Inflammation lecture 4

Dr Heyam Awad

FRCPath

Chemical mediators

- 1- locally produced or secreted by cells at the site of inflammation.

or

- 2- circulating in the plasma in an inactive form that need to be activated at the site of inflammation

- Preformed mediators are stored in cell granules… released quickly when needed
- Other mediators need to be synthesized… need time to act

- Preformed VS synthesized

Action of mediators

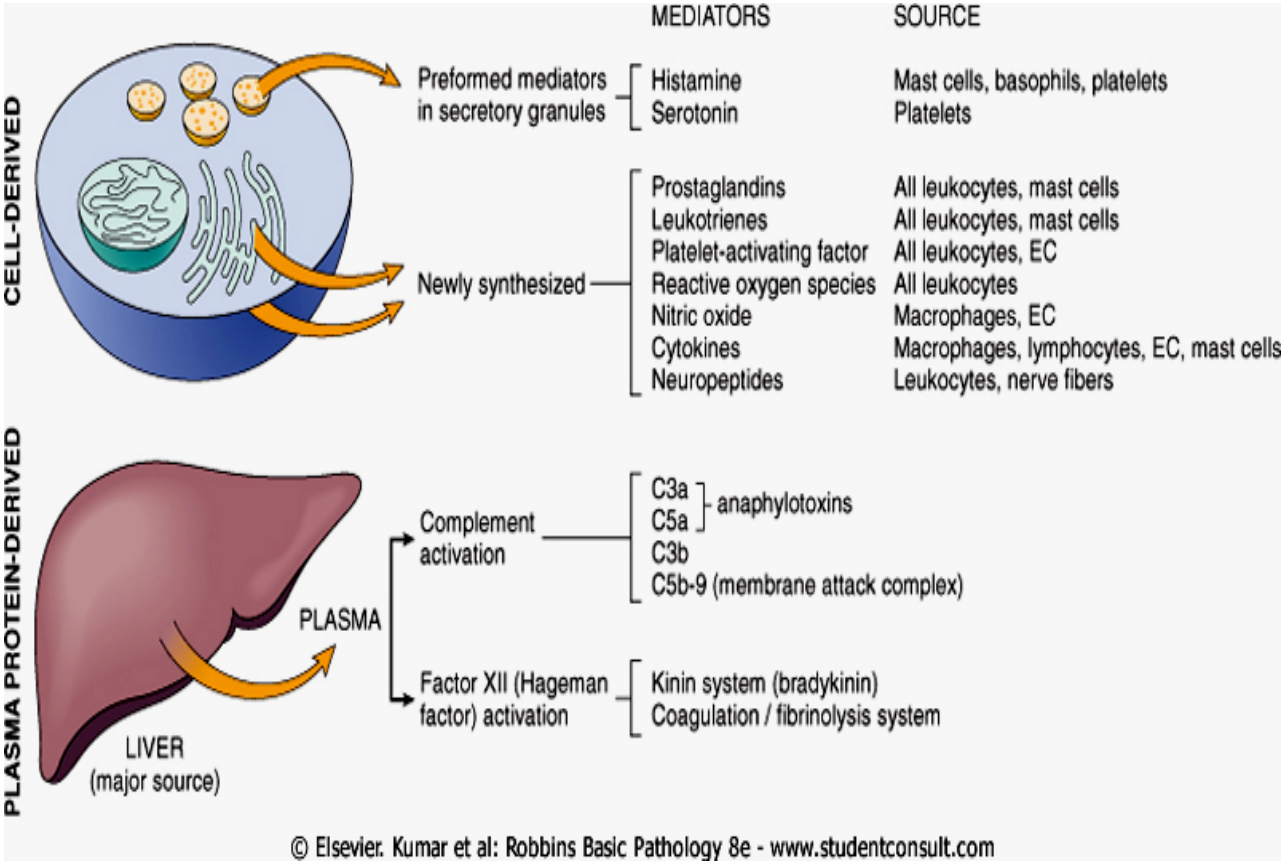
- Act by binding to receptors.
- One mediator… several actions.
- One mediator… receptors on several cells.

