Arachidonic Acid Metabolites and Inflammation

Joseph Fantone, M.D.
Host Defense 2/12  10-11:00am
<table>
<thead>
<tr>
<th>INFLAMMATORY MEDIATORS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PLASMA DERIVED</strong></td>
</tr>
<tr>
<td>• COMPLEMENT CASCADE</td>
</tr>
<tr>
<td>C3a, C5a</td>
</tr>
<tr>
<td>• COAGULATION CASCADE</td>
</tr>
<tr>
<td>Thrombin, plasmin</td>
</tr>
<tr>
<td><strong>CELL-DERIVED</strong></td>
</tr>
<tr>
<td>• VASOACTIVE AMINES</td>
</tr>
<tr>
<td>histamine, serotonin</td>
</tr>
<tr>
<td>• OXYGEN METABOLITES</td>
</tr>
<tr>
<td>hydrogen peroxide (H₂O₂)</td>
</tr>
<tr>
<td>superoxide anion (O₂⁻)</td>
</tr>
<tr>
<td>hypochlorous acid (HOCl⁻)</td>
</tr>
<tr>
<td>• ARACHIDONIC ACID METABOLITES</td>
</tr>
<tr>
<td>cyclooxygenase-derived</td>
</tr>
<tr>
<td>lipoxygenase-derived</td>
</tr>
<tr>
<td>• CYTOKINES</td>
</tr>
<tr>
<td>Interleukins</td>
</tr>
<tr>
<td>Chemokines</td>
</tr>
<tr>
<td>Interferons</td>
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<tr>
<td>Tumor Necrosis Factor</td>
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<tr>
<td>Growth Factors</td>
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</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

Arachidonic acid + Lysophospholipid

Phospholipase C

Arachidonic acid + phospholyl-R

Diacylglycerol

Diacylglyceride lipase

Arachidonic acid + HO-CH

Diacylglyceride lipase

Cyclooxygenase 1 + Lipoxygenase Products
Cyclooxygenase 2
Leukotriene Synthesis

Arachidonic Acid → 5-HPETE → Leukotriene A (LTA) → Leukotriene B (LTB) → Leukotriene C (LTC) → Leukotriene D (LTD)

Lipoxygenase and Glutathione-S-transferase pathways are involved in the conversion of arachidonic acid into leukotrienes.
<table>
<thead>
<tr>
<th>CELL</th>
<th>PRODUCT</th>
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</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:

Prostaglandin E₂/Prostacyclin
- Immunoregulatory
  - 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>
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<tr>
<th>Product</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukotriene $B_4$</td>
<td>Neutrophil Activation&lt;br&gt;- degranulation</td>
</tr>
<tr>
<td>Mast cell activation&lt;br&gt;- degranulation</td>
<td></td>
</tr>
<tr>
<td>Leukotriene $C,D,E$ (SRS-A)</td>
<td>Causes smooth muscle contraction&lt;br&gt;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/
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 cysteiny1 leukotrienes
Non- Steroidal Anti-Inflammatory Compounds

- Aspirin (acetysalicylic acid)
- Ibuprofen (propionic acid derivatives)
- Indomethacin (indole derivatives)
- Tylenol (Acetominopohen)
- 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.

\[
\begin{align*}
\text{COOH} & \quad \text{O} \\
\text{OCCH}_3 & \\
\text{ASPIRIN} & \\
+ & \\
\text{H}_2\text{N-ENZYME} & \\
\rightarrow & \\
\text{COOH} & \quad \text{OH} \\
\text{O} & \\
\text{OCCH}_3 & \\
\text{+} & \\
\text{CH}_3\text{C} & - \quad \text{H}_2\text{N-ENZYME} \\
\text{(INACTIVE)} & \\
\end{align*}
\]
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……
Thrombus Formation

- Elastic Lamina
- Platelets
- Basement Membrane
- Endothelium
- 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

Cell membrane
Phospholipids

+ Phospholipase

Arachidonic acid
**Acute inflammation: lipid mediators**

1. **Stimulus**
2. **Phospholipase**
3. **Cell membrane Phospholipids**
   - Arachidonic acid
4. **COX-1+2**
   - Prostaglandins
     - Prostaglandin E$_2$
     - Prostacyclin PGI$_2$
5. **COX-1**
   - Thromboxanes
     - TXB$_2$
6. **Lipoxygenases (5-LO)**
   - Leukotrienes
     - LTB$_4$
     - LTC$_4$, LTD$_4$
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$_2$

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$_2$

Anti-thrombotic

Pro-thrombotic

Platelets

TXB2
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

Prostacyclin PGI\textsubscript{2} vs TXB\textsubscript{2}

- **Anti-thrombotic**
- **Pro-thrombotic**

**Therapeutic targets**

**Endothelium**

COX-2 $\rightarrow$ Ibuprofen* $\rightarrow$ COX-1

Prostacyclin PGI\textsubscript{2} $\rightarrow$ Anti-thrombotic

**Platelets**

TXB\textsubscript{2} $\rightarrow$ Pro-thrombotic

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

**Therapeutic targets**

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

- **Platelets**
  - COX-1
  - TXB2

**Anti-thrombotic**

**Pro-thrombotic**

- Vioxx®
Acute inflammation: lipid mediators

**Endothelium**
- Prostacyclin PGI₂

**Platelets**
- TXB2

**Aspirin**
- Inhibits COX-1 irreversibly
- Inhibits COX-2 irreversibly

Anti-thrombotic

Pro-thrombotic

Therapeutic targets
INFLAMMATORY MEDIATORS

PLASMA DERIVED
• COMPLEMENT CASCADE
  C3a, C5a
• COAGULATION CASCADE
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CELL-DERIVED
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  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