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Arachadonic Acid Metabolism

M1 – Immunology Sequence

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Winter 2009

University of Michigan
Medical School

How many take aspirin, ibuprofen, tylenol, naproxen ?

Why???

INFLAMMATORY MEDIATORS

PLASMA DERIVED

- **COMPLEMENT CASCADE**
  C3a, C5a
- **COAGULATION CASCADE**
  Thrombin, plasmin

CELL-DERIVED

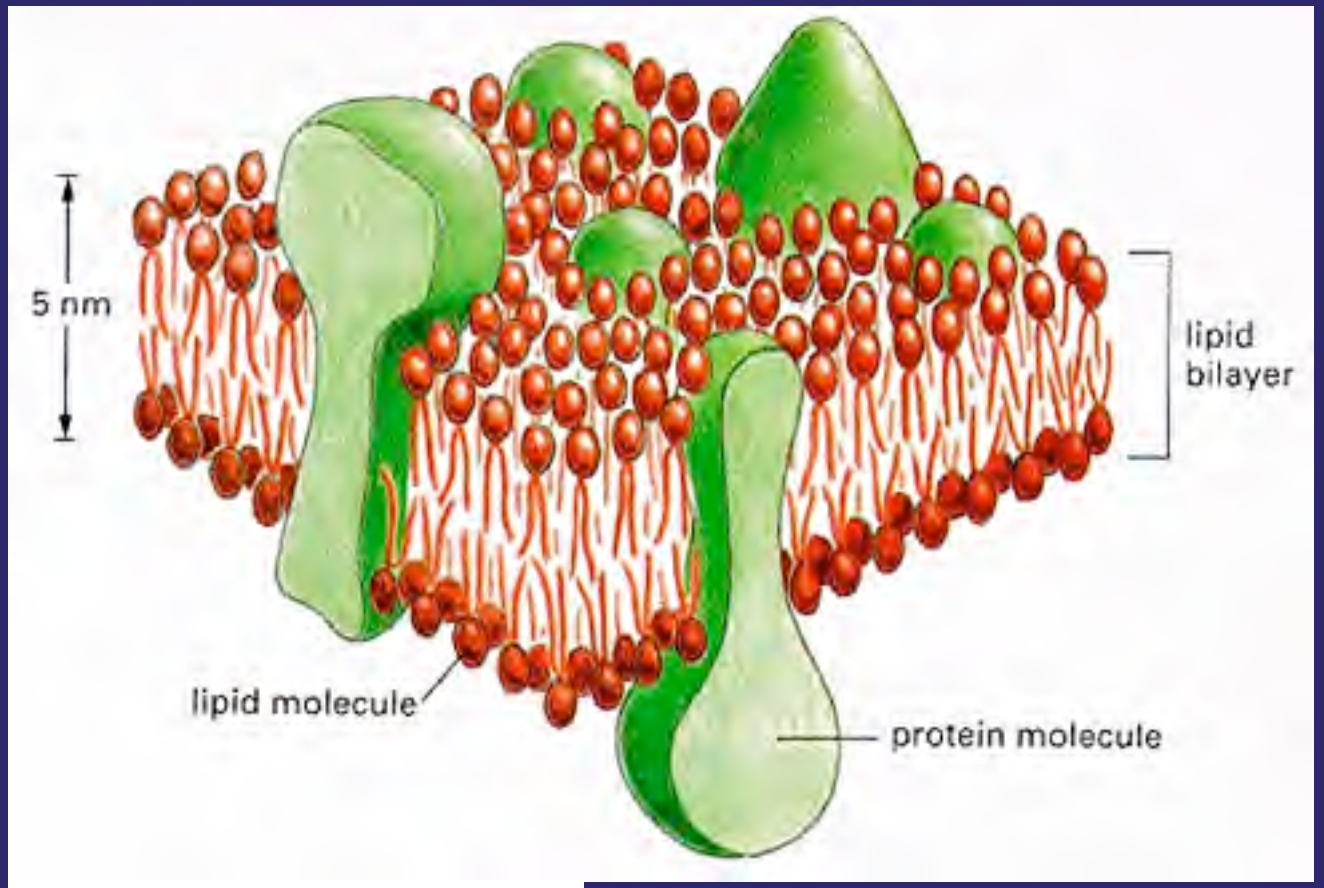
- **VASOACTIVE AMINES**
  histamine, serotonin
- **OXYGEN METABOLITES**
  hydrogen peroxide (H_20_2)
  superoxide anion (0_2^{-})
  hypochlorous acid ($HOCl^{-}$)
- **ARACHIDONIC ACID METABOLITES**
  cyclooxygenase-derived
  lipoxygenase-derived
- **CYTOKINES**
  Interleukins Chemokines
  Interferons Growth Factors
  Tumor Necrosis Factor

Intended Learning Outcomes To Understand The:

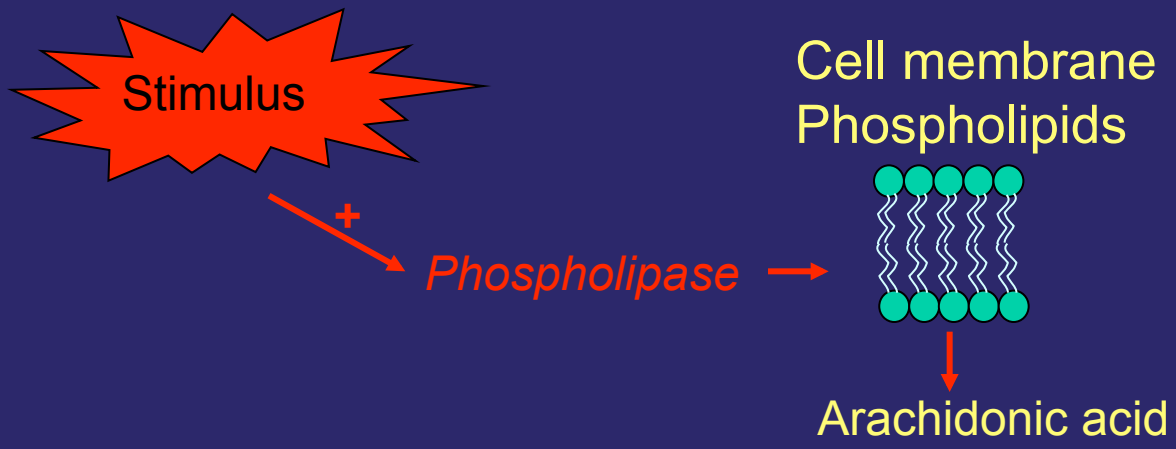
- Primary inflammatory mediators derived from the metabolism of arachidonic acid including their primary cellular source and biological activity.
- Effects of nonsteroidal anti-inflammatory compounds on blocking the production of arachidonic acid metabolites during disease
- Mechanism of aspirin therapy and diets rich in fish containing high levels of omega 3 fatty acids as potentially important in lowering the incidence of cardiovascular disease.

