2008-09

M1 - Immunology, Winter 2008

Fantone, J.; Pietropaolo, M. T.

http://hdl.handle.net/2027.42/64939
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 (H₂O₂)  
  superoxide anion (O₂⁻)  
  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
STIMULI

Cell Membrane Phospholipids

Lipoxygenase Pathway

HETES [mono & di]

Leukotriene [SRS-A]

Arachidonic Acid

PGG₂ → PGH₂

Cyclooxygenase

PGI₂ (unstable)

PGE₂

TXA₂ (unstable)

6-Keto PGF₁α

TXB₂
Leukotriene Synthesis

Arachidonic Acid

5-HPETE

Leukotriene A (LTA)

Leukotriene B (LTB)

Leukotriene C (LTC)

Leukotriene D (LTD)

Lipoxygenase

Glutathione-S-transferase
<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>Prostacycllin</td>
</tr>
</tbody>
</table>
ARACHIDONIC ACID

LIPOXGENASE PATHWAY

5-HYDROPEROXYEICOSATETRAENOIC ACID (5-HPETE)

→ LTA₄ (UNSTABLE)

→ LTB₄

→ LTC₄

→ LTD₄

CYCLOOXYGENASE PATHWAY

PGH₂ → PG₂

PGI₂ (UNSTABLE)

PGE₂

PGF₂

5-Keto PGF₁₂

TxA₂ (UNSTABLE)

TxB₂
## Biological Function

### Cyclooxygenase-derived Products:

<table>
<thead>
<tr>
<th>Prostaglandin E₂/Prostacyclin</th>
<th>Immunoregulatory</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

| Thromboxoxane                    | 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>
</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
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/
Immunopathology of Rheumatoid Arthritis

- Complement
  - Anti-altered IgG
  - Altered IgG
- Fixation Activation
- Chemotaxis
- Phagolysosome
  - Lysosomal Enzymes
  - Collagenase
  - Neutral Proteases
  - Phospholipase
  - Nonsteroidal Anti-inflammatory Agents
  - Arachidonic acid
  - Prostaglandins
- Nerve Sensitization
  - Vasodilation
- Activated oxygen ($O_2$, $H_2O_2$)
- Cartilage
  - Subchondral bone plate

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 (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
THE HOMEOSTATIC BALANCE

PGI₂ ENDOTHELIOUM

TXA₂ PLATELETS
Thrombus Formation

- Elastic Lamina
- Basement Membrane
- Endothelium
- platelets

Injury → ADP → Thromboxane → Aggregation

Collagen

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 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

Cell membrane
Phospholipids

+ Phospholipase

Arachidonic acid
Acute inflammation: lipid mediators

Stimulus

Cell membrane
Phospholipids

Arachidonic acid

Phospholipase

COX-1+2
Prostaglandins
Prostaglandin E_2
Prostacyclin PGI_2

COX-1
Thromboxanases
TXB_2

Lipoxygenases (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 E₂
Prostacyclin PGI₂

COX-1
Thromboxanes
TXB₂

Lipooxigenases (5-LO)
Leukotrienes
LTB₄
LTC₄, LTD₄

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

An important role in vascular homeostasis

- Endothelium
  - Prostacyclin $\text{PGI}_2$
  - Anti-thrombotic

- Platelets
  - Thromboxane $\text{TXB}_2$
  - Pro-thrombotic

Prostaglandins play a crucial role in balancing the anti-thrombotic and pro-thrombotic effects in acute inflammation.
Acute inflammation: lipid mediators

Therapeutic targets

Endothelium

COX-2

Prostacyclin PGI₂

Anti-thrombotic

Platelets

COX-1

TXB2

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

**Ibuprofen**

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

Therapeutic targets

Endothelium

COX-2

Vioxx®

Prostacyclin PGI₂

Anti-thrombotic

Platelets

COX-1

TXB2

Pro-thrombotic
Aspirin inhibits COX-2 irreversibly.

Endothelium:
- Prostacyclin PGI₂

Platelets:
- TXB₂

Aspirin inhibits COX-1 irreversibly.

Therapeutic targets:

Anti-thrombotic
Pro-thrombotic
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 (HOCI$^-$)
• ARACHIDONIC ACID METABOLITES
  cyclooxygenase-derived
  lipoxygenase-derived
• CYTOKINES
  Interleukins
  Chemokines
  Interferons
  Tumor Necrosis Factor
  Growth Factors