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# ARACHIDONIC ACID METABOLITES IN INFLAMMATION

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10-11:00am

## **Intended Learning Outcomes:**

1. Understand the major inflammatory mediators derived from the metabolism of arachidonic acid including their primary cellular source and biological activity.
2. Understand the effects of nonsteroidal anti-inflammatory compounds on blocking the production of arachidonic acid metabolites during disease ( including COX-1 versus COX-2 inhibitors).
3. Understand the 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.

## **Glossary:**

**Phospholipase:** An enzyme found in the membrane of cells. When activated this enzyme can cleave specific chemical moieties of phospholipids. (Phospholipase A: cleaves at the #2 position of a phospholipid and releases the fatty acid found in that position and generates a lysophospholipid. Phospholipase C: cleaves at the #3 position and releases a phosphoryl-R group and generates diacylglycerol)

**Cyclooxygenase (COX):** A major enzyme of the cascade that metabolizes arachidonic acid. This enzyme metabolizes arachidonic acid to a common lipid intermediate, which can be further metabolized to different biologically important mediators depending upon the specific inflammatory cell. Cyclooxygenase's enzymatic activity is blocked by nonsteroidal anti-inflammatory drugs. There are 2 types of COX (1 and 2) COX-1 appears to be important in many normal physiologic responses, while COX-2 appears to be important in inflammation.

**Lipoxygenase:** Another major enzyme of the cascade that metabolizes arachidonic acid. There are a number of different lipoxygenase enzymes, however one of the more important is the 5-lipoxygenase. This enzyme is important for the synthesis of various leukotrienes.

**Thromboxane (TX):** A major arachidonic acid metabolite of platelets, that is synthesized first via the cyclooxygenase pathway, resulting in a common lipid intermediate and then by thromboxane synthetase to generate thromboxane. It is a powerful platelet aggregating agent.

**Prostacyclin (PGI):** A major arachidonic acid metabolite of endothelial cells, that is synthesized first via the cyclooxygenase pathway, resulting in a common lipid intermediate and then by prostacyclin synthetase to generate prostacyclin. It is a powerful inhibitor of platelet aggregation.

**Prostaglandin (PG):** An arachidonic acid metabolite produced by a number of different cells; however, with regards to inflammation, the macrophage is an important source of this lipid

mediator. It is synthesized first via the cyclooxygenase pathway, resulting in a common lipid intermediate and then by prostaglandin synthetase to generate prostaglandin. This lipid mediator is involved in regulating the immune/inflammatory system.

**Leukotrienes (LT):** An arachidonic acid metabolite produced by a number of different cells; however, with regards to inflammation, neutrophils (LTB<sub>4</sub>) and mast cells and macrophages (LTC<sub>4</sub>) are cellular sources. It is synthesized via the lipoxygenase pathway. LTB<sub>4</sub> is involved in leukocyte trafficking (chemotaxis) and LTC<sub>4</sub> is involved in smooth muscle contraction.

**Nonsteroidal anti-inflammatory drugs (NSAID):** A group of pharmacological agents that can block the ability of the cyclooxygenase enzyme to metabolize arachidonic acid. This action in turn blocks the production of all downstream arachidonic acid metabolites.

### LIPID MEDIATORS OF INFLAMMATION

The importance of this field was recognized with the awarding of the Nobel Prize in physiology and medicine in 1982 to John Vane, Sune Bergstrom, and Bengt Samuelsson for their collective work on the biochemistry and physiologic activities of arachidonic acid metabolites. However, the medicinal mechanism(s) of action of certain plant-derived agents, which were used throughout the ages, was found to exert their effects via altering the metabolism of arachidonic acid (a fatty acid found in the cell membrane). For example, an extract of birch bark was known to possess antipyretic activities and reduce headaches. The active ingredient was salicylic acid; a derivative (acetylsalicylic acid or aspirin) is one of the most commonly used drugs in the world.

Metabolites of arachidonic acid are known to be important in the normal physiology, as they influence the nervous, reproductive, gastrointestinal, and renal system, as well as regulate body temperature and aid in host defense. This discussion will mainly focus on the role of arachidonic acid metabolites during inflammation.

#### A. The Biochemistry of Arachidonic Acid Metabolism

Enzymes:	Phospholipases Cyclooxygenase 1 (Constitutively expressed) Cyclooxygenase 2 (induced during inflammation by various cytokines (IL-1 and TNF)) Lipoxygenase
End Products:	Thromboxane (TXA) Prostacyclin (PGI) Prostaglandin (PGE) Hydroxyeicosatetraenoic acids (HETEs) Leukotrienes

#### B. Cell Specificity for the Generation of Arachidonic Acid Metabolites During Inflammation

Polymorphonuclear Leukocytes (PMNs, neutrophils)  
Leukotriene B<sub>4</sub>, (LTB<sub>4</sub>)

Platelets  
Thromboxane A<sub>2</sub> (TXA<sub>2</sub>)

Endothelial Cells  
Prostacyclin I<sub>2</sub> (PGI<sub>2</sub>)

Mast Cells  
Leukotrienes (LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub>)

Macrophages  
Prostaglandins  
Leukotrienes

### C. Biological Activity of Arachidonic Acid Metabolites Generated During Inflammation

PGI<sub>2</sub> and PGE<sub>2</sub>

inhibits platelet aggregation  
induces vasodilatation  
suppress inflammatory cell activation

TX

induces platelet aggregation  
induces vasoconstriction

LTB<sub>4</sub>

promotes chemotaxis of phagocytic leukocytes (especially PMNs)

LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>

induces contraction of smooth muscle  
increases vascular permeability

### D. In vivo Effects of Arachidonic Acid Metabolites

Fever (PGE)  
Pain (PG)  
Regulate Blood Flow (PG, TXB)

### E. Regulation of Arachidonic Acid Metabolism

Exogenous Regulation

Aspirin – acetylation of cyclooxygenase  
nonsteroidal anti inflammatory drugs – inhibit cyclooxygenase  
ibuprofen  
naproxen

indomethacin  
Vioxx  
Celebrex

Glucocorticoids

#### F. Cardiovascular problems induced by COX-2 inhibitors

Disrupts the balance between the expression of prostacyclin (an anti-thrombotic agent) and thromboxane (a pro-thrombotic agent).

#### G. Aspirin Therapy as an Antithrombogenic Agent

Aspirin blockade of cyclooxygenase enzyme in platelets as compared to endothelial cells

#### H. Omega-3 fatty acids and Cardiovascular Disease

Diets high in fish oil (omega 3 fatty acids) lower incidence of heart disease?