Regulation of mediators' actions

The actions of most mediators are tightly **regulated by:**

- Quick decay (e.g., arachidonic acid metabolites)
- Enzymatic inactivation (e.g., kininase inactivates bradykinin)
- elimination (e.g., antioxidants scavenge toxic oxygen metabolites),
- inhibition (complement-inhibitory proteins)

The principal chemical mediators of inflammation



Vasoactive amines

histamine and serotonin

Histamine

- causes vasodialtion, increased permeability.
- Responsible for edema.
- Preformed in mast cells, basophils and platelets.
- Inactivated by histaminase.

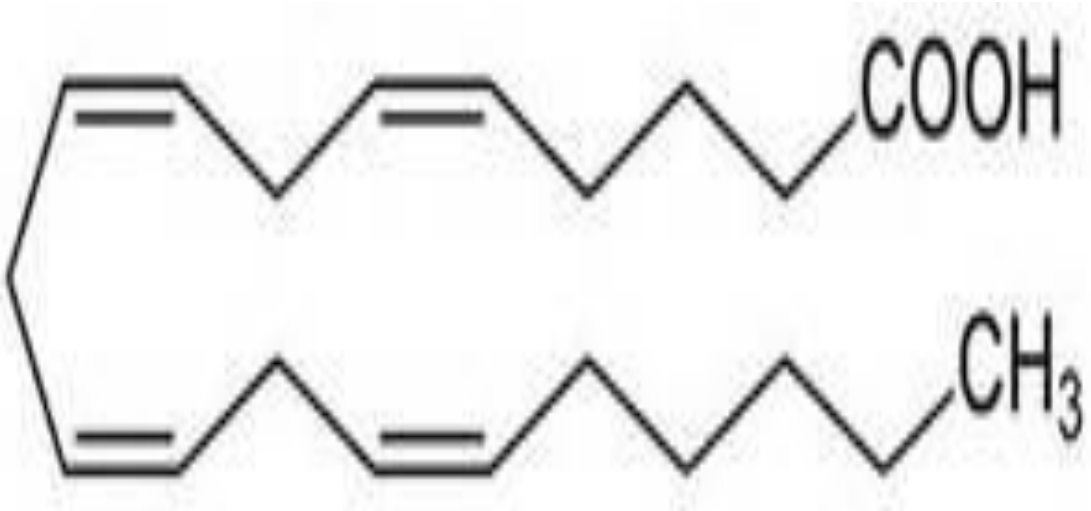
serotonin

- Stored in platelet granules
- Vasoconstrictor, especially during clot formation.
- neurotransmitter.

Platelet activating factor

- Generated from membrane phospholipids by phospholipase A2.
- Neutrophils, monocytes, basophils, platelet, endothelial cells and other cells.
- Potent broncho-constrictor.
- Potent vasodilator.
- Stimulates synthesis of other mediators.

