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 + Lysophospholipid

Phospholipase A

Lysophospholipid

Phospholipase C

Arachidonic acid + Diacylglycerol

Diacylglyceride lipase

Arachidonic acid + HO-CH

Cyclooxygenase 1 + Lipooxygenase Products

Cyclooxygenase 2
Leukotriene Synthesis

Arachidonic Acid

Lipoxygenase

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>
ARACHIDONIC ACID

LIPOXGENASE PATHWAY

5-HYDROPEROXIDICOSATETRAENIC ACID (5-HPETE)

\[ \text{LTA}_4 \] (UNSTABLE)

\[ \text{LTC}_4 \]

\[ \text{LTD}_4 \]

\[ \text{LTE}_4 \]

CYCLOOXYGENASE PATHWAY

\[ \text{PGG}_2 \] → \[ \text{PGH}_2 \]

\[ \text{PGI}_2 \] (UNSTABLE)

\[ \text{PGE}_2 \]

\[ \text{PGF}_2 \]

\[ 5\text{-Keto PGF}_1 \]

\[ \text{TXA}_2 \] (UNSTABLE)

\[ \text{TXB}_2 \]
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:**

<table>
<thead>
<tr>
<th>Product</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukotriene $\text{B}_4$</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
Hypothalamus

Production of Fever

Viruses, Bacteria, Toxins → Activated Phagocytic Leukocytes → Endogenous Pyrogen → 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 cysteiny1 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** (Valdecoxiib) 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, THEREBY 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
- 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 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

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$_4$
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

An important role in vascular homeostasis

**Endothelium**

- Prostacyclin PGI$_2$
- Anti-thrombotic

**Platelets**

- TXB2
- Pro-thrombotic

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**Acute inflammation: lipid mediators**
Acute inflammation: lipid mediators

**Therapeutic targets**

- 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

Prostacyclin PGI₂

COX-2

Ibuprofen*

COX-1

TXB₂

Platelets

Anti-thrombotic

Pro-thrombotic

COX-1

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

**Endothelium**

- Prostacyclin PGI₂
- All cells but the platelet can resynthesize the enzymes

**Platelets**

- TXB₂
- **Aspirin** inhibits COX-1 irreversibly

**Anti-thrombotic**

**Pro-thrombotic**
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  Chemokines
  Interferons
  Tumor Necrosis Factor
  Growth Factors