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
Arachidonic acid

**Phospholipid**

- **Phospholipase A**
  - Lysophospholipid + Arachidonic acid

- **Phospholipase C**
  - Diacylglycerol
    - Diacylglyceride lipase
      - Arachidonic acid + HO-CH

**Cyclooxygenase 1 + Lipooxygenase Products**

**Cyclooxygenase 2**
Leukotriene Synthesis

Arachidonic Acid → 5-HPETE → Leukotriene A (LTA)

Glutathione-S-transferase

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 + 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:

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

Viruses Bacteria Toxins → Activated leukocytes → Endogenous pyrogen → Hypothalamus

Arachidonic Acid → Prostaglandin E2 → Temperature

Aspirin NSAIDs

Shivering Sweating Vasomotor tone

(e.g. Interleukin-1)
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
- Cartilage
- Nerve Sensitization
- Vasodilation

Nonsteroidal Anti-inflammatory Agents
Arachidonic acid → Prostaglandins
Activated oxygen
(O₂, H₂O₂)

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 cysteiny l 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 ACETYLATED 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

BY: Chaval Btasil
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THE HOMEOSTATIC BALANCE

PGI₂
ENDOTHELium

TXA₂
PLATELETS

BY: Gretaz
GNU 1.2
Thrombus Formation

- Elastic Lamina
- Basement Membrane
- Endothelium
- platelets
- Injury
- ADP
- Thromboxane
- Collagen
- Aggregation
- Organization
- Plaque

THROMBUS
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.
lipid mediators of Inflammation

Stimulus

+ Phospholipase

Cell membrane
Phospholipids

Arachidonic acid
Acute inflammation: lipid mediators

Stimulus

Phospholipase

Arachidonic acid

Cell membrane
Phospholipids

COX-1+2
Prostaglandins
Prostaglandin E\textsubscript{2}
Prostacyclin PGI\textsubscript{2}

COX-1
Thromboxanes
TXB\textsubscript{2}

Lipooxigenases (5-LO)
Leukotrienes
LTB\textsubscript{4}
LTC\textsubscript{4}, LTD\textsubscript{4}
Acute inflammation: lipid mediators

Stimulus

Cell membrane
Phospholipids

Arachidonic acid

Phospholipase

Prostaglandins
- Prostaglandin E$_2$
- Prostacyclin PGI$_2$

Thromboxanes
- TXB$_2$

Leukotrienes
- LTB$_4$
- LTC$_4$, LTD$_4$

COX-1+2

COX-1

Lipooxigenases (5-LO)

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
Prostacyclin PGI$_2$

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

Therapeutic targets

Endothelium

COX-2

Prostacyclin PGI₂

Anti-thrombotic

Platelets

COX-1

TXB2

Pro-thrombotic

*Classical NSAID, it inhibits both COX enzymes

Ibuprofen*
Acute inflammation: lipid mediators

**Therapeutic targets**

- Prostacyclin (PGI₂)
- Thromboxane B₂ (TXB₂)

**Endothelium**

- COX-2
- Prostacyclin PGI₂

**Platelets**

- COX-1
- Thromboxane B₂ (TXB₂)

**Antithrombotic**

**Prothrombotic**
Acute inflammation: lipid mediators

Therapeutic targets

Endothelium

Prostacyclin PGI₂

Aspirin inhibits COX-2 irreversibly

All cells but the platelet can resynthesize the enzymes

Platelets

TXB2

Aspirin inhibits COX-1 irreversibly

Pro-thrombotic

Anti-thrombotic
INFLAMMATORY MEDIATORS

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