CHEMICAL MEDIATORS OF ACUTE INFLAMMATION

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Learning objectives:

- By the end of this lecture student should be able to;
- Describe chemical mediators of acute inflammation
- Enumerate cell derived mediators and cell producing those mediators
- Discuss in detail, the cell derived mediators.

Definition:

- Any chemical that acts on blood vessels, inflammatory cells, or other cells to help in initiating an inflammatory response.
- Mediators may be produced by cells at the site of inflammation or they may be synthesized by the liver and released in plasma as inactive precursors.

- Mediators can be

A. Cell derived mediators:

B. Plasma derived mediators:

A. Cell derived mediators:

- Cells from which the mediators are derived include.

1. Tissue macrophages
2. Dendritic cells
3. Mast cells
4. Endothelial cells
5. Neutrophils recruited to site of inflammation
6. Platelets

The mediators produced by these cells are.

1. Vasoactive amines
2. Arachidonic acid metabolites.
3. Platelet activating factor.
4. Cytokines and Chemokines.
5. Free radicals (ROS and NO)
6. Lysosomal enzymes.

B. Liver/Plasma derived mediators:

1. Complement system
2. The Kinin system
3. The clotting system
4. Fibrinolytic system

1. Vasoactive Amines:

a. Histamine:

- Histamine is produced by many cells, particularly mast cells adjacent to vessels, as well as circulating basophils and platelets.
- Preformed and stored in mast cell granules.
- Released after degranulation

- Stimuli for degranulation are;
- Physical (trauma, heat, cold etc.)
- Antibodies attached to mast cells
- Aanaphylatoxins C3a and C5a, products of complement system.
- Antibodies and anaphylatoxins bind to mast cell surface and cause degranulation.

- Functions:
- Histamine causes arteriolar dilation and vascular permeability (post capillary venules) by causing endothelial cells contraction leading to increase in interendothelial gaps.
- Performs its function by binding to H1 receptors.
- Soon after its release, histamine is inactivated by histaminase.

b. Serotonin (5-hydroxytryptamine):

- Also a preformed vasoactive mediator with effects similar to those of histamine.
- More potent than Histamine.
- Found primarily within platelet .
- Also present in neuroendocrine cells of GIT
- Act as neurotransmitter in GIT.

2. Arachidonic Acid (AA) Metabolites:

- They are Prostaglandins, Leukotrienes, and Lipoxins.
- They can mediate virtually every step of inflammation.
- Leukocytes, mast cells, endothelial cells, and platelets are the major sources of AA metabolites in inflammation.
- AA is a 20-carbon fatty acid and present mainly as a component of cell membrane lipids.

- Released from these phospholipids due to cellular phospholipases (Phospholipase A2).
- Phospholipases are activated by mechanical, chemical, or physical stimuli.
- AA metabolites also called Eicosanoids.
- In Greek, Eicosa=20

- AA metabolism proceeds along one of two major enzymatic pathways.

1. Cyclooxygenase pathway
2. Lipoxygenase pathway

- Cyclooxygenase pathway:
- Cyclooxygenase (COX) is an enzyme that acts on arachidonic acid to produce prostaglandin E_2 (PGE_2),

$PGF_{2\alpha}$, PGD_2, PGI_2 (prostacyclin), and thromboxane A_2 (TXA_2).

- PGD_2 is the major metabolite of the cyclooxygenase pathway in mast cells.
- PGs are produced by mast cells, macrophages, endothelial cells, and many other cells.

