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$_2$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
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
Leukotriene Synthesis

1. Lipoxygenase
   - Arachidonic Acid → 5-HPETE

2. Glutathione-S-transferase
   - 5-HPETE
   - 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>Thromboxoxane</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>Prostacycllin</td>
</tr>
</tbody>
</table>
Biological Function

Cyclooxygenase-derived Products:

Prostaglandin $E_2$ / 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:

- 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

Production of Fever

Viruses
Bacteria
Toxins

Activated leukocytes
Endogenous pyrogen

Phagocytic leukocytes

Arachidonic acid
Prostaglandin E2
Temperature

(e.g. Interleukin-1)

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 cysteinyi 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!!
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.

\[
\text{COOH} - \text{OCCH}_3 + \text{H}_2\text{N-ENZYME} \rightarrow \text{COOH} + \text{CH}_3\text{C}--\text{H}_2\text{N-ENZYME} \quad \text{(INACTIVE)}
\]
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......
THE HOMEOSTATIC BALANCE

PGI₂
ENDOTHELIUM

TXA₂
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 generate 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 $\rightarrow$ COX-1 (constitutive) $\rightarrow$ PG E$_2$ (Renal function) $\rightarrow$ Thromboxane A$_2$ (Platelet function) $\rightarrow$ Prostacycline (PGL$_2$) (Gastric Protection) $\rightarrow$ Pro-inflammatory PGs and other inflammatory mediators $\rightarrow$ Inflammation $\rightarrow$ Inflammatory Stimuli
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
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Lipooxigenases (5-LO)
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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

Therapeutic targets

Endothelium
- Prostacyclin PGI$_2$
- Anti-thrombotic

Platelets
- TXB2
- Pro-thrombotic

COX-2

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

Therapeutic targets

Endothelium

COX-2

Prostacyclin PGI$_2$

Ibuprofen*

COX-1

TXB2

Platelets

Anti-thrombotic

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

Endothelium

Prostacyclin PGI$_2$

Aspirin
inhibits COX-2 irreversibly

Therapeutic targets

Platelets

TXB2

Aspirin
inhibits COX-1 irreversibly

All cells but the platelet can resynthesize the enzymes

Anti-thrombotic

Pro-thrombotic

Aspirin inhibits COX-2 irreversibly

Aspirin inhibits COX-1 irreversibly
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