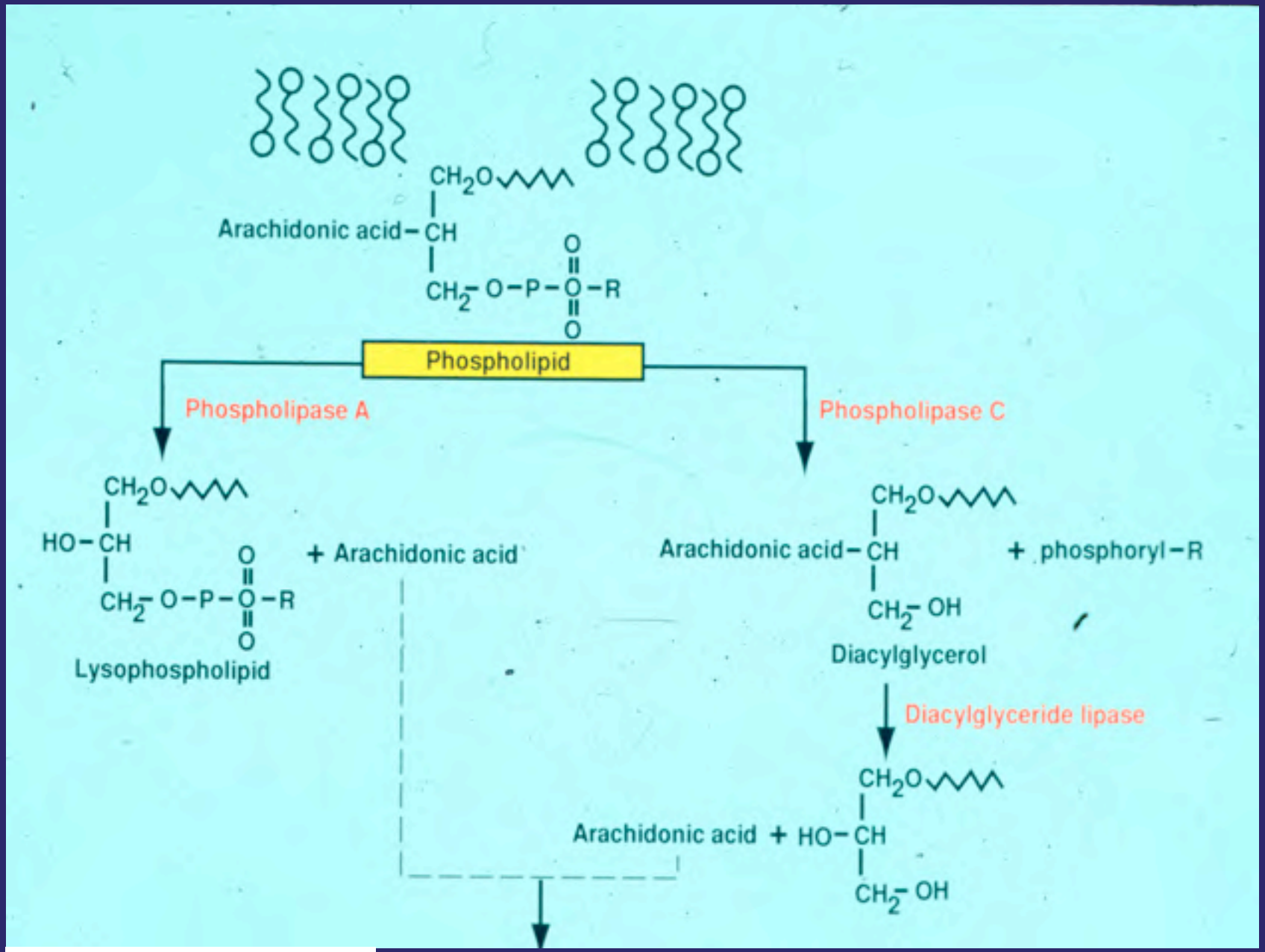
What is Arachidonic Acid?

How And Where Is Arachidonic Acid Generated?