- Prostaglandins cause

1. Vasodilation
2. Fever
3. Pain

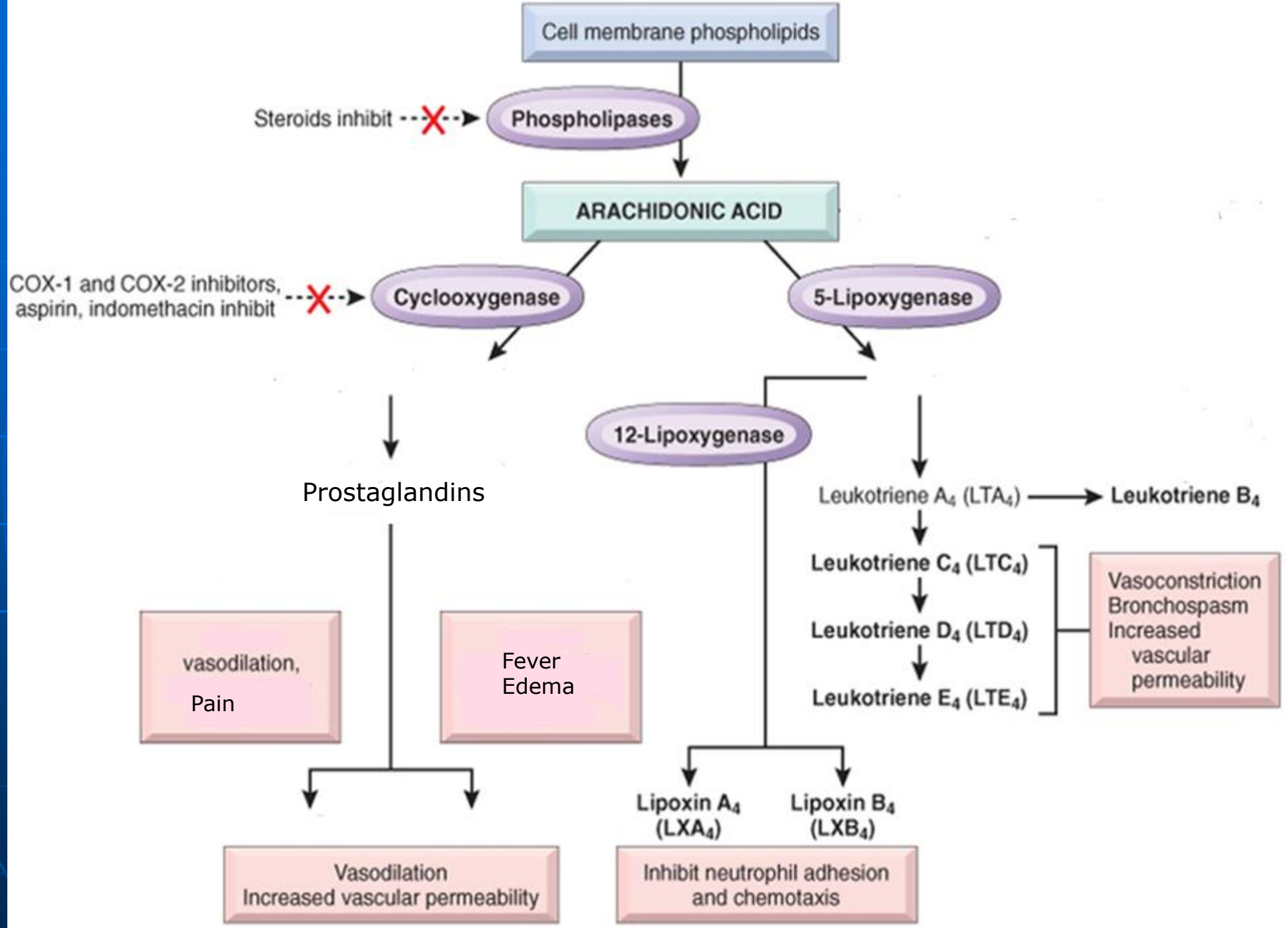
- There are two COX enzymes, COX1 and COX2.
- COX1 present in almost all tissues.
- COX2 present in mast cells, endothelial cells and platelets.

- COX1 is associated with electrolyte balance and GIT cytoprotection.
- So blocking COX2 alone spares beneficial effects of COX1.
- NSAIDs block both enzymes
- COX2 only inhibitors have been developed and are in use.

- Lipoxygenase pathway:
- 5-Lipoxygenase is the predominant AA-metabolizing enzyme in neutrophils.
- It acts on Arachidonic acid and converts it into Leukotriens which include LTA4, LTB4,LTC4,LTD4 and LTE4.
- Leukotriens cause.

