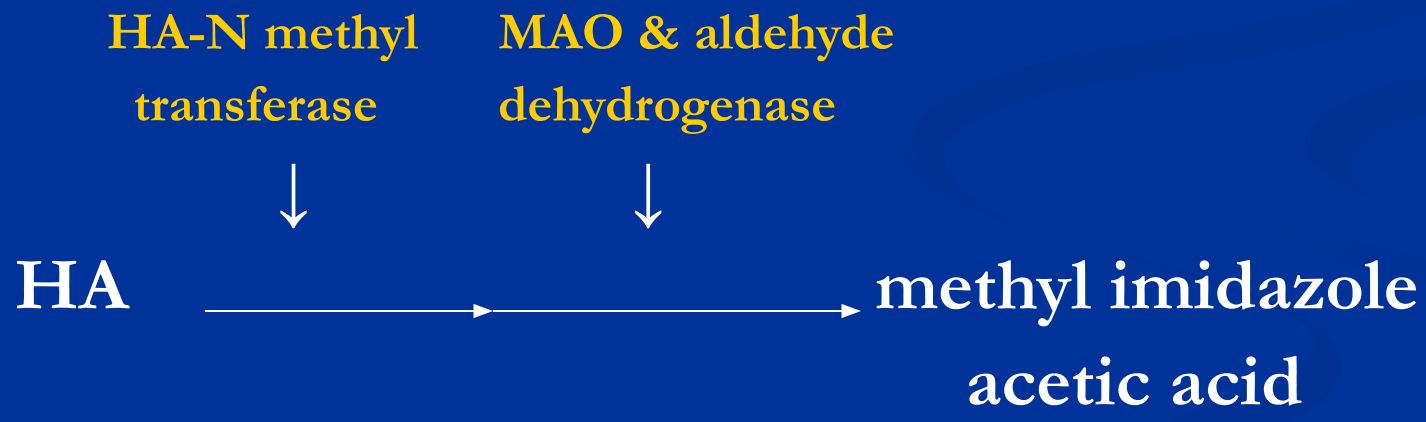
  - Bronchoconstriction (predominant H_1)

  - Increased acid secretion (H_2)

- + ve chronotropic & inotropic effect (H_2)

- Mast cell feedback control of HA release (H_2)

- **Metabolism of histamine:**



- **Inhibitors of histamine release:**

  - Cromolyn sodium (sodium cromoglycate)

    Nedocromil sodium

        Given by inhalation and eye drops

    Ketotefen

        Given orally

  Stabilize mast cells; inhibit mast cells degranulation

  Do not block Ag-Ab binding to mast cells

  Do not lead to bronchodilatation

Used mainly as a prophylactic agents in patients with:

- Mild to moderate asthma (Ag, exercise, dry air-induced)
- Hay fever
- Conjunctivitis
- Systemic mastocytosis

- Drugs ↑ cAMP

Epinephrine, Isoproterenol, Theophylline → ↑ cAMP → ↓ HA release

- **Classical antihistamines**

Many are available

Differ in pharmacokinetic properties (DOA, potency, lipid solubility…etc) and in severity of side effects

Effective orally and parenterally

- **General effects to antihistamines:**
  - Inhibit effects of HA on permeability and smooth muscles
  - Mild local anesthetic effect
  - Anticholinergic effect

**Antihistamines cannot block totally hypersensitivity reaction

- **Major clinical uses to antihistamines:**

- Allergic reactions (acute hives, urticaria, hay fever, allergic rhinitis, mild anaphylaxis…etc)

- Motion sickness (antiemetic effect)

- Sleeping aid (OTC preparations)

- **Major side effects to antihistamines**

  - Sedation and drowsiness
  - Anticholinergic effect
  - Teratogenicity
  - Overdosage → convulsions and coma

- **Antihistamines preparations:**

  - Sedating (1st generation) (more lipid soluble → CNS)

  Diphenhydramine, Dimenhydrinate, Chlorpheniramine, pyrilamine, Carbinoxamine, Triprolidine, Tripelennamine, Promethzine, Meclizine, Cyclizine, Cyproheptadine…

- Non-sedating (2nd generation)