Lipid Mediators of Inflammation

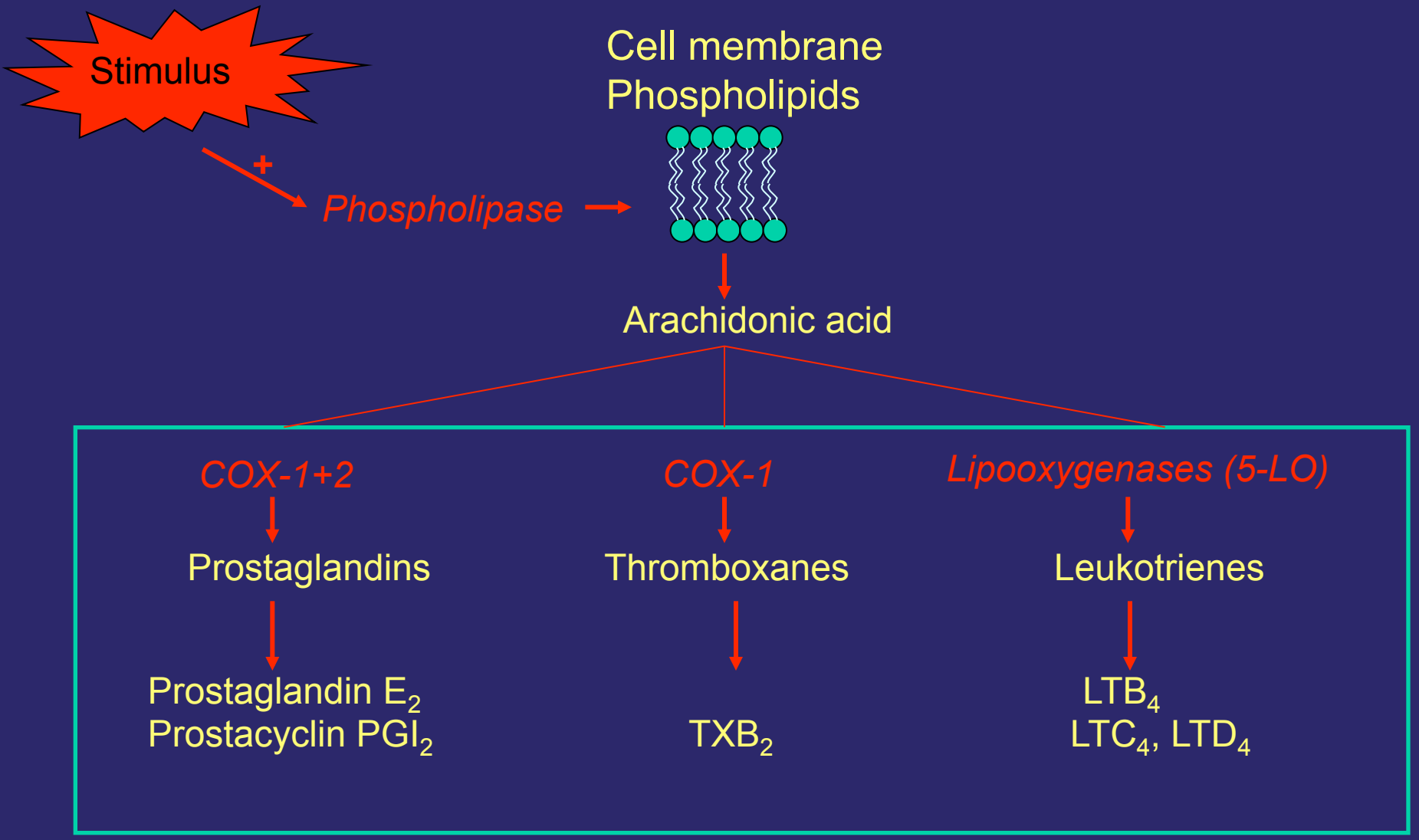


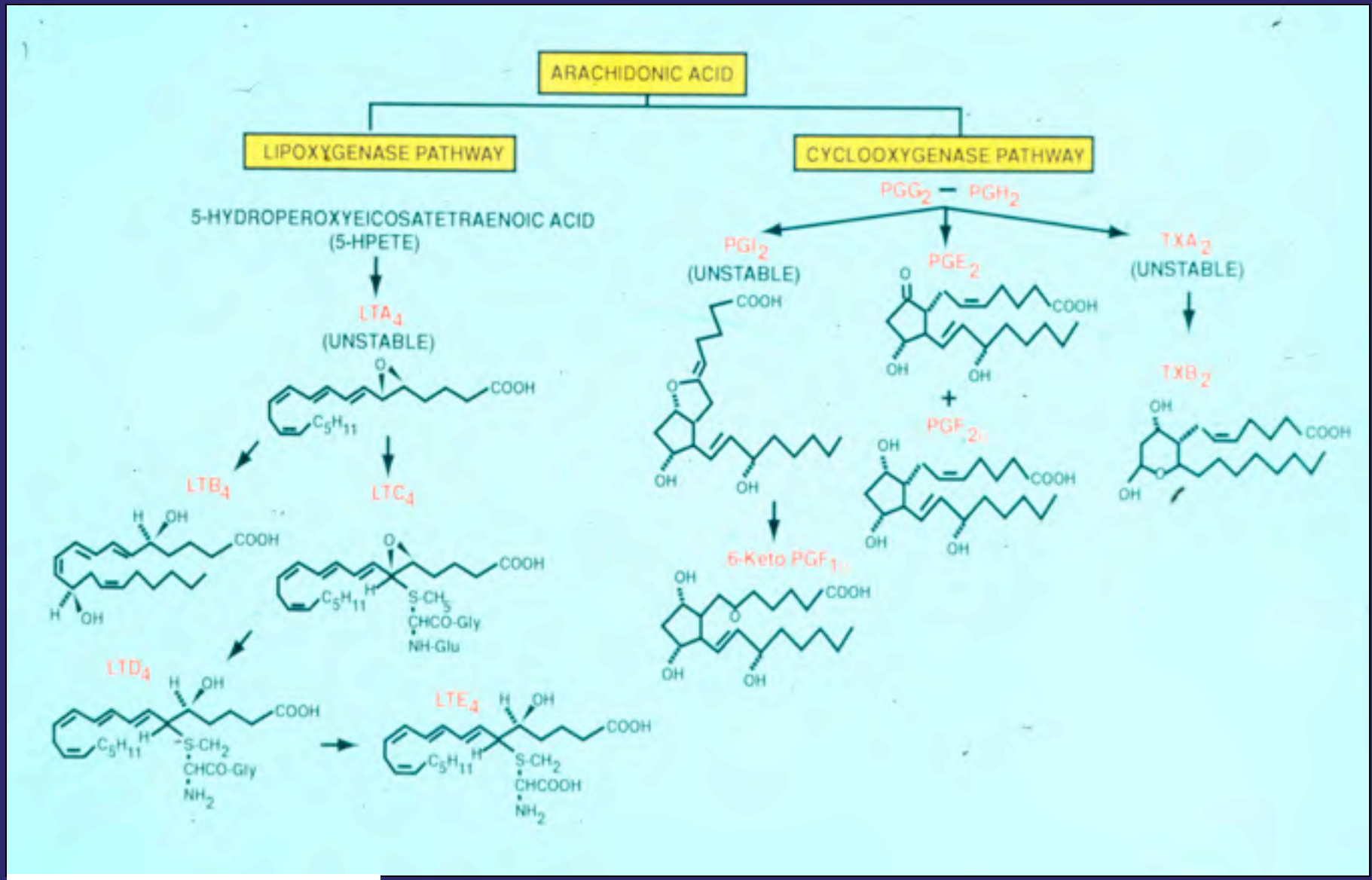


What are the primary products derived from arachidonic acid?

- Cyclooxygenase (COX)
- Lipoxygenase (LO)

Acute inflammation: lipid mediators





CELL SPECIFICITY OF ARACHIDONIC ACID-DERIVED PRODUCTS

CELL	PRODUCT
Neutrophils	Leukotrienes
Macrophage/Monocyte	Prostaglandins + Leukotrienes
Platelets	Thromboxane
Endothelial Cells	Prostacyclin

In Vivo Effects of Arachidonic Acid Derived Products: Regulates

- **Thermostatic Set Point (Fever)**
- **Pain (Interacts with pain receptors)**
- **Blood Flow**
- **Leukocyte Activity**
- **Platelet Function**

Biological Function of Arachidonic Acid Products

Cyclooxygenase-derived Products:

Prostaglandin E_2/Prostacyclin

Immunoregulatory
- **Inhibits Immune cell activation**
- **Inhibits cytokine production**
- **Inhibits mast cell activation**

