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

Copyright 2008, 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 and Inflammation

Joseph Fantone, M.D.
Host Defense 2/12  10-11:00am
INFLAMMATORY MEDIATORS

PLASMA DERIVED
- COMPLEMENT CASCADE
  C3a, C5a
- COAGULATION CASCADE
  Thrombin, plasmin

CELL-DERIVED
- VASOACTIVE AMINES
  histamine, serotonin
- OXYGEN METABOLITES
  hydrogen peroxide (H$_2$O$_2$)
  superoxide anion (O$_2^-$)
  hypochlorous acid (HOCl$^-$)
- ARACHIDONIC ACID METABOLITES
  cyclooxygenase-derived
  lipoxygenase-derived
- CYTOKINES
  Interleukins
  Chemokines
  Interferons
  Tumor Necrosis Factor
  Growth Factors
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.
YOU ARE WHAT YOU EAT
Arachidonic acid

Phospholipid

Phospholipase A

Lysophospholipid

Phospholipase C

Arachidonic acid + Arachidonic acid

Diacylglycerol

Diacylglyceride lipase

Cyclooxygenase 1 + Lipoxigenase Products

Cyclooxygenase 2
Leukotriene Synthesis

Arachidonic Acid → 5-HPETE → Leukotriene A (LTA) → Leukotriene B (LTB) → Leukotriene C (LTC) → Leukotriene D (LTD)

Lipoxygenase

Glutathione-S-transferase
# Cell Dependent End-Product Specificity of Arachidonic Acid-Derived Products

<table>
<thead>
<tr>
<th>CELL</th>
<th>PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>Leukotrienes</td>
</tr>
<tr>
<td>Macrophage/Monocyte</td>
<td>Prostaglandins +</td>
</tr>
<tr>
<td></td>
<td>Leukotrienes</td>
</tr>
<tr>
<td>Platelets</td>
<td>Thromboxane</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>Prostacyclin</td>
</tr>
</tbody>
</table>
Biological Function

Cyclooxygenase-derived Products:

Prostaglandin $E_2$/Prostacyclin
- Immunoregulatory
  - Inhibits immune cell activation
  - Inhibits cytokine production
  - Inhibits mast cell activation
- Blocks platelet aggregation
- Increases vasodilation
- Stimulates adenylate cyclase

Thromboxane
- Causes vasoconstriction
- Induces platelet aggregation
Biological Function

Lipoxygenase-derived Products:

Leukotriene $B_4$  
Neutrophil Activation  
- degranulation

Mast cell activation  
- degranulation

Leukotriene C,D,E  
(SRS-A)  
Causes smooth muscle contraction  
Increases vascular permeability
In Vivo Effects of Arachidonic Acid Derived Products

• Regulates Thermostatic Set Point (Fever)
• Regulates Pain (Interacts with pain receptors)
• Regulates Blood Flow
• Regulates Leukocyte Activity
Hypothalamus

Production of Fever

Viruses → Bacteria → Toxins

Activated leukocytes → Endogenous pyrogen

Phagocytic leukocytes

Arachidonic Acid → Prostaglandin E2 → Temperature

(e.g. Interleukin-1)

Aspirin NSAIDs

Shivering Sweating Vasomotor tone
Rheumatoid Arthritis distorts joints

Source: http://www.nih.gov/
Chemotactic Activity of LTB4

BY: Greg Luerman

GNU 1.2

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

- **Modulate Cyclooxygenase Activity:**
  - Blocks Cyclooxygenase-derived products
  - COX-1 and COX-2 inhibitors

- **Modulate specific enzymes down-stream from COX:**
  - Thromboxane synthetase inhibitors

- **Modulate lipoxygenase activity:**
  - Block 5-lipoxygenase enzyme
  - Small molecule receptor antagonists for cysteiny1 leukotrienes
Non- Steroidal Anti-Inflammatory Compounds

- Aspirin (acetylsalicylic acid)
- Ibuprofen (propionic acid derivatives)
- Indomethacin (indole derivatives)
- Tylenol (Acetaminophen)
- 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
Complications!!
INHIBITS CYCLO-OXYGENASE ENZYME IRREVERSIBLY BY ACETYLATING THE ENZYME AT THE ACTIVE SITE, THUS THE PRODUCTION OF ENDOPEROXIDES AND THEIR DERIVATIVES, INCLUDING PROSTAGLANDINS, THROMBOXANES, AND PROSTACYCLINS WILL BE INHIBITED.
BOTH INHIBIT CYCLO-OXYGENASE ACTIVITY BY BINDING REVERSIBLY TO THE ACTIVE SITE OF THE ENZYME, THUS BLOCKING THE FORMATION OF PROSTAGLANDINS, THROMBOXANES, AND PROSTACYCLINS.
AN ASPIRIN A DAY