Astemizole, Loratadine
Desloratadine, Fexofenadine,
Citrizine…etc

Representative H_1 Receptor Antagonists

Drug	Trade Name	Duration of Action (hr)	Sedative Activity	Anti–Motion Sickness Activity	Anticholinergic Activity
First-Generation Antihistamines					
Ethanolamines					
Carbinoxamine	Rondec	3–6	++		+++
Clemastine	Tavist	12	++		+++
Diphenhydramine	Benadryl	4–6	+++	++	+++
Dimenhydrinate	Dramamine	4–6	+++	++	+++
Ethylenediamines					
Pyrilamine	Ryna	4–6	++		+
Tripelennamine	PBZ	4–6	++		+
Alkylamines					
Chlorpheniramine	Chlor-Trimeton	4–6	+		+
Brompheniramine	Dimetane	4–6	+		+
Piperazines					
Cyclizine	Marezine	4–6	+	++	++
Hydroxyzine	Atarax		+++	+++	+++
Meclizine	Antivert	12–24	+	++	++
Phenothiazines					
Promethazine	Phenergan	4–6	+++	+++	+++
Piperidines					
Cyproheptadine	Periactin	4–6	++		++
Second-Generation Antihistamines					
Piperidines					
Loratadine	Claritin	24			
Fexofenadine	Allegra	12			
Piperazines					
Cetirizine	Zyrtec	12–24			

+, slight activity, ++, moderate activity, +++, marked activity

Eicosanoids
Prostaglandins and leucotreines

Eicosanoids
Prostaglandins and leucotreines

Derivatives of the naturally occurring polyunsaturated 20-carbon fatty acid arachidonic acid

Important mediators of inflammation

Have essential physiological actions

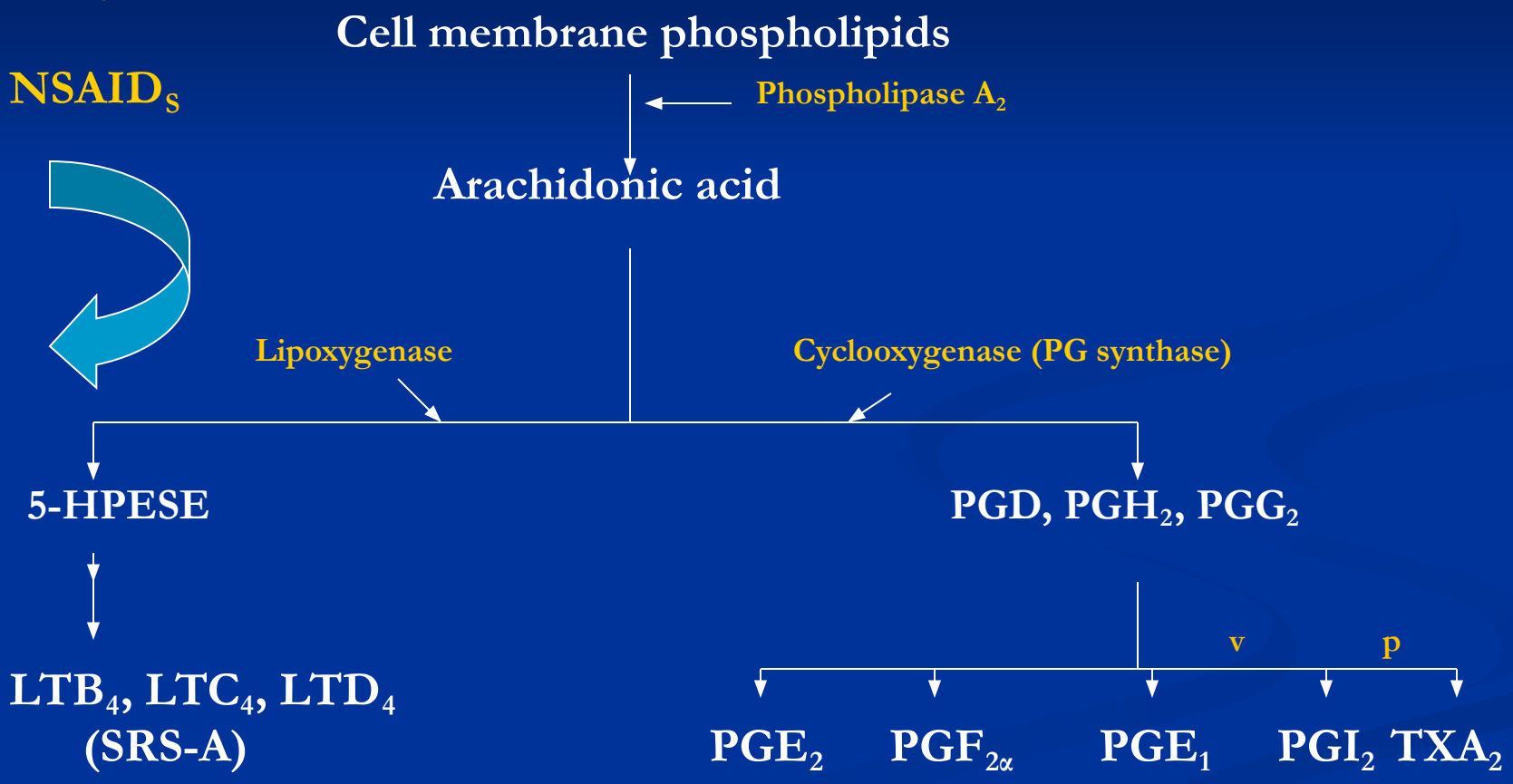
Their effects are believed to be receptor mediated

