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\textsubscript{2}O\textsubscript{2})
  superoxide anion (O\textsubscript{2}^{-})
  hypochlorous acid (HOCl\textsuperscript{-})
• 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 + Arachidonic acid

Phospholipase C

Arachidonic acid

Diacylglycerol

Diacylglyceride lipase

Arachidonic acid + HO-CH

Cyclooxygenase 1 + Lipoxygenase Products

Cyclooxygenase 2
STIMULI

Cell Membrane Phospholipids

PHOSPHOLIPASE A2

LIPOXYGENASE PATHWAY

HETEs [mono & di]

LEUKOTRIENE [SRS-A]

Arachidonic Acid

CYCLOOXYGENASE

PGG₂ → PGH₂

PGI₂ UNSTABLE

PGE₂

TXA₂ UNSTABLE

6-Keto PGF₁α

PGF₂α

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>Thromboxane</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>Prostacyclin</td>
</tr>
</tbody>
</table>
## Biological Function

### Cyclooxygenase-derived Products:

<table>
<thead>
<tr>
<th>Product</th>
<th>Effect</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:**

- **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

Arachidonic Acid $\rightarrow$ Prostaglandin E2 $\rightarrow$ 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
  - Activated oxygen ($O_2, H_2O_2$)

- Fixation Activation
  - Lysosomal Enzymes
    - Collagenase
    - Neutral Proteases
    - Phospholipase

- Chemotaxis
  - Nerve Sensitization
    - Vasodilation

- Cartilage
  - Subchondral bone plate

- Nonsteroidal Anti-inflammatory Agents
  - Arachidonic acid
    - Prostaglandins

Source: Undetermined
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 cysteinyl 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 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

PGI\(_2\)  ENDOTHELIUM

TXA\(_2\)  PLATELETS
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.
lipid mediators of Inflammation

Stimulus

+ Phospholipase

Cell membrane
Phospholipids

Arachidonic acid
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\(_4\)
Acute inflammation: lipid mediators

Stimulus

Cell membrane
Phospholipids

Arachidonic acid

+ Phospholipase

COX-1+2
Prostaglandins
Prostaglandin E\(_2\)
Prostacyclin PG\(_{\text{II}}\)

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
An important role in vascular homeostasis

Acute inflammation: lipid mediators

Endothelium

Prostacyclin PGI$_2$

Anti-thrombotic

Pro-platelets

TXB2

Pro-thrombotic
Acute inflammation: lipid mediators

Therapeutic targets

Endothelium

COX-2

Prostacyclin PGI$_2$

Anti-thrombotic

Platelets

COX-1

TXB2

Pro-thrombotic

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

Endothelium

Prostacyclin PGI\textsubscript{2}

Anti-thrombotic

Platelets

Thromboxane TXB\textsubscript{2}

Pro-thrombotic

Therapeutic targets

Ibuprofen*

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

**Therapeutic targets**

- **Endothelium**
  - Prostacyclin PGI$_2$
  - COX-2
- **Platelets**
  - TXB2
  - COX-1

**Anti-thrombotic**

**Pro-thrombotic**

- **Vioxx®**
Acute inflammation: lipid mediators

Prostacyclin PGI₂

Therapeutic targets

Endothelium

Platelets

Aspirin inhibits COX-2 irreversibly

Aspirin inhibits COX-1 irreversibly

Prostacyclin PGI₂

TXB2

All cells but the platelet can resynthesize the enzymes

Anti-thrombotic

Pro-thrombotic
INFLAMMATORY MEDIATORS

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  Tumor Necrosis Factor
  Growth Factors