1. Chemotaxis
2. Increase vascular permeability
3. Brochospasm.

- Lipoxins are produced by Arachidonic acid due to action of 12-lipoxygenase enzyme.
- Lipoxins function mainly as inhibitors of inflammation.
- They actually inhibit neutrophil chemotaxis and their adhesion to endothelium.
- Important lipoxins include Lipoxin A_4 and Lipoxin B_4


Cell membrane phospholipids
Steroids inhibit
Phospholipases
ARACHIDONIC ACID
COX-1 and COX-2 inhibitors, aspirin, indomethacin inhibit
Cyclooxygenase
5-Lipoxygenase
12-Lipoxygenase
Prostaglandins
Leukotriene A4 (LTA4)
Leukotriene B4
Leukotriene C4 (LTC4)
Leukotriene D4 (LTD4)
Leukotriene E4 (LTE4)
Vasoconstriction
Bronchospasm
Increased vascular permeability
vasodilation,
Pain
Fever
Edema
Lipoxin A4 (LXA4)
Lipoxin B4 (LXB4)
Vasodilation
Increased vascular permeability
Inhibit neutrophil adhesion and chemotaxis

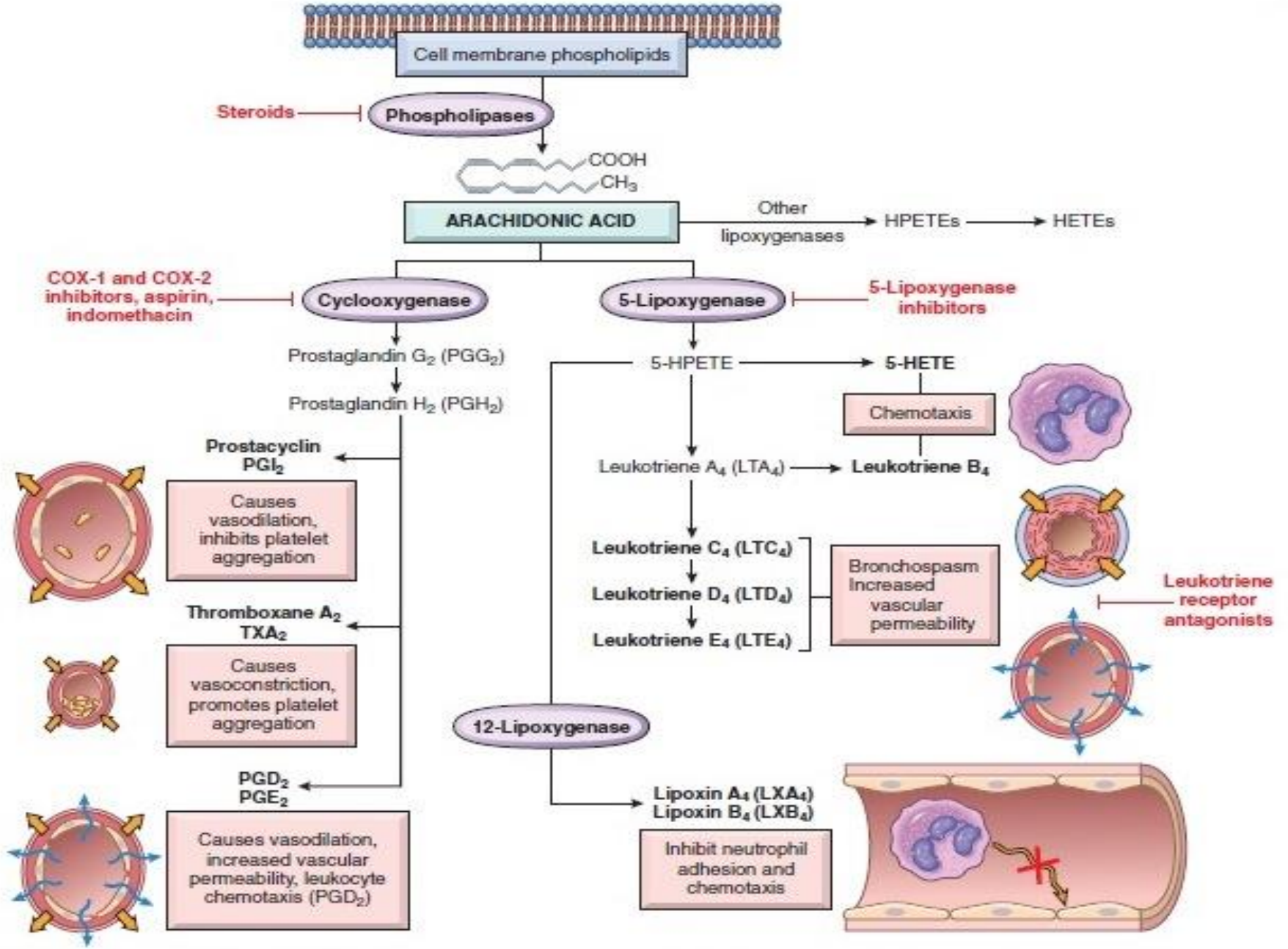


Figure 3.10 Production of arachidonic acid metabolites and their roles in inflammation. Note the enzymatic activities whose inhibition through pharmacologic intervention blocks major pathways (denoted with a red *X*). *COX-1, COX-2,* Cyclooxygenase 1 and 2; *HETE,* hydroxyeicosatetraenoic acid; *HPETE,* hydroperoxyeicosatetraenoic acid.

3. Platelet-Activating Factor:

- Platelet-activating factor (PAF) is another phospholipid-derived mediator.
- PAF is generated from the membrane phospholipids of neutrophils, monocytes, basophils, endothelial cells, and platelets by the action of phospholipase A2.
- It causes platelets aggregation, causes vasoconstriction and bronchoconstriction.
- Induces vasodilation and vascular permeability at low conc.

4.Cytokoines:

- Cytokines are polypeptides that are produced by many cell types.
- Important cytokines are Interleukines (abbreviated as IL and numbered like IL1, IL2 etc) and Tumor Necrosis factor
- Out of these main cytokines are IL1 and TNF

- TNF and IL-1 are produced by activated macrophages as well as mast cells, dendritic cells and endothelial cells.
- Their secretion is stimulated by microbial products and tissue breakdown products.
- Known as master cytokines.
- Functions of IL-1 and TNF : The principal role of these cytokines is endothelial activation.