Prostaglandin Receptors

Receptor (PG)	Signal Transduction	Distribution
DP_1 (PGD_2)	AC↑, [cAMP]↑	Platelets, VSM, nervous tissue, retina, small intestine, ileum, lung, stomach, uterus
DP_2 (PGD_2)	Mobilize intracellular $[Ca^{2+}]$	Eosinophils, basophils, Th2 cells
EP_1 (PGE_2)	phosphoinositol turnover↑, $[Ca^{2+}]$↑	Kidney, lung, spleen, skeletal muscle, testis uterus
EP_2 (PGE_2)	AC↑, [cAMP]↑	Lung, placenta
EP_3 (PGE_2)	Most receptors AC↓, [cAMP]↓, some AC↑ and [cAMP]↑	Kidney, stomach, uterus, pancreas, adrenal, testis, ovary, small intestine, brain, spleen, colon, heart, liver, skeletal muscle, lung, thymus, ileum

EP_4 (PGE_2)	AC↑, [cAMP]↑	Small intestine, lung, thymus, kidney, uterus, pancreas, spleen, heart, stomach, brain, ileum, peripheral blood mononuclear cells
FP (PGF_2)	phosphoinositol turnover↑, $[Ca^{2+}]$↑	Corpus luteum, uterus, stomach, kidney, heart, lung, eye, liver
IP (PGI_2)	AC↑, [cAMP]↑	Platelets, VSM, kidney, thymus, liver, lung, spleen, skeletal muscle, heart, pancreas
TP (TXA_2)	phosphoinositol turnover↑, $[Ca^{2+}]$↑	Platelets, VSM, thymus, spleen, lung, kidney, heart, uterus

- Synthesis:


Cell membrane phospholipids
NSAIDS
Phospholipase A2
Arachidonic acid
Lipoxygenase
Cyclooxygenase (PG synthase)
5-HPESE
PGD, PGH2, PGG2
v
p
LTB4, LTC4, LTD4
(SRS-A)
PGE2
PGF2α
PGE1
PGI2
TXA2

- **PG's are involved in:**

  - Inflammatory reactions
  - Platelet aggregation
  - Control of B.P (diameter of blood vessels)
  - Contraction of the uterus
  - Protection of the stomach and duodenum…etc

- **Leukotreines are involved in:**

  - Inflammatory reactions

  - Allergic reactions

SRS-A (slow reacting substance of anaphylaxis)

Believed to be a mixture of LTB_4, LTC_4, LTD_4 and is responsible for the severe bronchoconstriction in patients with anaphylaxis or bronchial asthma

