M1 - Immunology, Winter 2008

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<http://hdl.handle.net/2027.42/64939>
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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

Phospholipase C

Lysophospholipid

Arachidonic acid

Diacylglycerol

Diacylglyceride lipase

Cyclooxygenase 1 + Lipoxygenase Products

Cyclooxygenase 2
**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>Thromboxoxane</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>Prostacyclin</td>
</tr>
</tbody>
</table>
Biological Function

Cyclooxygenase-derived Products:

Prostaglandin E$_2$/Prostacyclin  Immuno-regulatory
- 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:**

<table>
<thead>
<tr>
<th>Leukotriene B(_4)</th>
<th>Neutrophil Activation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- degranulation</td>
</tr>
<tr>
<td>Mast cell activation</td>
<td>- degranulation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Leukotriene C,D,E (SRS-A)</th>
<th>Causes smooth muscle contraction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increases vascular permeability</td>
</tr>
</tbody>
</table>
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
Production of Fever

Hypothalamus

Viruses, Bacteria, Toxins → Activated Leukocytes → Endogenous Pyrogen → Phagocytic Leukocytes

(e.g. Interleukin-1)

Arachidonic Acid → Prostaglandin E2 → Temperature

Aspirin, NSAIDs

Shivering, Sweating, Vasomotor Tone
Rheumatoid Arthritis distorts joints

Source: http://www.nih.gov/
Immunopathology of Rheumatoid Arthritis

- Complement
- Fixation Activation
- Granules
- Phagolysosome
- Collagenase Neutral Proteases Phospholipase
- Cartilage
- Nerve Sensitization
- Vasodilation
- Subchondral bone plate

Activated oxygen ($O_2, H_2O_2$)

Anti-altered IgG

Altered IgG

Chemotaxis

Lysosomal Enzymes

Nonsteroidal Anti-inflammatory Agents

Arachidonic acid

Prostaglandins

Source: Undetermined
Chemotactic Activity of LTB4

BY: Greg Luerman
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 cysteinyl leukotrienes
Non-Steroidal Anti-Inflammatory Compounds

- Aspirin (acetysalicylic 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.
INDOMETHACIN

IBUPROFEN

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
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THE HOMEOSTATIC BALANCE

PGI\textsubscript{2}  
ENDOTHELIUM

TXA\textsubscript{2}  
PLATELETS

BY: Gretaz  GNU 1.2
Thrombus Formation

- Elastic Lamina
- Basement Membrane
- Endothelium
- platelets
- Injury
- ADP
- Thromboxane
- Collagen
- Aggregation
- Organization
- Plaque
Can Aspirin Act As An Anti-thrombogenic Agent?

- Inhibits platelet aggregation by blocking platelet-derived thromboxane 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) —> Inflammation

COX-2 (inducible) —> Pro-inflammatory PGs and other inflammatory mediators —> Inflammatory Stimuli
Stimulus

Phospholipase

Cell membrane
Phospholipids

Arachidonic acid

lipid mediators of Inflammation
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**
  - Phospholipase

- **Cell membrane**
  - Phospholipids

- **Arachidonic acid**

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

- **COX-1**
  - Thromboxanes
    - TXB$_2$

- **Lipooxygenases (5-LO)**
  - Leukotrienes
    - LTB$_4$
    - LTC$_4$, LTD$_4$

**Vasodilation, Increase vascular permeability, Control platelet aggregation, Chemotaxis, Pain, Fever**
Acute inflammation: lipid mediators

An important role in vascular homeostasis

Endothelium

Prostacyclin PGI\(_2\) → TXB2

Anti-thrombotic ← Pro-thrombotic

Platelets
Prostacyclin $\text{PGI}_2$

$\text{TXB}_2$

Anti-thrombotic

Pro-thrombotic

Endothelium

Platelets

COX-2

Prostanoids

COX-1

Therapeutic targets

Endothelium

Platelets

COX-2

Prostanoids

COX-1

Therapeutic targets

Prostanoids

Anti-thrombotic

Pro-thrombotic

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

**Endothelium**
- Prostacyclin PGI$_2$
- Anti-thrombotic

**Platelets**
- TXB2
- Pro-thrombotic

**Therapeutic targets**
- COX-2
- COX-1
- Ibuprofen*

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

Therapeutic targets

Endothelium

COX-2

Prostacyclin PGI$_2$

Anti-thrombotic

Vioxx®

COX-1

TXB2

Pro-thrombotic

Platelets


Acute inflammation: lipid mediators

**Therapeutic targets**

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

**Platelets**
- TXB2
- **Aspirin** inhibits COX-1 irreversibly
- All cells but the platelet can resynthesize the enzymes

**Anti-thrombotic**

**Pro-thrombotic**
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