Blocks platelet aggregation

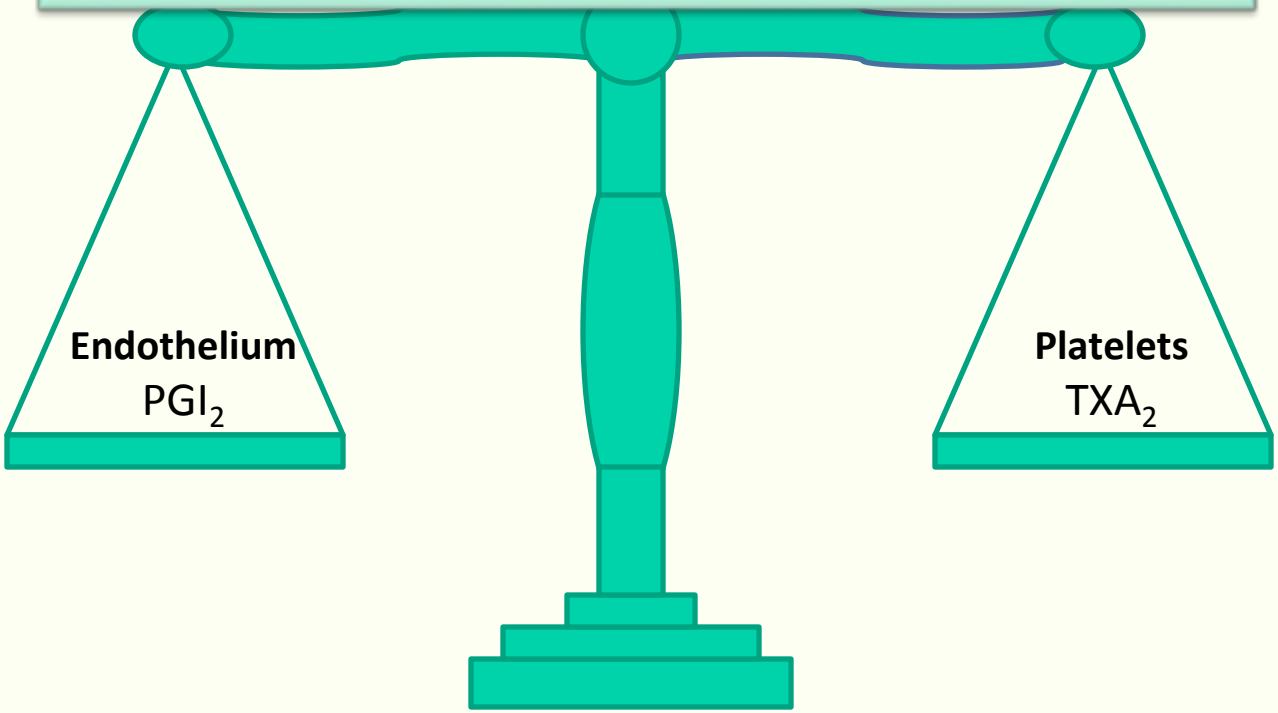
Increases vasodilation

Thromboxane

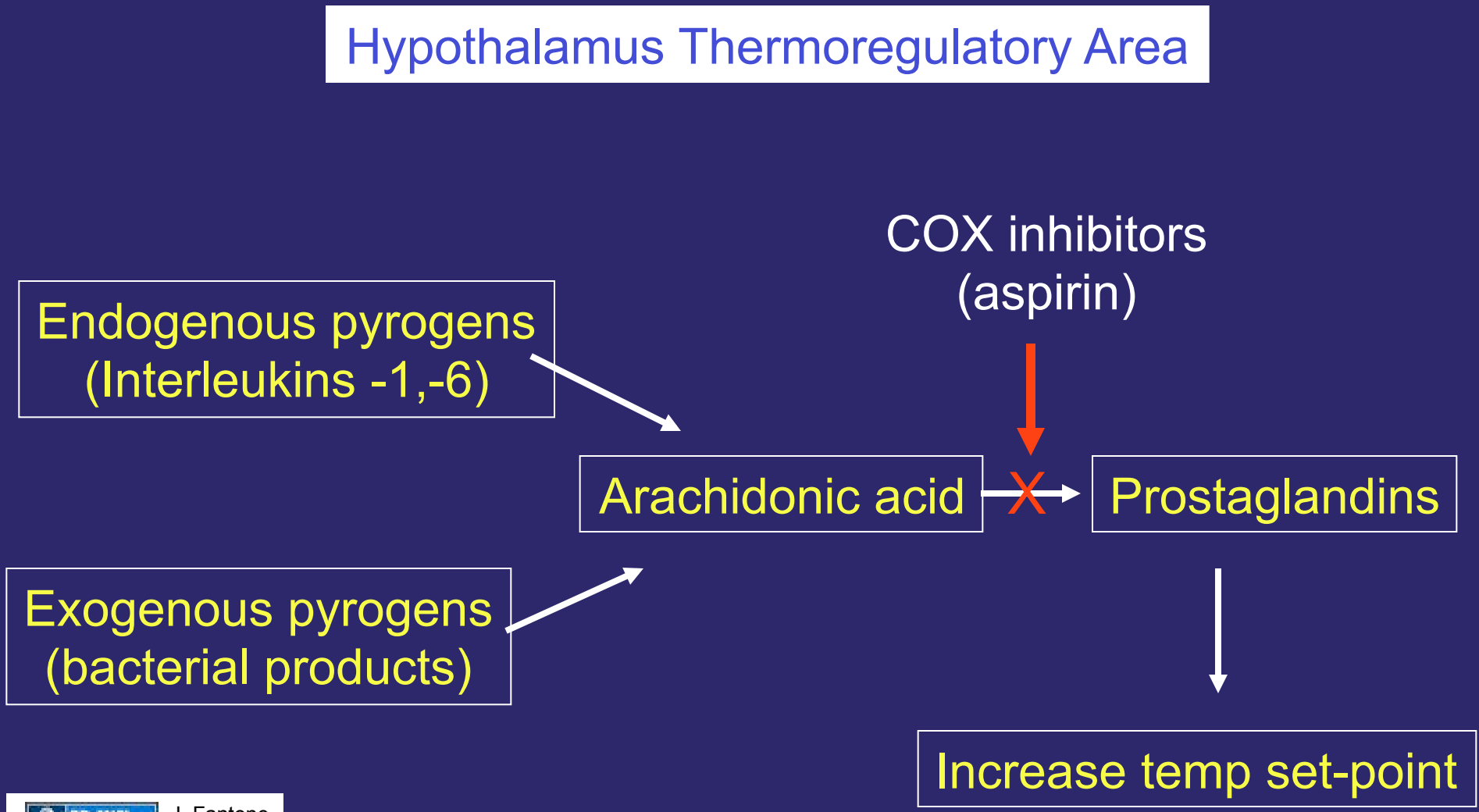
Causes vasoconstriction

Induces platelet aggregation

The Homeostatic Balance



Production of Fever



Biological Function

Lipoxygenase-derived Products:

Leukotriene B_4	**Neutrophil Activation** **- chemotaxis** **- degranulation**
	Mast cell activation **- degranulation**
Leukotriene C,D,E (SRS-A)	**Smooth muscle contraction** **Increase vascular permeability**

Pharmacologic Regulation of Arachidonic Acid-Derived Products: Modulate

- Phospholipase activity:
  - Suppress the release of arachidonic acid (no substrate available)
  - Blocks both COX and LO-derived products
- Cyclooxygenase Activity:
  - Blocks Cyclooxygenase-derived products
  - COX-1 and COX-2 inhibitors
- Specific enzymes down-stream from COX:
  - Thromboxane synthetase inhibitors
- Lipoxygenase activity:
  - Block 5-lipoxygenase enzyme
  - Small molecule receptor antagonists for cysteinyl leukotrienes

Non- Steroidal Anti-Inflammatory Compounds; NSAIDS

- Aspirin (acetysalicylic acid)
- Ibuprofen (propionic acid derivatives)
- Indomethacin (indole derivatives)
- Tylenol (acetominophen)
- COX-2 Inhibitors (Vioxx, celebrex, Bextra)

COX-2 Inhibitors

- CELEBREX (Celecoxib) Pfizer-(Pharmacia)
- BEXTRA (Valdecoxib) Pfizer
- VIOXX (Rofecoxib) Merck