Roughly 80 million aspirin tablets are consumed daily in the USA.
Of those:
  72% are taken for disease prevention
  28% are taken for pain
Reduce the risk of heart attack or stroke with……

Aspirin

BY: Chaval Btasil
http://creativecommons.org/licenses/by-sa/3.0/deed.en
THE HOMEOSTATIC BALANCE

PGI₂
ENDOTHELium

TXA₂
PLATELETS

BY: Gretaz
GNU 1.2
Can Aspirin Act As An Anti-thrombogenic Agent?

- Inhibits platelet aggregation by blocking platelet-derived thromoboxane production

- Blocks platelet cyclooxygenase for the life of the platelet, as no new protein synthesis occurs

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

Physiologic Stimuli → COX-1 (constitutive) → PG E₂ (Renal function)

Thromboxane A₂ (Platelet function)

Prostacycline (PGL₂) (Gastric Protection)

COX-2 (inducible) → Pro-inflammatory PGs and other inflammatory mediators → Inflammation

Inflammatory Stimuli
lipid mediators of Inflammation

Stimulus

+ Phospholipase

Cell membrane
Phospholipids

Arachidonic acid
Acute inflammation: lipid mediators

Stimulus

+ Phospholipase

Cell membrane Phospholipids

Arachidonic acid

COX-1+2
- Prostaglandins
  - Prostaglandin E$_2$
  - Prostacyclin PGI$_2$

COX-1
- Thromboxanes
  - TXB$_2$

Lipooxigenases (5-LO)
- Leukotrienes
  - LTB$_4$
  - LTC$_4$, LTD$_4$
Acute inflammation: lipid mediators

Stimulus

Cell membrane
Phospholipids

Phospholipase

Arachidonic acid

COX-1+2
Prostaglandins
Prostaglandin E\(_2\)
Prostacyclin PGI\(_2\)

COX-1
Thromboxanes
TXB\(_2\)

Lipoxygenases (5-LO)
Leukotrienes
LTB\(_4\)
LTC\(_4\), LTD\(_4\)

Acute inflammation: lipid mediators

An important role in vascular homeostasis

- Prostacyclin PGI$_2$
- TXB2
- Endothelium
- Platelets
- Anti-thrombotic
- Pro-thrombotic
Acute inflammation: lipid mediators

Therapeutic targets

Endothelium

COX-2

Prostacyclin $\text{PGI}_2$

Anti-thrombotic

Platelets

COX-1

$\text{TXB}_2$

Pro-thrombotic

NSAIDs inhibit both COX-1 and COX-2; COXIBs inhibit COX-2
Acute inflammation: lipid mediators

**Prostacyclin PGI\textsubscript{2}**

**TXB\textsubscript{2}**

**Anti-thrombotic**

**Pro-thrombotic**

- **Endothelium**
  - **COX-2**
  - Prostacyclin PGI\textsubscript{2}
  - Anti-thrombotic

- **Platelets**
  - **COX-1**
  - TXB\textsubscript{2}
  - Pro-thrombotic

**Ibuprofen**

*Classical NSAID, it inhibits both COX enzymes*
Acute inflammation: lipid mediators

Endothelium

Prostacyclin PGI₂

Platelets

TXB₂

COX-1

COX-2

Vioxx®

Therapeutic targets

Anti-thrombotic

Pro-thrombotic
Acute inflammation: lipid mediators

**Therapeutic targets**

- **Aspirin** inhibits COX-2 irreversibly
  - **Endothelium**
  - Prostacyclin PGI₂
  - Anti-thrombotic

- Aspirin inhibits COX-1 irreversibly
  - **Platelets**
  - TXB₂
  - Pro-thrombotic

All cells but the platelet can resynthesize the enzymes
PLASMA DERIVED
  • COMPLEMENT CASCADE
    C3a, C5a
  • COAGULATION CASCADE
    Thrombin, plasmin

CELL-DERIVED
  • VASOACTIVE AMINES
    histamine, serotonin
  • OXYGEN METABOLITES
    hydrogen peroxide (H$_2$O$_2$)
    superoxide anion (O$_2^-$)
    hypochlorous acid (HOCl$^-$)
  • ARACHIDONIC ACID METABOLITES
    cyclooxygenase-derived
    lipoxygenase-derived
  • CYTOKINES
    Interleukins
    Chemokines
    Interferons
    Tumor Necrosis Factor
    Growth Factors