2008-09

M1 - Immunology, Winter 2008

Fantone, J.; Pietropaolo, M. T.

Unless otherwise noted, the content of this course material is licensed under a Creative Commons Attribution – NonCommercial - Share Alike 3.0 License.

Copyright 2007, Joseph Fantone.

The following information is intended to inform and educate and is not a tool for self-diagnosis or a replacement for medical evaluation, advice, diagnosis or treatment by a healthcare professional. You should speak to your physician or make an appointment to be seen if you have questions or concerns about this information or your medical condition. You assume all responsibility for use and potential liability associated with any use of the material.

Material contains copyrighted content used in accordance with U.S. law. Copyright holders of content included in this material should contact open.michigan@umich.edu with any questions, corrections, or clarifications regarding the use of content. The Regents of the University of Michigan do not license the use of third party content posted to this site unless such a license is specifically granted in connection with particular content objects. Users of content are responsible for their compliance with applicable law. Mention of specific products in this recording solely represents the opinion of the speaker and does not represent an endorsement by the University of Michigan.

Viewer discretion advised. Material may contain medical images that may be disturbing to some viewers.
ARACHIDONIC ACID METABOLITES IN INFLAMMATION

J. Fantone, M.D.
2/12/08
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 block 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 lipoxygenases 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 (LTB4) and mast cells and macrophages (LTC4) are cellular sources. It is synthesized via the lipoxygenase pathway. LTB4 is involved in leukocyte trafficking (chemotaxis) and LTC4 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 B4, (LTB4)

Platelets
   Thromboxane A2 (TXA2)

Endothelial Cells
   Prostacyclin I2 (PGI2)

Mast Cells
   Leukotrienes (LTC4, LTD4, LTE4)

Macrophages
   Prostaglandins
   Leukotrienes

C. Biological Activity of Arachidonic Acid Metabolites Generated During Inflammation

PGI2 and PGE2
   inhibits platelet aggregation
   induces vasodilatation
   suppress inflammatory cell activation

TX
   induces platelet aggregation
   induces vasoconstriction

LTB4
   promotes chemotaxis of phagocytic leukocytes (especially PMNs)

LTC4, LTD4, and LTE4
   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
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?