Lipooxygenase: Lungs, W.B.C's, Platelets

Cyclooxygenase (COX): All tissues

COX_1: Stomach, Kidneys, Platelets

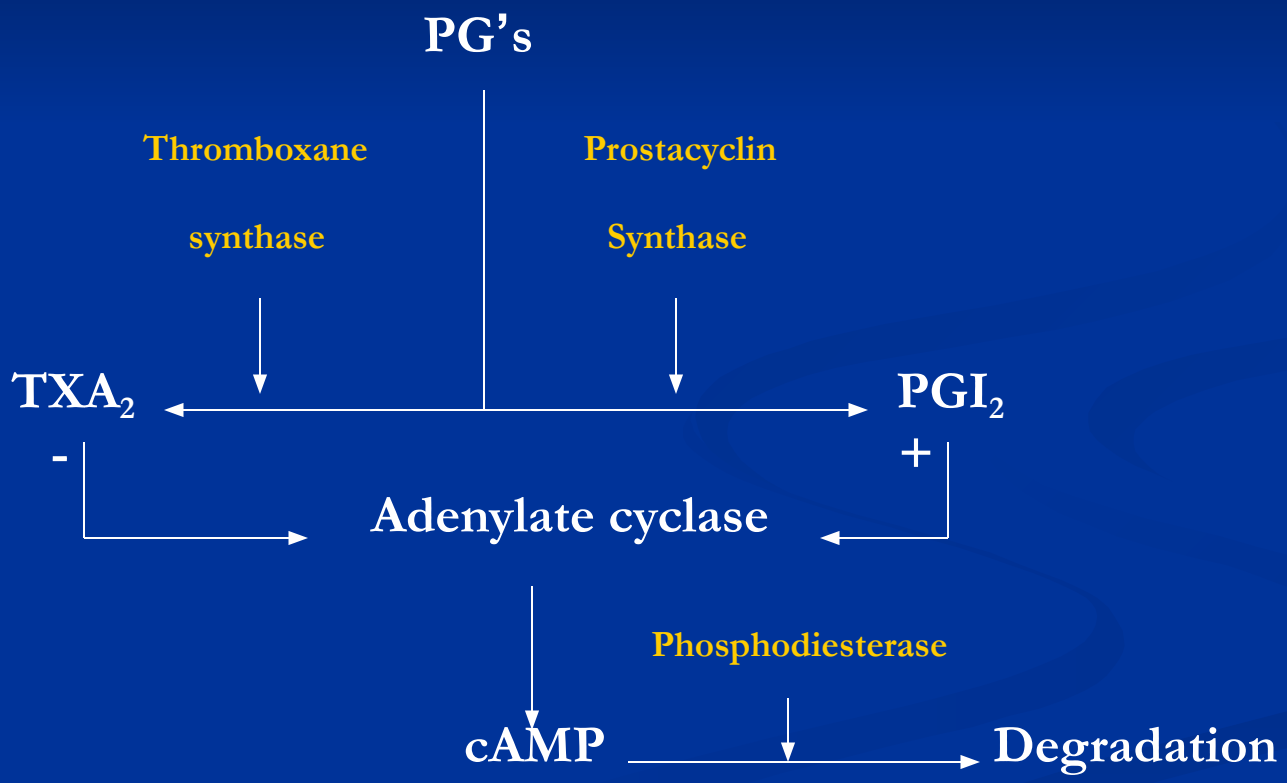
COX_2: Other tissues

Prostacyclin synthase: Blood vessels

Thromboxane synthase: Platelets

- **PG's MOA:**

Receptor mediated



- **Inhibitors of PG synthesis:**
  - Phospholipase A_2 inhibitors

    Glucocorticoids
    Phenothiazines
    Local anesthetics
    Antimalarial agents

- Cyclooxygenase inhibitors

* Nonselective: Block COX_1 & COX_2

NSAIDs (Aspirin, Ibuprofen, Indomethacin, Piroxicam, Diclofenac Na+ K+, Mefenamic acid, Sulfenpyrazone, Phenybutazone, Sulindac...etc)

* Selective: Block only COX_2

Meloxicam, Rofecoxib, Etoricoxib; Etodolac, Valdecoxib; Nabumetone…etc

- Thromboxane synthase inhibitors

  Dazoxiben, Hydralazine

- Antagonists and inhibitors of leukotrienes synthesis:

  Given orally to patients with bronchial asthma and have potential use in allergy

  *Lipoxygenase inhibitors

  Zileuton

  *Leukotrienes antagonists

  Zafirlukast, Montelukast…

- **Aspirin**

- Has the best antiplatelet activity (inhibits vascular cyclooxygenase reversibly and platelet cyclooxygenase irreversibly)
- Has the best antiinflammatory effect (inhibits PG synthesis and increases synthesis of natural antiinflammatory substances e.g. lipoxins and resolvins)
- Large doses of aspirin inhibits both cyclooxygenase and lipoxygenase enzymes
- The analgesic, antipyretic, antiinfalammatory and antiplatelet activities to aspirin are mainly due to inhibition of PG synthesis

- **Major pharmacological effects to PGs:**

- CVS: $E, I_2 \rightarrow$ vasodilatation $\rightarrow \downarrow$ B.P
  $TXA_2 \rightarrow$ vasoconstriction
- Blood: E_1, I_2 (prostacyclin) $\rightarrow \downarrow$ platelet aggregation
  $TXA_2 \rightarrow \uparrow$ platelet aggregation
- Bronchi: $I_2, E \rightarrow$ dilatation
  $F \rightarrow$ constriction
- Uterus: $E, F_{2\alpha}$ strong contractors
- Stomach: E, A, I_2 $\downarrow$ acid $\uparrow$ mucus

**Clinical application is based on either mimicking physiological effects by exogenous PGs or, in pathological situations, preventing their synthesis

- **Available PG's, their clinical uses and dosage forms (adm.):**

- Abortifacient, labor inducers:

Gemeprost (E_1) vaginal pessaries

Dinoprostone (E_2) oral, vag. tab., I.V infusion

Dinoprost ($F_{2\alpha}$) oral, I.V infusion, intrauterine, intracervical, intraamniotic

- Peptic ulcer disease

Misoprostol (E_1) oral

- Antiplatelet, peripheral vascular disease, Raynaud's disease

  Epoprostenol (I_2), Iloprost (I_2) I.V infusion

- Keeping patent ductus arteriosus, impotency

  Alprostadil (PGE_1) I.V infusion, injection into penis (I.V) & urethral suppositories

- Postpartum hemorrhage

  Carboprost ($F_{2\alpha}$) I.M