Eicosanoids

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- **Eicosanoids** are endogenously generated fatty acids, synthesized by all cells from arachidonic acid.

- **Eicosanoids** include:

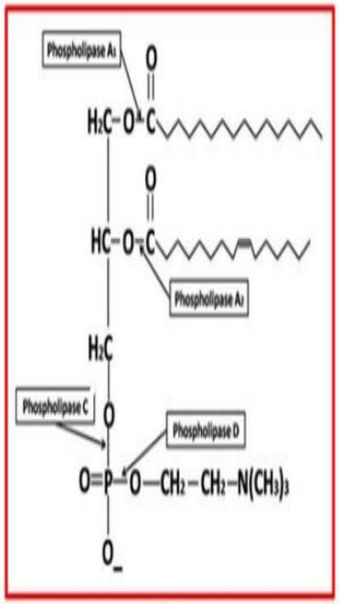
  * prostaglandins (PG)
  *thromboxanes (TX)
  *leukotrienes (LT)
  *lipoxins (LX).

- Synthesis:

* starts with a stimulus such as hormones, immunoglobulins, and microbial products, leading to activation of two types of phospholipase enzymes, PLA2 and PLC.

*PLA2 helps release arachidonic acid from the cell membrane.

* PLC induces the formation of DAG which is converted by lipase enzyme to arachidonic acid.



Two enzymes act on arachidonic acid,

1-cyclooxygenase enzymes 2- lipoxygenase enzyme.

1-Cyclo-oxygenase pathway:

Converts arachidonic acid to PGH2 which is converted by PG synthases to PGE, PGI2 (prostacyclin), PGD2, and PGF2α. By thromboxane synthase, PGH2 is converted to TXA2.

- Three types of COX enzymes are present:

*COX1: has housekeeping function as gastric protection.

*COX2: is inducible and responsible for inflammatory processes.