Osteoarthritis

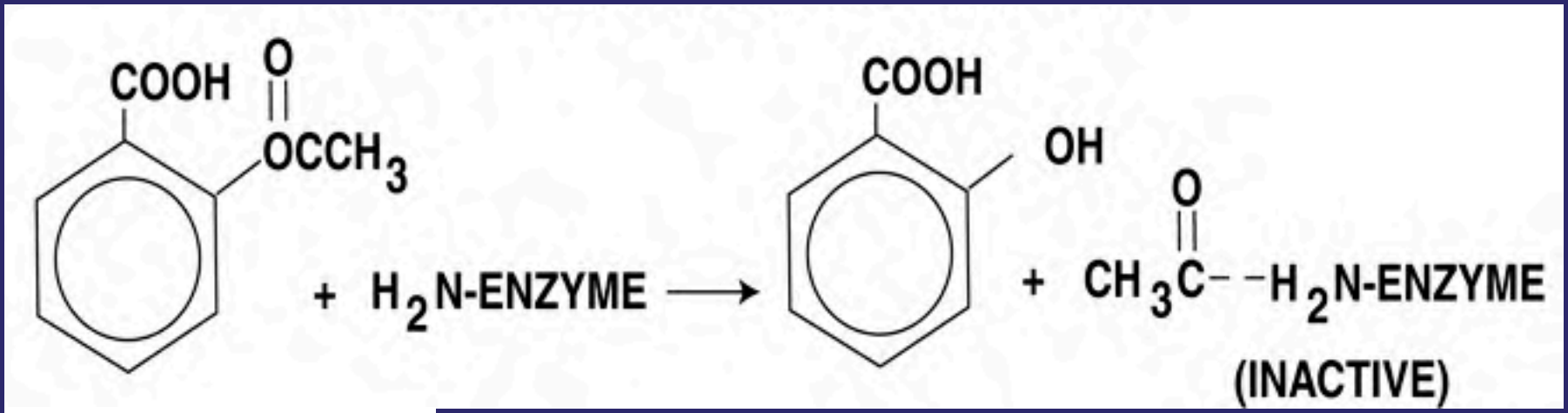
Rheumatoid arthritis

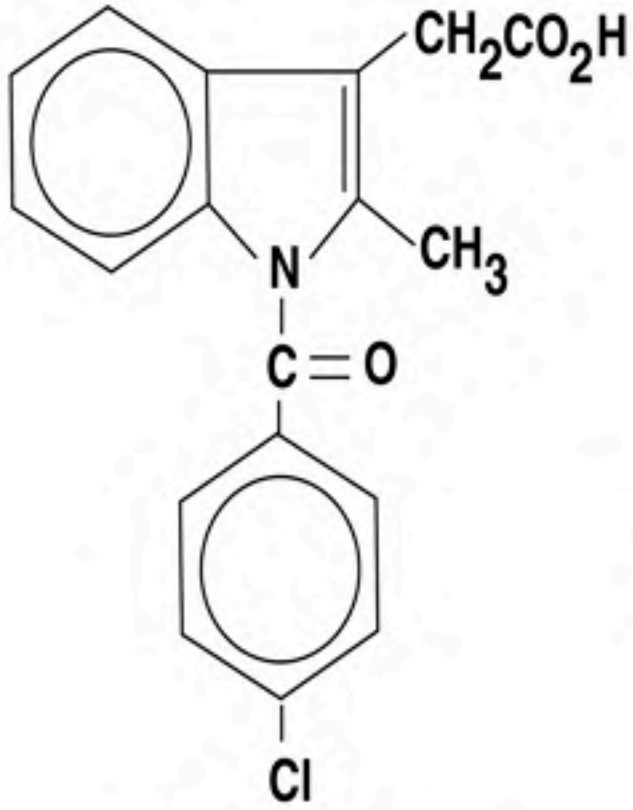
Primary dysmenorrhea

Pain management

Aspirin

- Irreversible inhibition of cyclooxygenase
- Acetylates active site of enzyme
- Decreased production of products (e.g. prostaglandins, prostacylcins & thromboxanes)



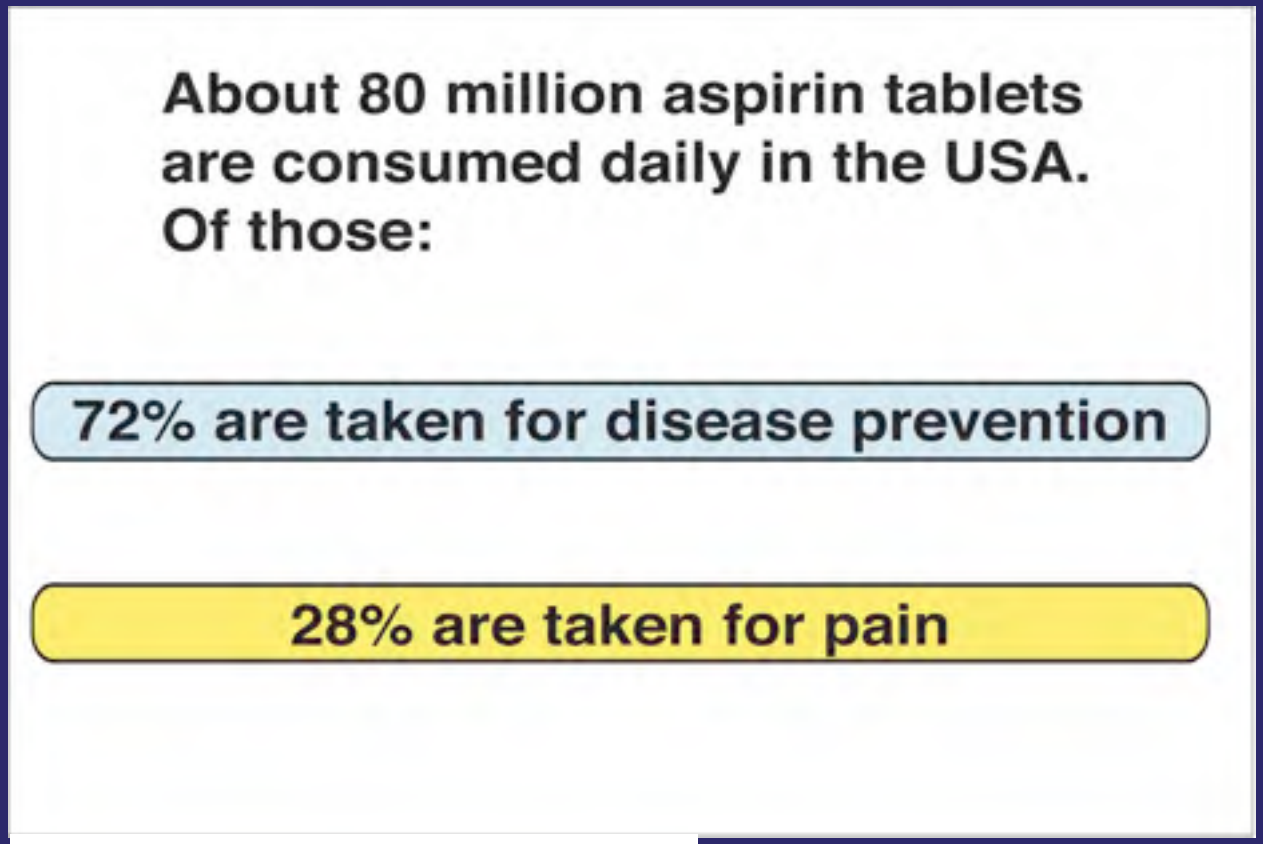


INDOMETHACIN

IBUPROFEN

NSAIDS: Inhibit cyclooxygenase: reversible binding to active site of enzyme

AN ASPIRIN A DAY



The Homeostatic Balance

Aspirin Anti-thrombogenic Activity

- Inhibits platelet aggregation; blocks platelet-derived thromoboxane production

- Blocks platelet cyclooxygenase for the life of the platelet; no new protein synthesis