Arachidonic acid metabolites



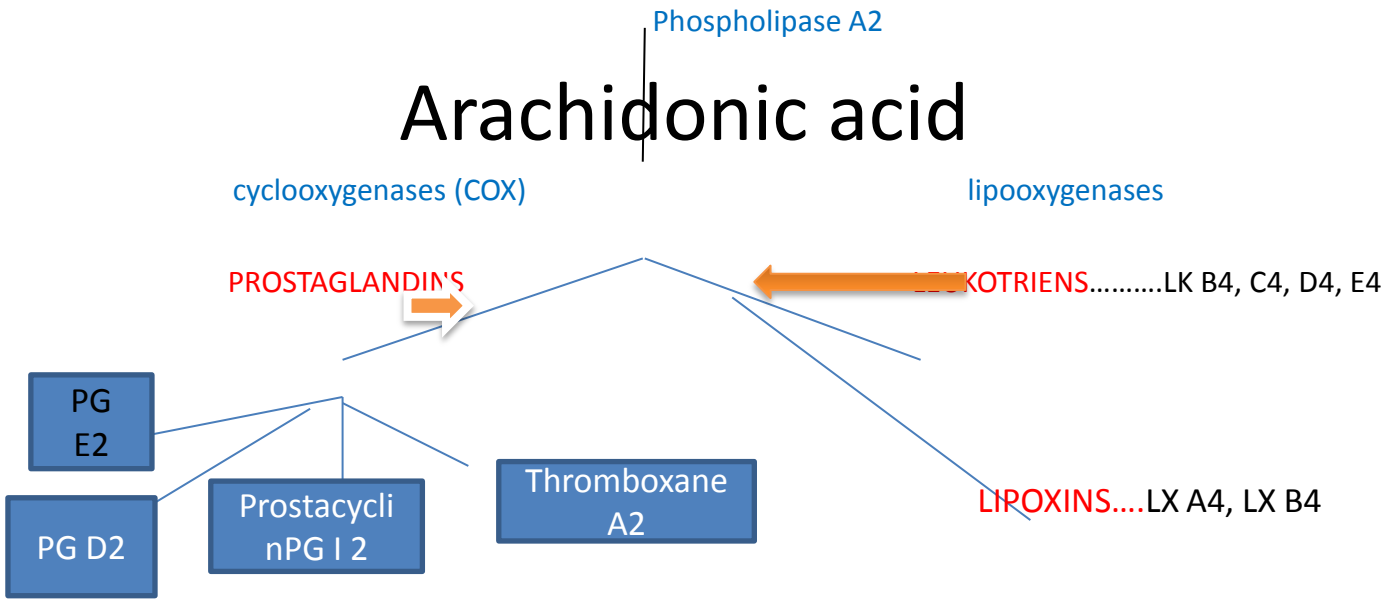
SOURCES OF AA

Arachidonic acid (AA) metabolites

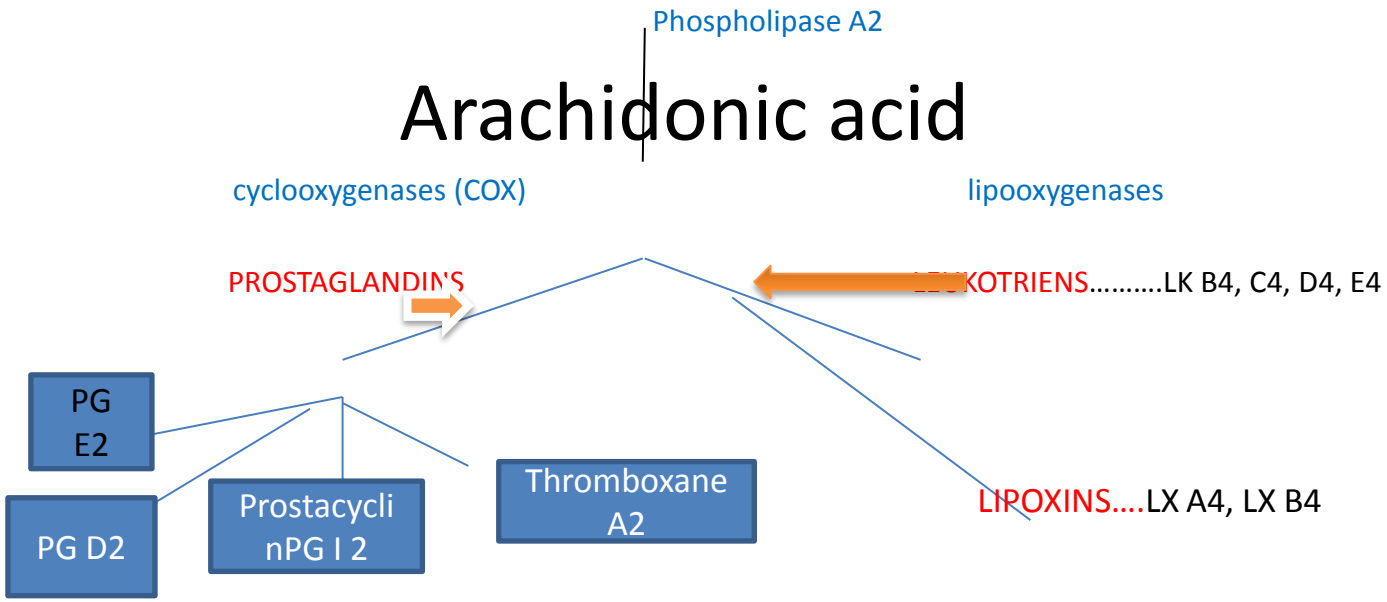
- AA … fatty acid present in cell membrane.
- Phospholipase, during inflammation releases it from membrane to cytoplasm.
- Two enzymes act upon it to form two families of mediators.
- Metabolites: eicosanoids (20 carbon) fatty acids.