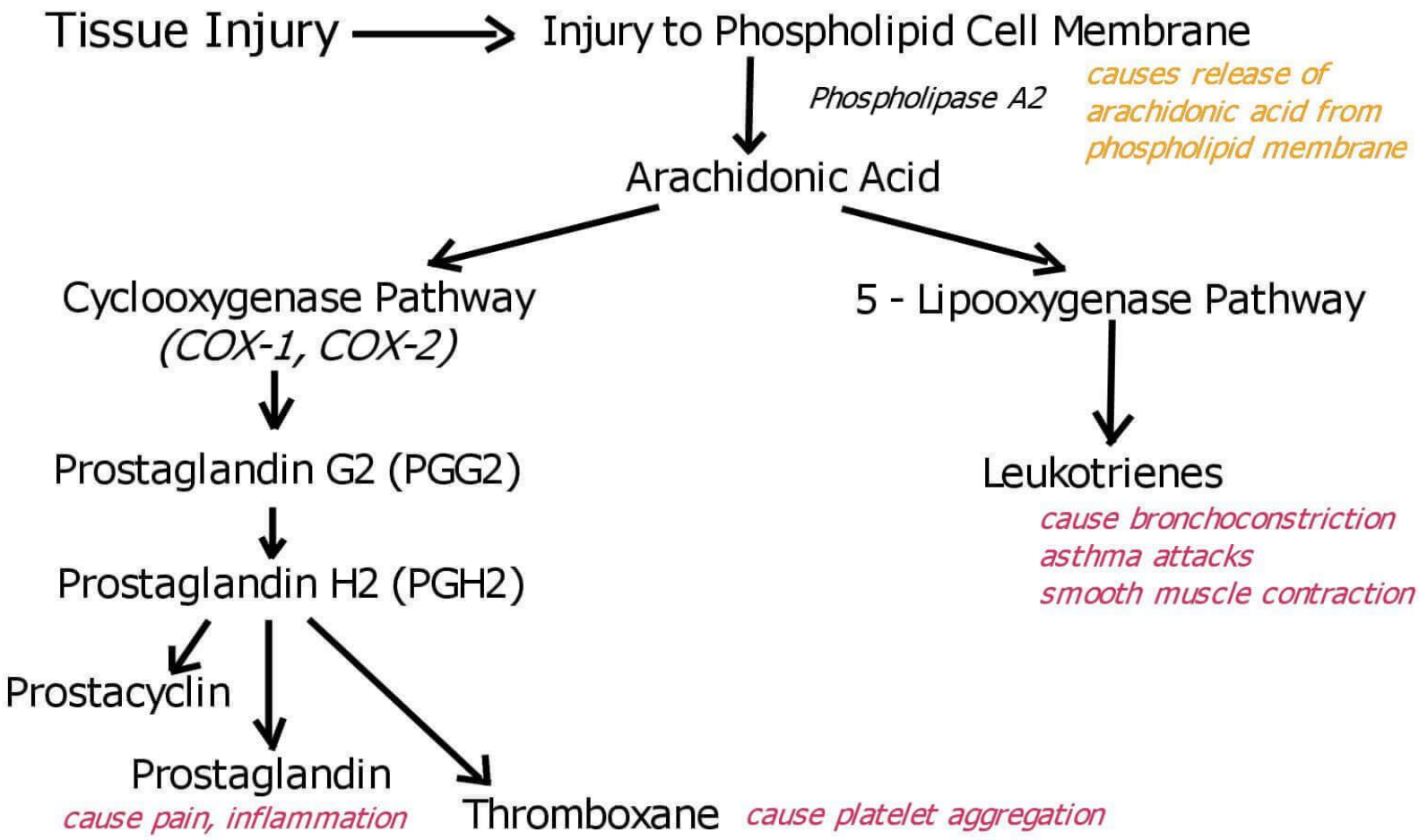
*COX3: present in the CNS

2- Lipooxygenase pathway

*5-Lipoxygenase enzyme acts on arachidonic acid, yielding the unstable LTA4 which is converted to LTB4 and LTC4. LTC4 is converted to LTD4 which in turn is converted to LTE4.

*LTB4 and LTD4 are potent bronchoconstrictors.

Arachidonic Acid Pathway



Pharmacodynamics of eicosanoids:

- Mechanism of action:

Eicosanoids produce their effects through binding with specific receptors which are G-coupled proteins. The contractile effect is mediated by IP3, while the relaxant effect is mediated by c.AMP.

