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M1 - Immunology, Winter 2008

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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

LIPOXYGENASE PATHWAY

5-HYDROPEROXYEICOSATETRAENOIC ACID (5-HPETE)

↑

LTA₄ (UNSTABLE)

↓

LTB₄

↑

LTC₄

↓

LTD₄

LTE₄

CYCLOOXYGENASE PATHWAY

PGG₂ → PGH₂

PGI₂ (UNSTABLE)

PGE₂

↑

PGF₂α

↓

TXA₂ (UNSTABLE)

TXB₂

5-Keto PGF₁α
Leukotriene Synthesis

Arachidonic Acid

Lipoxygenase

5-HPETE

Leukotriene A (LTA)

Glutathione-S-transferase

Leukotriene B (LTB)

Leukotriene C (LTC)

Leukotriene D (LTD)
<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 + 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:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin $E_2$/Prostacyclin</td>
<td>Immunoregulatory</td>
</tr>
<tr>
<td></td>
<td>• Inhibits immune cell activation</td>
</tr>
<tr>
<td></td>
<td>• Inhibits cytokine production</td>
</tr>
<tr>
<td></td>
<td>• Inhibits mast cell activation</td>
</tr>
<tr>
<td></td>
<td>Blocks platelet aggregation</td>
</tr>
<tr>
<td></td>
<td>Increases vasodilation</td>
</tr>
<tr>
<td></td>
<td>Stimulates adenylate cyclase</td>
</tr>
<tr>
<td>Thromboxoxane</td>
<td>Causes vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Induces platelet aggregation</td>
</tr>
</tbody>
</table>
### Biological Function

#### Lipoxygenase-derived Products:

<table>
<thead>
<tr>
<th>Product</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukotriene B(_4)</td>
<td>Neutrophil Activation</td>
</tr>
<tr>
<td></td>
<td>- degranulation</td>
</tr>
<tr>
<td>Mast cell activation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- degranulation</td>
</tr>
<tr>
<td>Leukotriene C,D,E (SRS-A)</td>
<td>Causes smooth muscle contraction</td>
</tr>
<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
Hypothalamus

Production of Fever

Viruses
Bacteria
Toxins

Phagocytic leukocytes

Activated leukocytes
Endogenous pyrogen

Arachidonic Acid
Prostaglandin E2
Temperature

Aspirin
NSAIDs

Shivering
Sweating
Vasomotor tone

(e.g. Interleukin-1)
Rheumatoid Arthritis distorts joints

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

PMN

Vascular endothelium

PMN

PMN

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 (acetysalicylic acid)
- Ibuprofen (propionic acid derivatives)
- Indomethacin (indole derivatives)
- Tylenol (Acetominophen)
- 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 ACETYLATED 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 cyclooxygenase 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

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Thrombus Formation

Elastic Lamina

platelets

Endothelium

Basement Membrane

Injury

ADP

Thromboxane

Collagen

Aggregation

Organization

Plaque

THROMBUS
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 generate 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.
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 E₂
Prostacyclin PGI₂

COX-1
Thromboxanes
TXB₂

Lipoxygenases (5-LO)
Leukotrienes
LTB₄
LTC₄, LTD₄
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\(_2\)

Lipooxigenases (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$_2$
  - Anti-thrombotic

- **Platelets**
  - TXB2
  - 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

**Therapeutic targets**

- **Endothelium**
  - COX-2
  - Prostacyclin PGI$_2$
  - Anti-thrombotic

- **Platelets**
  - COX-1
  - TXB2
  - Pro-thrombotic

---

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

**Therapeutic targets**

- COX-2
- Vioxx®
- COX-1

**Endothelium**

- Prostacyclin PGI₂
  - Anti-thrombotic

**Platelets**

- TXB2
  - Pro-thrombotic
Acute inflammation: lipid mediators

Prostacyclin PGI₂

Aspirin inhibits COX-2 irreversibly

All cells but the platelet can resynthesize the enzymes

TXB₂

Aspirin inhibits COX-1 irreversibly

Endothelium

Platelets

Anti-thrombotic

Pro-thrombotic

Therapeutic targets
INFLAMMATORY MEDIATORS

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  Chemokines
  Interferons
  Tumor Necrosis Factor
  Growth Factors