White board activity

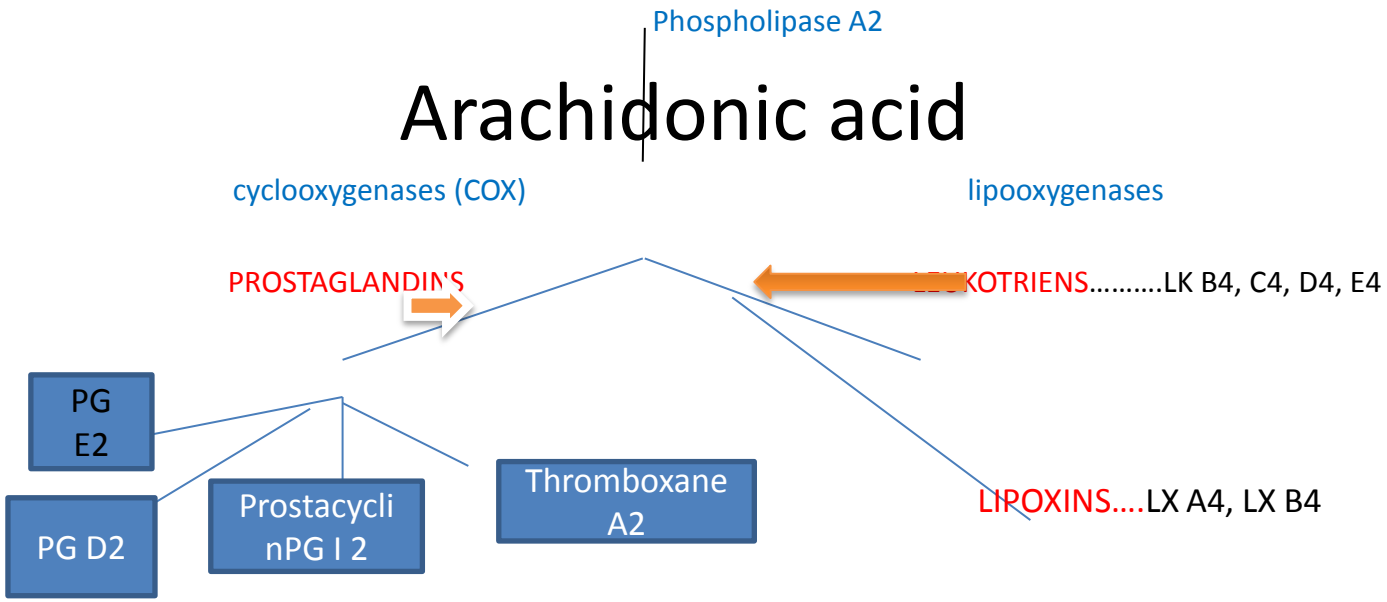
Membrane phospholipid



Membrane phospholipid



Membrane phospholipid



Cyclooxygenase pathway

Produces: prostaglandins.

- PG E2
- PG I 2(Prostacyclin)
- PG D2
- THROMBOXANE A2

- PG E2 and PG D2 have similar effect:

-vasodilatation.

-edema.

-pain.

-interact with cytokines to cause fever.

Thromboxane A2	prostacyclin
Produced in platelets	Produced in endothelial cells
vasoconstrictor	vasodilator
Stimulate platelet aggregation	Inhibit platelet aggregation

Lipooxygenase pathway

- Produced leukotrienes and lipoxins.

Leukotrienes LT

- LT B4… CHEMOTACTIC AGENT. Produced mainly in neutrophils

- LT C4
- LT D4
- LT E4

C4, D4 AND E4…. Cause bronchospasm and increased vascular permeability.