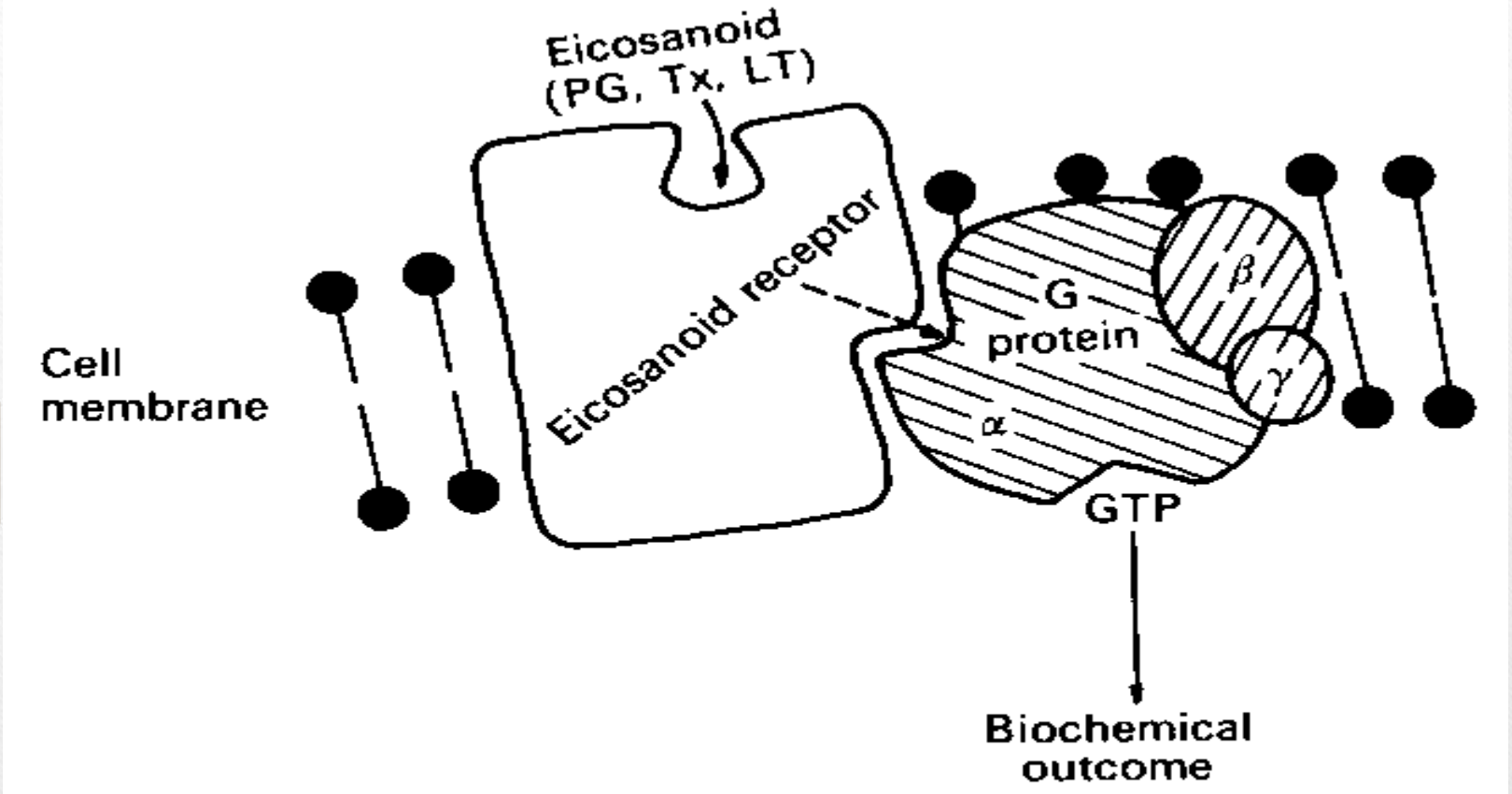


Fig. 5. General biochemical mechanism of eicosanoid actions

Eicosanoids interact with specific receptors coupled to G proteins. Receptor occupancy in the presence of GTP

- **Actions:**

1- Smooth muscles:

On vascular smooth muscles, PGE2, PGI2, and PGD2 produce arteriolar vasodilatation, while PGF2α and TXA2 are vasoconstrictors.

On GIT, PGF2α, and PGE2 produce contraction of longitudinal muscle, causing colicky pain.

On respiratory muscles, contraction occurs by PGF2α and TXA2 and is relaxed by PGE1, PGE2, and PGI2. All leukotrienes are potent bronchoconstrictors.

One the uterus, PGF2α produces contraction of the pregnant and non-pregnant uterus, while PGE2 produces contraction of the pregnant uterus and relaxation of the non-pregnant uterus

2- Blood platelets:

TXA2 facilitates platelet aggregation through increasing inositol triphosphate with increasing intracellular calcium.

PGI2 inhibits platelet aggregation through increasing cAMP.

3- Nervous system:

Fever: PGE1 and PGE2 stimulate the thermoregulatory system, increasing body temperature and causing fever.

4- Stomach:

PGE has a cytoprotective effect on the gastric mucosa.

The ulcers induced by corticosteroids and NSAIDs may result from inhibition of PG generation from gastric mucosa.

5- Kidney:

PGE2 and PGI2 increase glomerular filtration through their vasodilator effect.

6-Eye:

PGE and PGF decrease IOP by increasing the outflow of aqueous humor from the anterior chamber.

7- Inflammatory and immune response:

During inflammation and immune response, there is an increase in PGE2, PGI2, and LTs which are powerful vasodilators, leading to redness and hotness of inflamed area. Vasodilatation also increases capillary permeability causing edema.

LTB4 is a potent chemo-attractant to neutrophils.