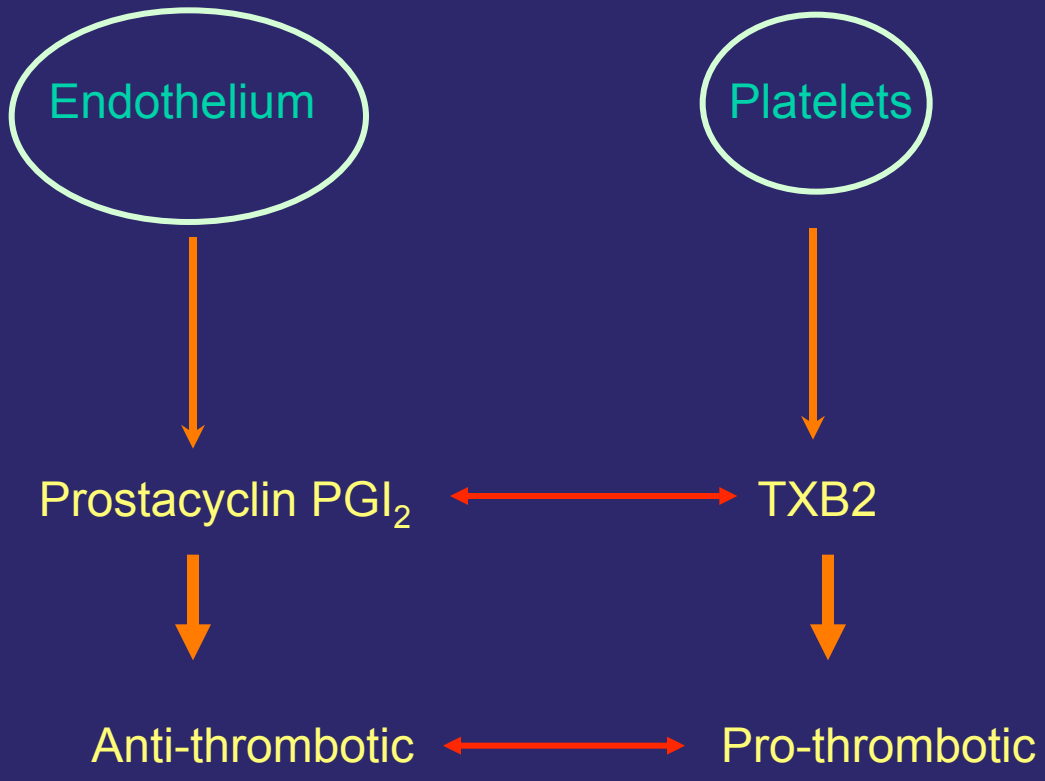
- Blocks endothelial cell-derived prostacyclin

- Suppression of endothelial cell-derived prostacyclin is short lived as endothelial cells can generation new cyclooxygenase enzyme