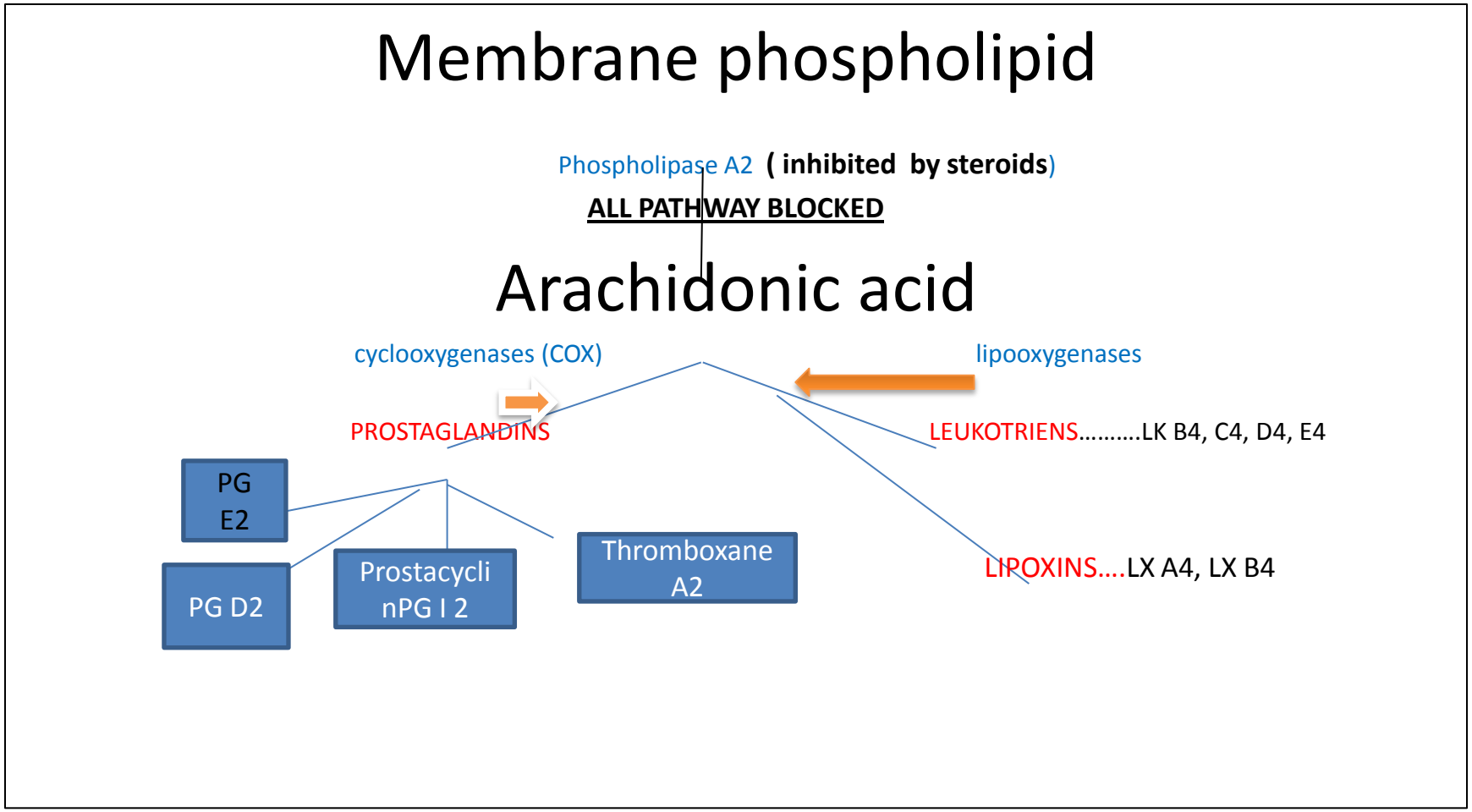
These are produced mainly in mast cells.

Lipoxins (LX)

- LX A4 AND LX B4
- Anti-inflammatory effects.
- Inhibit neutrophil adhesion and chemotaxis.