- Both TNF and IL-1 stimulate the expression of adhesion molecules on endothelial cells.
- Help microbial products to stimulate neutrophils and macrophages.
- Stimulate production of other cytokines.
- Although TNF and IL-1 are secreted by macrophages and other cells at sites of inflammation, they may

enter the circulation and act at distant sites to induce the systemic acute-phase reaction.

- It is often associated with infection and inflammatory diseases.
- The features of this reaction are.

1. Fever
2. Lethargy (weakness)
3. Cachexia
4. Synthesis of acute phase proteins by liver (CRP and others).

5. Neutrophil and ACTH release into circulation

- TNF antagonists are of help in chronic inflammatory conditions (RA, Psoriasis etc.).

5. Chemokines:

- Chemokines are a family of small (8 to 10 kDa) proteins
- Act as chemoattractants for leukocytes.
- Because chemotactic cytokines hence called so.
- About 40 different chemokines and 20 different receptors for chemokines have been identified

- Classified into four major groups, according to the arrangement of cysteine (C) residues.
- C-X-C chemokines e.g. IL8 (now CXCL8)
- C-C chemokines
- C chemokines
- CX_3 chemokines

6. Free radicals:

a. Reactive Oxygen Species:

- Reactive Oxygen Species (ROS) are synthesized via the NADPH oxidase pathway and are released from neutrophils and macrophages after they are activated by microbes etc.
- They include superoxide($0^{\cdot -}_2$) Hydrogen peroxide(H_2O_2) and $OH^{\cdot -}$

- The ROS in lysosomes function to destroy phagocytosed microbes.
- When secreted at low levels, ROS can increase levels of cytokines.
- At higher levels they cause endothelial cell damage and therefore increased vascular permeability.

b. Nitric oxide:

- NO is a soluble gas produced by many cells
- NO causes.

1. Relaxation of vascular smooth muscle (vasodilation).
2. Inhibition of platelet activation
3. Act as a microbicidal agent in activated macrophages.

7. Lysosomal enzymes:

- They are proteolytic enzymes and others substances present in lyosomes.
- Play role in microbial killing and tissue injury.
- Main enzymes include collagenase, elastase, hydrolases and lysozyme.