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

<table>
<thead>
<tr>
<th>PLASMA DERIVED</th>
<th>CELL-DERIVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>• COMPLEMENT CASCADE</td>
<td>• VASOACTIVE AMINES</td>
</tr>
<tr>
<td>C3a, C5a</td>
<td>histamine, serotonin</td>
</tr>
<tr>
<td>• COAGULATION CASCADE</td>
<td>• OXYGEN METABOLITES</td>
</tr>
<tr>
<td>Thrombin, plasmin</td>
<td>hydrogen peroxide ( (\text{H}_2\text{O}_2) )</td>
</tr>
<tr>
<td></td>
<td>superoxide anion ( (\text{O}_2^-) )</td>
</tr>
<tr>
<td></td>
<td>hypochlorous acid ( (\text{HOCl}^-) )</td>
</tr>
<tr>
<td></td>
<td>• ARACHIDONIC ACID METABOLITES</td>
</tr>
<tr>
<td></td>
<td>cyclooxygenase-derived</td>
</tr>
<tr>
<td></td>
<td>lipoxygenase-derived</td>
</tr>
<tr>
<td></td>
<td>• CYTOKINES</td>
</tr>
<tr>
<td></td>
<td>Interleukins</td>
</tr>
<tr>
<td></td>
<td>Chemokines</td>
</tr>
<tr>
<td></td>
<td>Interferons</td>
</tr>
<tr>
<td></td>
<td>Tumor Necrosis Factor</td>
</tr>
<tr>
<td></td>
<td>Growth Factors</td>
</tr>
</tbody>
</table>
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
Phospholipid

Phospholipase A

Phospholipase C

Arachidonic acid + Lysophospholipid

Arachidonic acid + Diacylglycerol

Diacylglyceride lipase

Cyclooxygenase 1 + Lipoxygenase Products
Cyclooxygenase 2
Cell Membrane Phospolipids

LIP OXYGENASE PATHWAY
HETES [mono & di]
LEUKOTRIENE [SRS-A]

Arachidonic Acid

PHOSPHOLIPASE A2

CYCLOOXYGENASE

PGG2 → PGH2

PGI2 UNSTABLE

PGE2

6-Keto PGF1α

TXA2 UNSTABLE

TXB2

PGF2α
**Leukotriene Synthesis**

1. **Arachidonic Acid**
   - Lipoxygenase
   - 5-HPETE
     - Glutathione-S-transferase
     - **Leukotriene A (LTA)**
     - **Leukotriene B (LTB)**
     - **Leukotriene C (LTC)**
     - **Leukotriene D (LTD)**
## 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>Thromboxxane</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>Prostacycllin</td>
</tr>
</tbody>
</table>
ARACHIDONIC ACID

LIPOXGENASE PATHWAY

5-HYDROPEROXYEICOSATETRAENOID ACID (5-HPETE)

\[ \text{LTA}_4 \] (UNSTABLE)

\[ \text{LTC}_2 \]

\[ \text{LTB}_2 \]

\[ \text{LTD}_4 \]

\[ \text{LTE}_4 \]

CYCLOOXYGENASE PATHWAY

\[ \text{PGG}_2 \rightarrow \text{PGH}_2 \]

\[ \text{PGI}_2 \] (UNSTABLE)

\[ \text{PGE}_2 \]

\[ \text{PGF}_2 \]

\[ \text{5-Keto PGF}_1 \]

\[ \text{TXA}_2 \] (UNSTABLE)

\[ \text{TXB}_2 \]
## Biological Function

### Cyclooxygenase-derived Products:

<table>
<thead>
<tr>
<th>Prostaglandin E&lt;sub&gt;2&lt;/sub&gt;/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>Blocks platelet aggregation</td>
<td></td>
</tr>
<tr>
<td>Increases vasodilation</td>
<td></td>
</tr>
<tr>
<td>Stimulates adenylate cyclase</td>
<td></td>
</tr>
</tbody>
</table>

| Thromboxxane                           | Causes vasoconstriction |
|                                        | Induces platelet aggregation |
# Biological Function

## Lipoxygenase-derived Products:

<table>
<thead>
<tr>
<th>Leukotriene C,D,E (SRS-A)</th>
<th>Causes smooth muscle contraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukotriene B_4</td>
<td>Neutrophil Activation</td>
</tr>
<tr>
<td></td>
<td>- degranulation</td>
</tr>
<tr>
<td></td>
<td>Mast cell activation</td>
</tr>
<tr>
<td></td>
<td>- degranulation</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 → Activated leukocytes → Endogenous pyrogen → 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
  - Lysosomal Enzymes
  - Collagenase
  - Neutral Proteases
  - Phospholipase

- Activated oxygen
  - \( \text{O}_2, \text{H}_2\text{O}_2 \)

- Nonsteroidal Anti-inflammatory Agents
  - Arachidonic acid
  - Prostaglandins

- Nerve Sensitization
  - Vasodilation

- Cartilage
  - Subchondral bone plate

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 cysteinyI 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

PGI₂ ENDOTHELium  TXA₂ PLATELETS
Thrombus Formation

- Elastic Lamina
- Basement Membrane
- Endothelium
- platelets

Injury → ADP → Thromboxane → Collagen → Aggregation → THROMBUS

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

+ Phospholipase

Phospholipids

Cell membrane

Arachidonic acid

COX-1+2
Prostaglandins
Prostaglandin E₂
Prostacyclin PGI₂

COX-1
Thromboxanes
TXB₂

Lipooxigenases (5-LO)
Leukotrienes
LTB₄
LTC₄, LTD₄
**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

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
- TXB2
- Pro-thrombotic

NSAIDs inhibit both COX-1 and COX-2; COXIBs inhibit COX-2
Prostacyclin PGI$_2$  
TXB$_2$

Anti-thrombotic  
Pro-thrombotic

**Therapeutic targets**

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

- **Platelets**
  - COX-1
  - TXB$_2$
  - Pro-thrombotic

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

Therapeutic targets

Endothelium

COX-2

Prostacyclin PGI₂

Anti-thrombotic

Platelets

COX-1

TXB2

Pro-thrombotic

Vioxx®
Acute inflammation: lipid mediators

**Therapeutic targets**

- **Aspirin** inhibits COX-2 irreversibly
- **Aspirin** inhibits COX-1 irreversibly

**Endothelium**
- Prostacyclin PGI$_2$
- All cells but the platelet can resynthesize the enzymes

**Platelets**
- TXB2

**Anti-thrombotic**

**Pro-thrombotic**
INFLAMMATORY MEDIATORS

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  Tumor Necrosis Factor
  Growth Factors