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 ($H_2O_2$)
    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

Phospholipase A

Lysophospholipid

Phospholipase C

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)
<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>Thromboxane</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>Prostacyclin</td>
</tr>
</tbody>
</table>
ARACHIDONIC ACID

LIPOXGENASE PATHWAY

5-HYDROPEROXEOIC ACID
(5-HPETE)

LTA₄
(UNSTABLE)

LTB₄

LTC₂

LTD₄

LTE₄

CYCLOOXYGENASE PATHWAY

PGD₂ → PGE₂

PGI₂ → TXA₂

(UNSTABLE)

(UNSTABLE)

PGE₂ + PGF₂α

5-Keto PGF₁α
## Biological Function

### Cyclooxygenase-derived Products:

<table>
<thead>
<tr>
<th>Product</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin E₂/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>Compound</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukotriene B&lt;sub&gt;4&lt;/sub&gt;</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>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
Production of Fever

Hypothalamus

Arachidonic Acid $\rightarrow$ Prostaglandin E2 $\rightarrow$ Temperature

Aspirin
NSAIDs

(e.g. Interleukin-1)

Shivering
Sweating
Vasomotor tone
Rheumatoid Arthritis distorts joints

Source: http://www.nih.gov/
Immunopathology of Rheumatoid Arthritis

- Complement
- Fixation
- Activation
- Anti-altered IgG
- Altered IgG
- Chemotaxis
- Phagolysosome
- Lysosomal Enzymes
- Collagenase
- Neutral Proteases
- Phospholipase
- Cartilage
- Subchondral bone plate
- Nerve Sensitization
- Vasodilation
- Arachidonic acid
- Prostaglandins
- Nonsteroidal Anti-inflammatory Agents

Activated oxygen
$(O_2, H_2O_2)$

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 cysteiny1 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!!
ASPIRIN

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.

\[
\text{COOH} \quad \text{O} \quad \text{OCCH}_3 \\
\text{COOH} \quad \text{O} \quad \text{OCCH}_3
\]

+ H\text{\textsubscript{2}}N-ENZYME \rightarrow 

\[
\text{COOH} \quad \text{OH} \quad \text{O} \\
\text{CH}_3\text{C}=-\text{H}_2\text{N-ENZYME} \quad \text{(INACTIVE)}
\]
INDOMETHACIN

IBUPROFEN

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......
THE HOMEOSTATIC BALANCE

PGI₂ ENDOTHELium

TXA₂ PLATELETS

BY: Gretaz
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 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

Cell membrane
Phospholipids

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$_4$

Stimulus + Phospholipase
Acute inflammation: lipid mediators

Stimulus

Cell membrane
Phospholipids

Phospholipase

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

Platelets

Prostacyclin PGI$_2$ ↔ TXB2

Anti-thrombotic ↔ Pro-thrombotic
Prostacyclin PGI_2

COX-2

Prostacyclin PGI_2

COX-1

TXB2

Anti-thrombotic

Pro-thrombotic

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

**Therapeutic targets**

- **Endothelium**
  - COX-2
    - Prostacyclin PGI₂
      - Anti-thrombotic
  - Ibuprofen*
      - COX-2

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

*Ibuprofen* is a classical NSAID that inhibits both COX enzymes.
Acute inflammation: lipid mediators

Endothelium

Prostacyclin PGI₂

COX-2

Vioxx®

Platelets

TXB2

COX-1

Anti-thrombotic

Pro-thrombotic

Therapeutic targets
**Acute inflammation: lipid mediators**

**Therapeutic targets**

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

**Endothelium**
- Prostacyclin $\text{PGI}_2$
- All cells but the platelet can resynthesize the enzymes

**Platelets**
- TXB2

**Anti-thrombotic**

**Pro-thrombotic**
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  cyclooxygenase-derived
  lipoxygenase-derived
• CYTOKINES
  Interleukins
  Chemokines
  Interferons
  Tumor Necrosis Factor
  Growth Factors