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
A diagram showing the breakdown of phospholipids into arachidonic acid and other compounds via phospholipase A and phospholipase C. The products of arachidonic acid include lysophospholipid and diacylglycerol, which can be further metabolized by cyclooxygenase 1 and lipoxygenase enzymes to produce various bioactive compounds.
Leukotriene Synthesis

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

Lipoxygenase

Leukotriene B (LTB) → Leukotriene C (LTC) → Leukotriene D (LTD)

Glutathione-S-transferase
### 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>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 $B_4$:
  - Neutrophil Activation
  - Mast cell activation

- 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

Arachidonic Acid → Prostaglandin E2 → Temperature

(e.g. Interleukin-1)

Phagocytic leukocytes → Activated leukocytes → Endogenous pyrogen

Viruses, Bacteria, Toxins

Aspirin, NSAIDs

Shivering, Sweating, Vasomotor tone
Rheumatoid Arthritis distorts joints

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

- **Complement**
- **Fixation Activation**
- **Lysosomal Enzymes**
- **Collagenase Neutral Proteases Phospholipase**
- **Nonsteroidal Anti-inflammatory Agents**
- **Arachidonic Acid**
- **Prostaglandins**
- **Nerve Sensitization**
- **Vasodilation**
- **Activated Oxygen** 
  \((O_2, H_2O_2)\)
- **Cartilage**
- **Subchondral Bone Plate**

*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 cysteinyl 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 ACETYLATING 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.
THE HOMEOSTATIC BALANCE

PGI₂
ENDOTHELUM

TXA₂
PLATELETS

BY: Gretaz
GNU 1.2
Thrombus Formation

- Elastic Lamina
- Basement Membrane
- Endothelium
- platelets
- Injury
- ADP
- Thromboxane
- Collagen
- Aggregation
- THROMBUS
- 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$_4$
Arachidonic acid 

Cell membrane
Phospholipids

+ Phospholipase

Stimulus

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

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**
  - COX-2
  - Prostacyclin $\text{PGI}_2$
  - 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

Ibuprofen*

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

Prostacyclin PGI$_2$

Therapeutic targets

COX-2

Endothelium

Platelets

COX-1

Prostacyclin PGI$_2$

TXB2

Anti-thrombotic

Pro-thrombotic

Vioxx®
Acute inflammation: lipid mediators

**Therapeutic targets**

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

**Endothelium**
- Prostacyclin PGI₂

**Platelets**
- TXB₂

All cells but the platelet can resynthesize the enzymes

Anti-thrombotic

Pro-thrombotic
INFLAMMATORY MEDIATORS

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  - 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