	PGE1,2	PGI2	F2α	TXA2	LTs
Vascular SM	VD	VD	VC	VC	VD
GIT SM	contraction		contraction		
Respiratory SM	BD	BD	BC	BC	BC+++ +++
Uterus SM	contraction		contraction		
Platelets		- aggregation		+ aggregation	
CNS	+ FEVER				
Stomach	+ protective				
Kideny	+ GFR	+GFR			
Eye	↓ IOP		↓ IOP		
Inflammation	↑				↑ Chem0-attracta nt

Uses of eicosanoids

1- Induction of labor and abortion: Both PGE and PGF2α cause contraction of the pregnant uterus and can be used for this purpose.

- Dinoprost (f2α)
- Cabroprost (f2α)
- Dinoprostone. (PGE)

2- Pulmonary hypertension: epoprostenol (PGI can be used by I.V. infusion.

3- Peripheral vascular diseases: PGE and PGI2 are used in cases of intermittent claudication and Raynaud's phenomenon.

4- To keep the patency of ductus arteriosus, PGE1 (alprostadil) can be used during surgery in pulmonary atresia and stenosis.

5- Peptic ulcer: PGE1 (misoprostol) is used as a cytoprotective drug in peptic ulcers and with NSAIDs to prevent the occurrence of the ulcer.

6- Glaucoma: latanoprost (F2α) can be used inopen-anglee glaucoma

Inhibitors of eicosanoids synthesis

1-Corticosteroids:

Stimulate the synthesis of lipocortin protein that inhibits activation of PLA2 and inhibits release of arachidonic acid. This leads to the inhibition of the synthesis of all types of eicosanoids.

2- Non-steroidal anti-inflammatory drugs:

NSAIDs inhibit cyclo-oxygenase enzyme activity, blocking both prostaglandins and thromboxanes with more increase in leukotrienes synthesis

- On COX enzyme, NSAIDs may be selective or non-selective:

Non-selective COX inhibitors: ibuprofen and aspirin which are equipotent on both COX-1 and COX-2.

Selective COX-2 inhibitors: as celecoxib and rofecoxib which are highly selective inhibitors of COX-2. These drugs have less adverse effects.

Acetaminophen is a selective antagonist at COX-3.

3-Thromboxane inhibitors:

Dazoxiben inhibits thromboxane synthase enzyme and blocks the synthesis of TXA2 inhibiting platelet aggregation.

4- Leukotrienes antagonists:

Zileulon: Inhibits 5-Lipoxygenase enzyme, inhibiting synthesis of leukotrienes and lipoxins. It has anti-asthmatic and anti-inflammatory effects.

- Zafirlukast & montelukast: are leukotrienes receptor antagonists. They have an anti-asthmatic effect.
- Salfasalazine: blocks LTB4, used in the treatment of ulcerative colitis.

Uses of eicosanoid synthesis inhibitors

(1) Inflammatory and immune diseases:

- **NSAIDs and corticosteroids** are used in rheumatoid arthritis.
- **NSAIDs** to relieve fever and pain.
- **Sulfasalazine** is used in ulcerative colitis.
- **Corticosteroids** are used to prevent transplant rejection. PGI2 and TXA2 inhibitors can be also used after organ transplantation.

(2) Patent ductus arteriosus:

•NSAIDs as indomethacin help the closure of the duct by inhibiting the continual synthesis of PGE2 and PGI2 by the ductal endothelium.

(3) Dysmenorrhoea:

•NSAIDs can be used due to increased levels of PGF2α in menstrual fluids in patients suffering from Dysmenorrhoea.

(4) Blood diseases:

•**Aspirin and dazoxiben** are used as antithrombotic agents in coronary heart diseases.

- (5)Bronchial asthma:

•**Leukotrienes antagonists** as zileuton, zafirlukast and montelukast can be used. Corticosteroids are also used in treatment of bronchial asthma.

	PGE1,2	PGI2	F2α	TXA2	LTs
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GIT SM	contraction		contraction		
Respiratory SM	BD	BD	BC	BC	BC+++ +++
Uterus SM	contraction		contraction		
Platelets		- aggregation		+ aggregation	
CNS	+ FEVER				
Stomach	+ protective				
Kideny	+ GFR	+GFR			
Eye	↓ IOP		↓ IOP		
Inflammation	↑				↑ Chemo-attractant


many
Thanks!