- Platelet activity is blocked more than endothelial cell activity

Acute inflammation: lipid mediators

An important role in vascular homeostasis



Acute inflammation: lipid mediators

Therapeutic targets

Endothelium

Platelets

Aspirin
inhibits COX-2 irreversibly

All cells but the platelet can resynthesize the enzymes

Aspirin
inhibits COX-1 irreversibly

Prostacyclin PGI_2 ↔ TXB2

Pro-thrombotic

Anti-thrombotic

Acute inflammation: lipid mediators

Therapeutic targets

Endothelium

Platelets

COX-2

COX-1

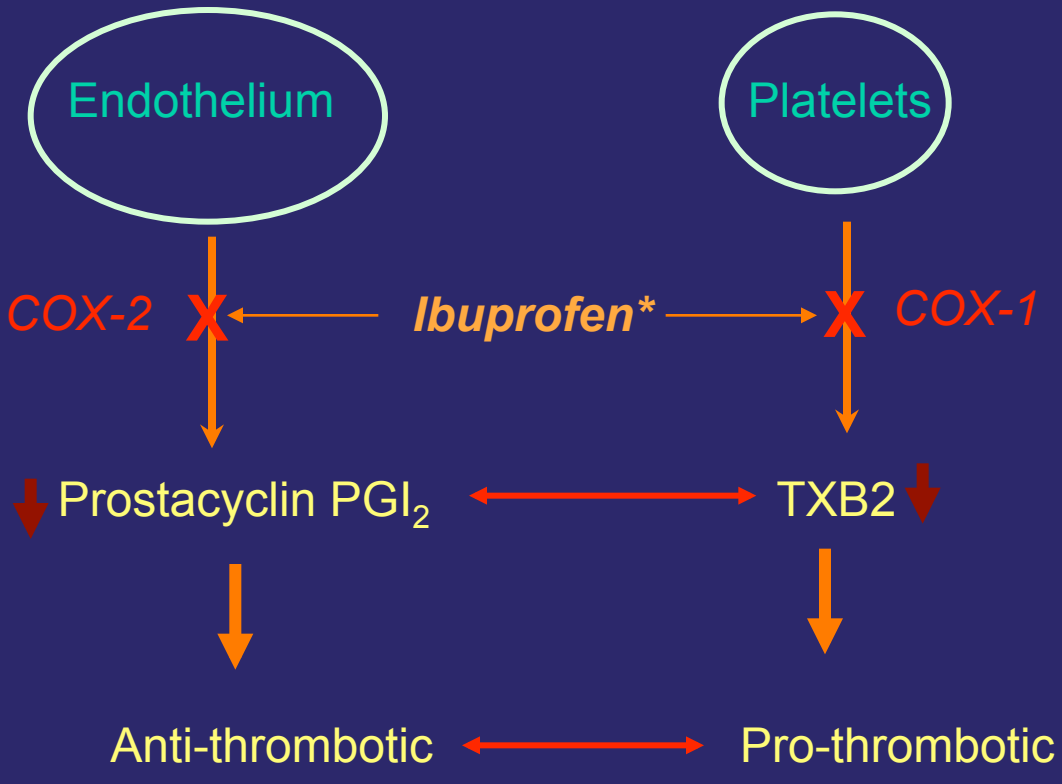
Prostacyclin PGI_2 ⟷ TXB2

Anti-thrombotic ⟷ Pro-thrombotic

NSAIDs inhibit both COX-1 and COX-2; COXIBs inhibit COX-2

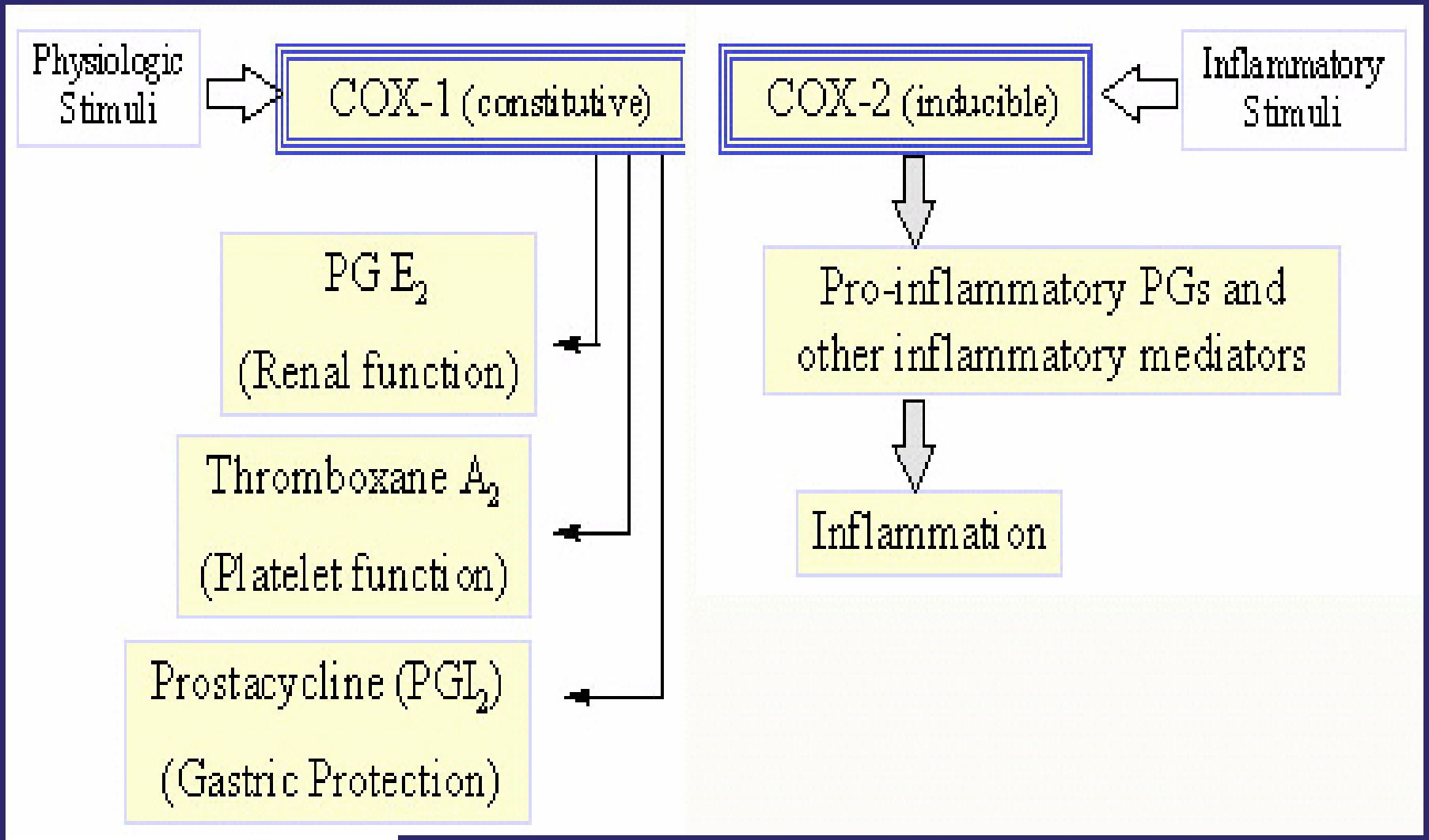
Acute inflammation: lipid mediators

Therapeutic targets



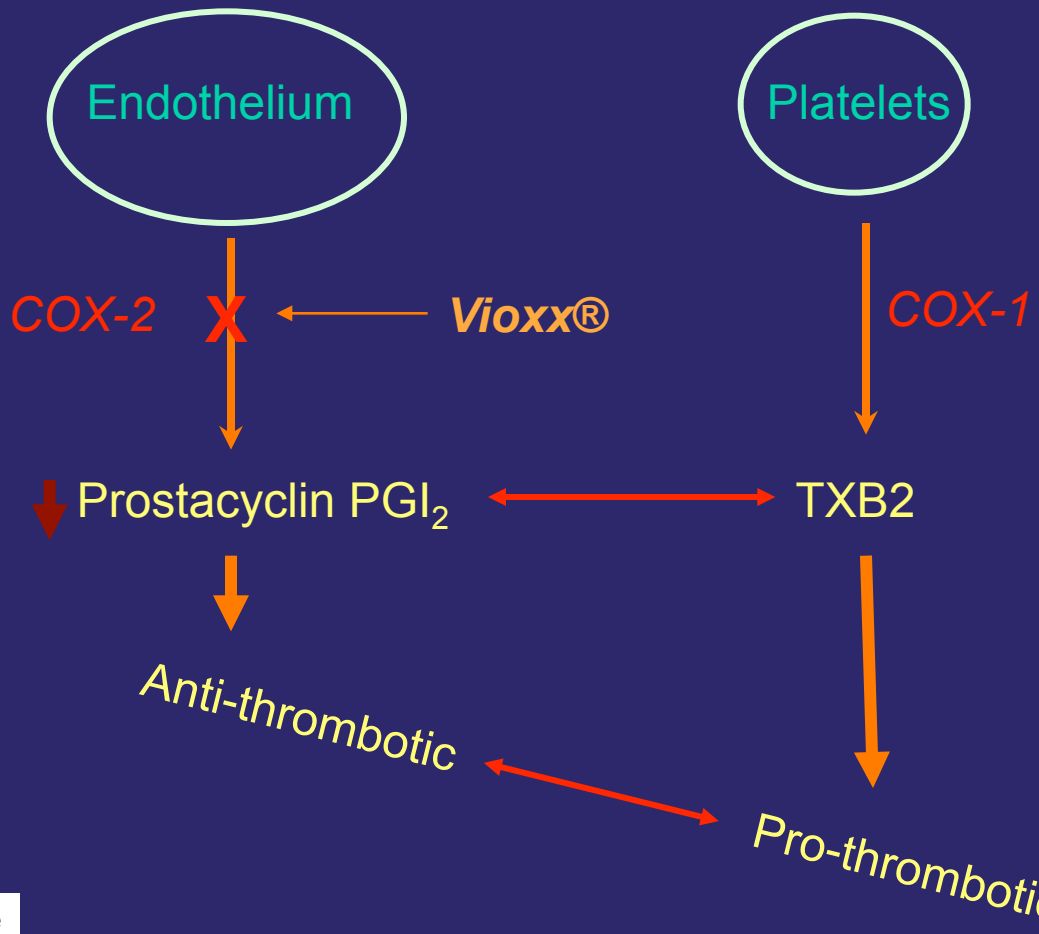
* Classical NSAID, it inhibits both COX enzymes

COX-2 inhibitors work by blocking COX-2 enzyme which is involved ingastrointestinal toxicity is reduced the inflammation pathway. By sparing COX-1



