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 (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
Arachidonic acid

Phospholipid

Phospholipase A

Lysophospholipid

Phospholipase C

Diacylglycerol

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

LIPOXYGENASE PATHWAY

5-HYDROPEROXIDEIOSATETRAENOIC ACID (5-HPETE)

   ↓

   LTA₄ (UNSTABLE)

   ↓

   LTB₄

   ↓

   LTC₄


CYCLOOXYGENASE PATHWAY

   PGG₂ → PGH₂

   ↓

   PGD₂ (UNSTABLE)

   ↓

   PGI₂

   ↓

   PGE₂

   ↓

   TXA₂ (UNSTABLE)

   ↓

   TXB₂

   ↓

   5-Keto PGF₁₂
# 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>Thromboxxane</td>
<td>Causes vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Induces platelet aggregation</td>
</tr>
</tbody>
</table>
Biological Function

**Lipoxygenase-derived Products:**

- **Leukotriene B₄**
  - 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

Production of Fever

Viruses
Bacteria
Toxins

Activated leukocytes
Endogenous pyrogen

Phagocytic leukocytes

Arachidonic Acid
Prostaglandin E2
Temperature

Aspirin
NSAIDs

(e.g. Interleukin-1)

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 cysteinyi leukotrienes
Non- Steroidal Anti-Inflammatory Compounds

- Aspirin (acetylsalicylic 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.

\[
\text{COOH} \quad \frac{O}{OCCH_3} \quad \text{H}_2\text{N-ENZYME} \quad \rightarrow \quad \text{COOH} \quad \frac{OH}{O} \quad \text{CH}_3\text{C}--\text{H}_2\text{N-ENZYME} \quad \text{(INACTIVE)}
\]
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
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.

Physiologic Stimuli → COX-1 (constitutive) → PG E₂ (Renal function) → Thromboxane A₂ (Platelet function) → Prostacycline (PGL₂) (Gastric Protection)

COX-2 (inducible) → Pro-inflammatory PGs and other inflammatory mediators → Inflammation

Inflammatory Stimuli
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 → Thromboxanones
  - TXB$_2$

- Lipooxygenases (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 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 PGI$_2$

Anti-thrombotic

Platelets

TXB2

Pro-thrombotic
Acute inflammation: lipid mediators

<table>
<thead>
<tr>
<th>Therapeutic targets</th>
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<tr>
<td>Endothelium</td>
</tr>
<tr>
<td>COX-2</td>
</tr>
<tr>
<td>Prostacyclin PGI₂</td>
</tr>
<tr>
<td>Anti-thrombotic</td>
</tr>
</tbody>
</table>

| Platelets           |
| COX-1               |
| TXB2                |
| Pro-thrombotic      |

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

**Endothelium**

- Prostacyclin (PGI₂)
- Anti-thrombotic

**Platelets**

- TXB₂
- Pro-thrombotic

**Therapeutic targets**

- COX-1
- COX-2

**Ibuprofen**

- 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

- Prostacyclin PGI₂
- TXB₂

Endothelium

Platelets

All cells but the platelet can resynthesize the enzymes

Anti-thrombotic

Pro-thrombotic
INFLAMMATORY MEDIATORS

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• COAGULATION CASCADE
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  cyclooxygenase-derived
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• CYTOKINES
  Interleukins
  Chemokines
  Interferons
  Tumor Necrosis Factor
  Growth Factors