Anti-inflammatory drugs affecting AA metabolites

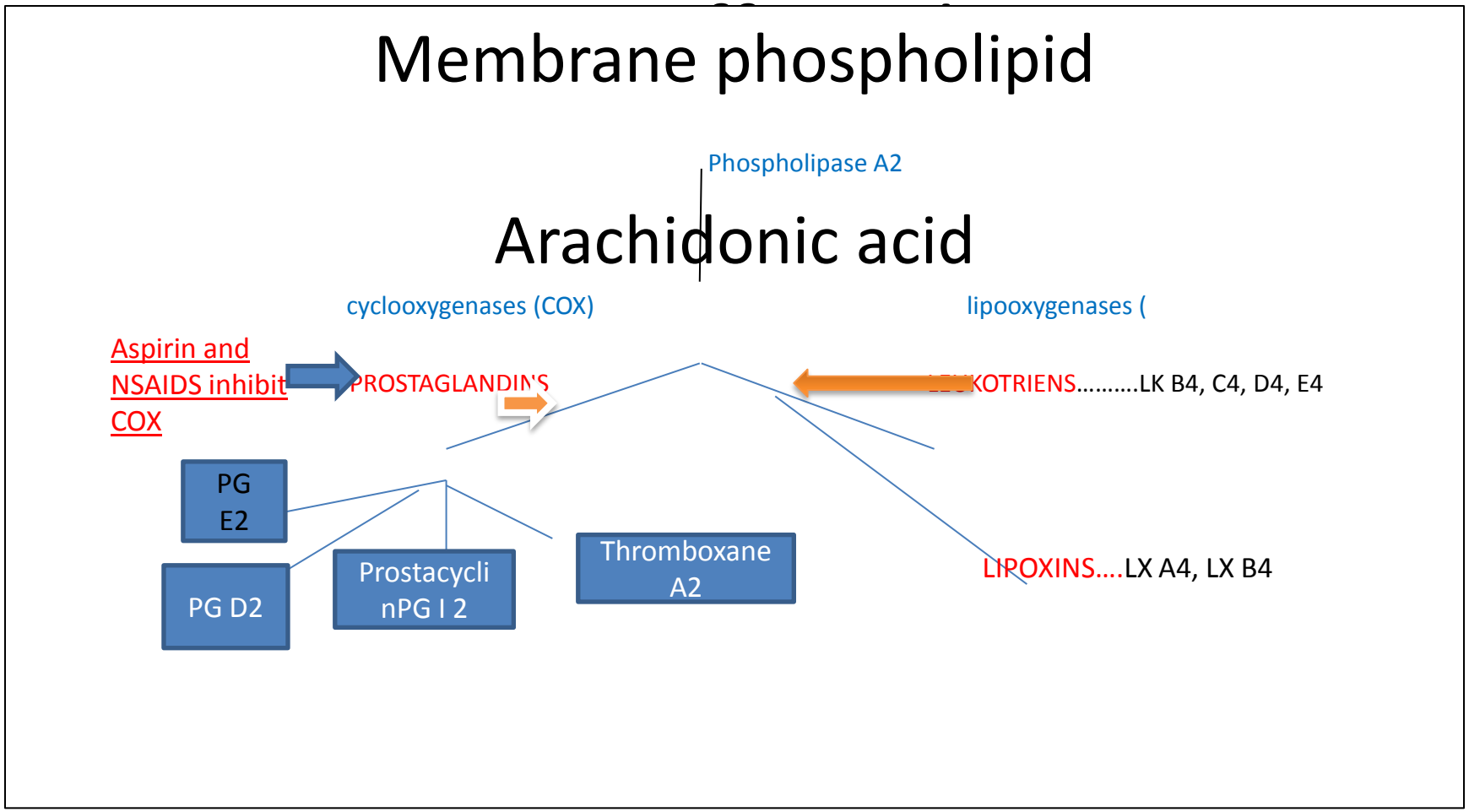
STEROID EFFECT



Steroids cut the stem.. All the tree falls

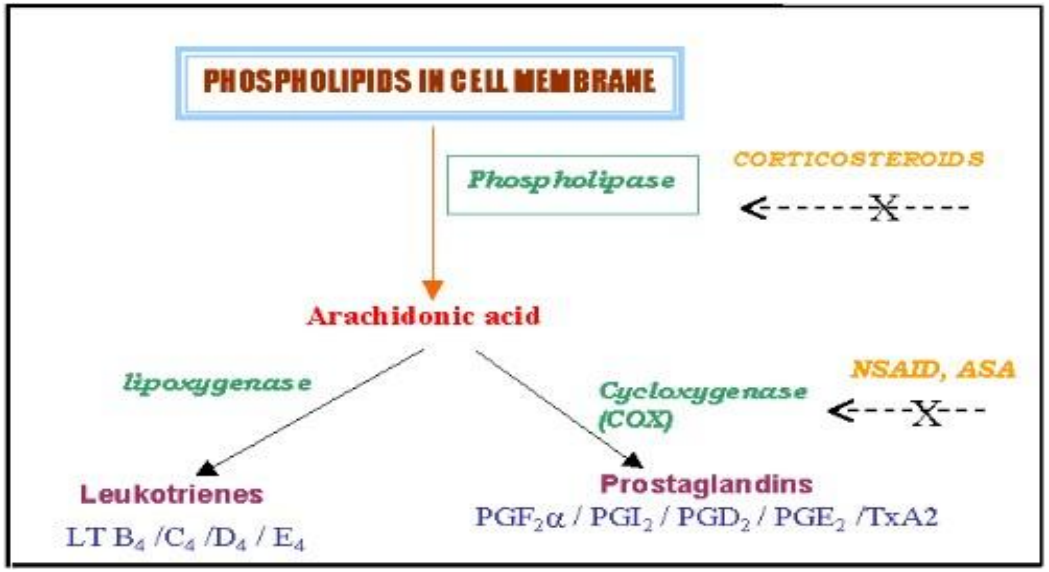
ASPIRIN AND NSAIDS inhibit COX family

PG inhibited… lipooxygenase pathway



NSAIDS and Aspirin cut COX trunk only!!

Antiinflammatory drugs



COX family

- COX is a family of several enzymes divided to two subfamilies COX 1 and COX2.

- COX 1 products are produced during inflammation but also in normal tissue where they protect the gastric mucosa and maintain fluid and electrolyte balance in the kidney.

- COX 2 products.. Only in inflammation

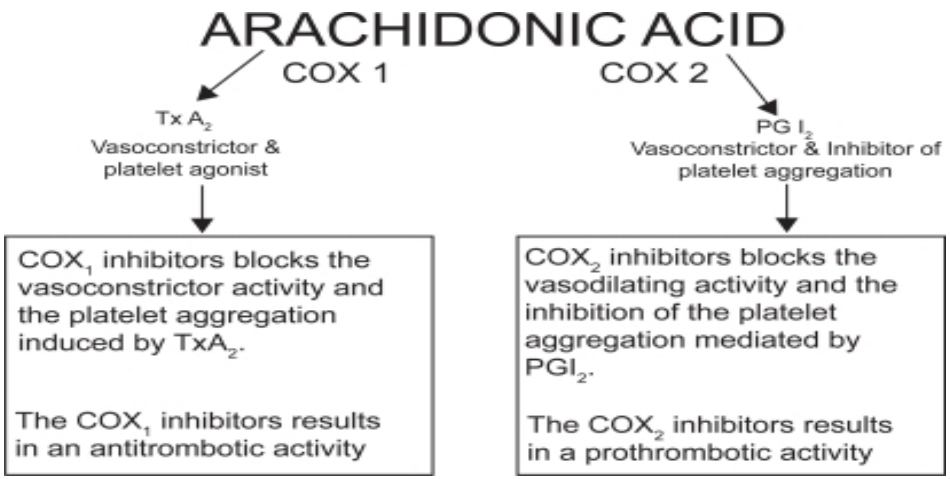
- When patients are given NSAIDS.. COX 1 and COX2 are inhibited.. That's why patients develop gastric upset (gastritis and ulcers).

- HOW to solve this?.... Cut only COX 2 trunk of the tree!
- New drugs: COX 2 inhibitors.. So products of COX 2 inhibited whereas COX 1 (protective, good prostaglandins) are produced normally.

PROBLEM with COX2 inhibitors

- Althogh COX 2 inhibitors protect the stomach, they can cause another problem!!!

- Thromboxane A2 is a product of COX1 family whereas prostacyclin is a product of COX 2…. So COX 2 inhibitors disturb the balance between these two .. resulting in increased risk of thrombi.


ARACHIDONIC ACID
COX 1
COX 2
Tx A2
Vasoconstrictor & platelet agonist
PG I2
Vasoconstrictor & Inhibitor of platelet aggregation
COX1 inhibitors blocks the vasoconstrictor activity and the platelet aggregation induced by TxA2.
The COX1 inhibitors results in an antitrombotic activity
COX2 inhibitors blocks the vasodilating activity and the inhibition of the platelet aggregation mediated by PGI2.
The COX2 inhibitors results in a prothrombotic activity

Principal Inflammatory Actions of Arachidonic Acid Metabolites (Eicosanoids)

Action	Eicosanoid
Vasodilation	PGI_2 (prostacyclin), PGE_1, PGE_2, PGD_2
Vasoconstriction	Thromboxane A_2,
Increased vascular permeability	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte adhesion	Leukotriene B_4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