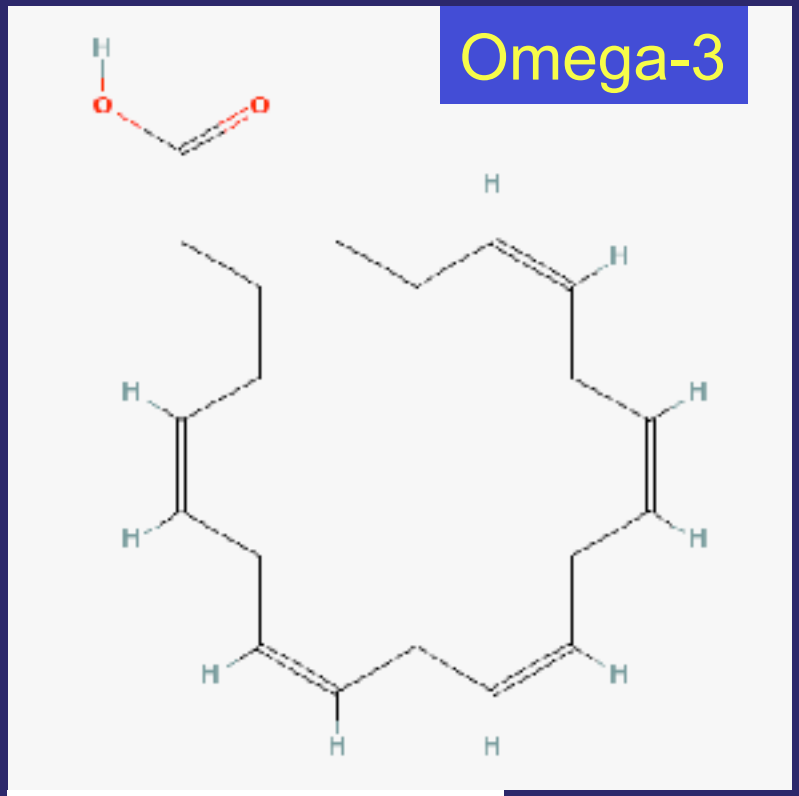
Acute inflammation: lipid mediators

Therapeutic targets



Fish Oil: Protective Effects

Eicosapentanoic Acid



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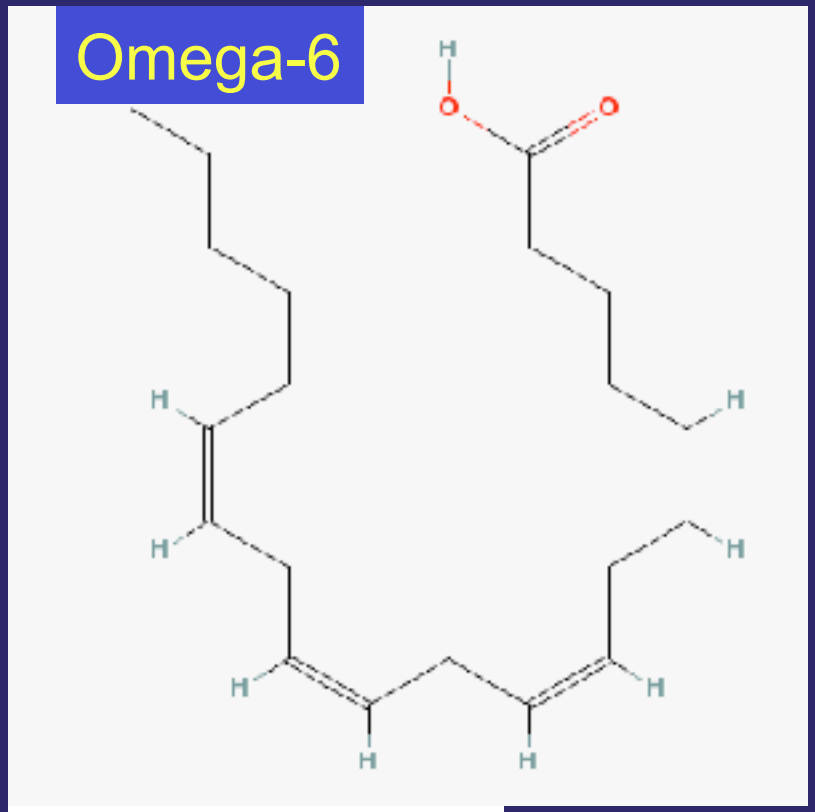
Arachidonic Acid



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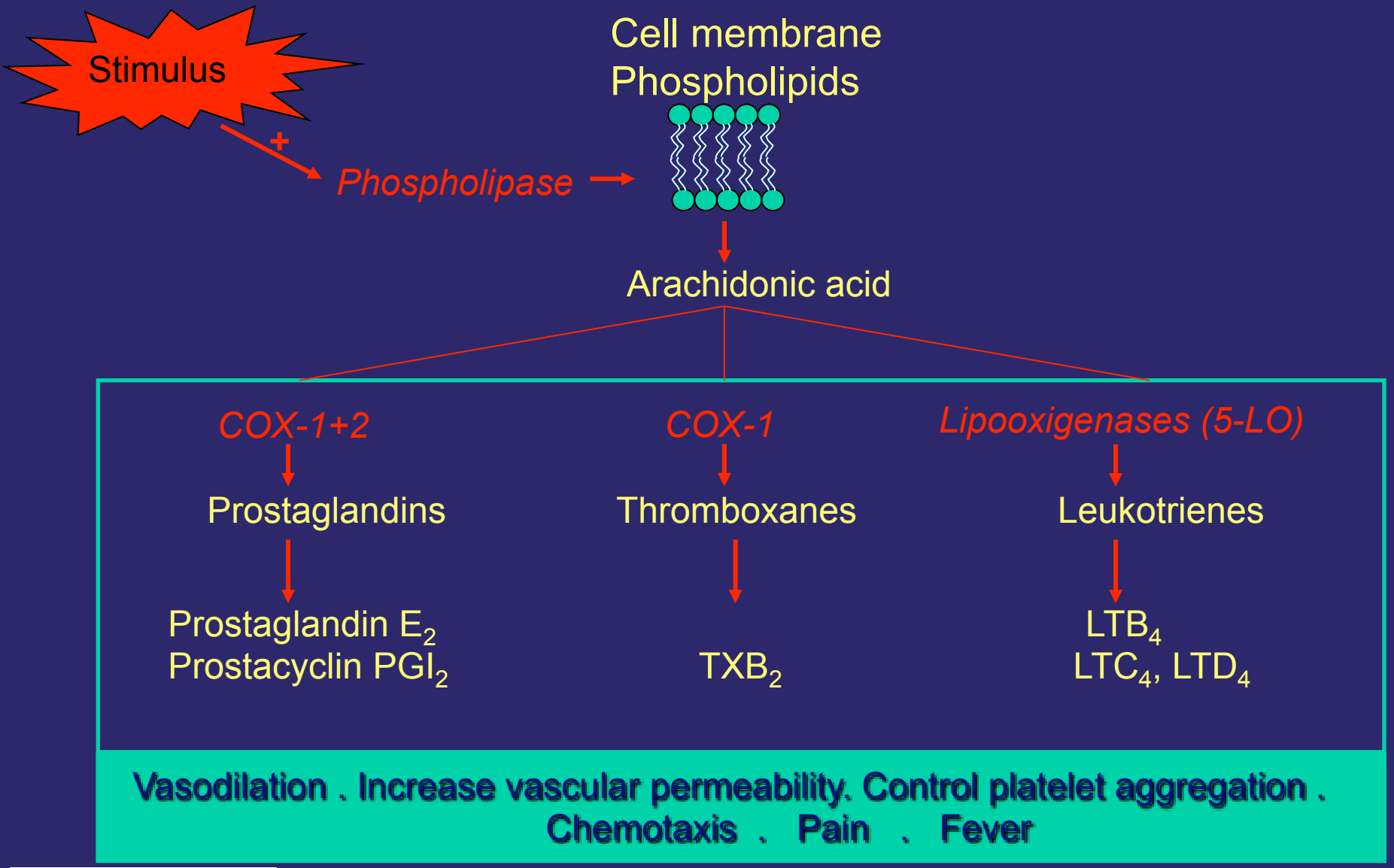
Acute inflammation: lipid mediators



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