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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

Arachidonic acid + phosphoryl-R

Diacylglycerol

Diacylglyceride lipase

Arachidonic acid + HO-CH

Cyclooxygenase 1 + Lipoxygenase Products

Cyclooxygenase 2
Leukotriene Synthesis

- **Arachidonic Acid**
- **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 + 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-HYDROPEROXYEICOSATETRAENOIC ACID (5-HETE)

- LTA₄ (UNSTABLE)
- LTB₄
- LTC₄

CYCLOOXYGENASE PATHWAY

- PGI₂ (UNSTABLE)
- PGE₂
- PGF₂

- 5-Keto PGI₂

- TXA₂ (UNSTABLE)
- TXB₂

PG₂ - PG₃₂
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:**

<table>
<thead>
<tr>
<th>Leukotriene B&lt;sub&gt;4&lt;/sub&gt;</th>
<th>Neutrophil Activation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- degranulation</td>
</tr>
<tr>
<td>Mast cell activation</td>
<td></td>
</tr>
<tr>
<td>- degranulation</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Leukotriene C,D,E (SRS-A)</th>
<th>Causes smooth muscle contraction</th>
</tr>
</thead>
<tbody>
<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
Production of Fever

Hypothalamus

- Arachidonic Acid
- Prostaglandin E2
- Temperature

Aspirin
NSAIDs

(e.g. Interleukin-1)

Shivering
Sweating
Vasomotor tone

Viruses
Bacteria
Toxins

Activated leukocytes
Endogenous pyrogen

Phagocytic leukocytes
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 (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.
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 ENDOTHELium

TXA₂ PLATELETS
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

Cell membrane
Phospholipids

Phospholipase

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

Vasodilation, Increase vascular permeability, Control platelet aggregation, Chemotaxis, Pain, Fever
Acute inflammation: lipid mediators

An important role in vascular homeostasis

Endothelium

Prostacyclin PGI$_2$

TXB2

Platelets

Anti-thrombotic

Pro-thrombotic
Acute inflammation: lipid mediators

Therapeutic targets

Endothelium

COX-2

Prostacyclin PGI₂

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 PGI\(_2\)

COX-2

Ibuprofen*

Platelets

TXB2

COX-1

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

**Therapeutic targets**

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

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**Endothelium**

- Prostacyclin PGI₂

**Platelets**

- TXB₂

**Anti-thrombotic**

**Pro-thrombotic**

All cells but the platelet can resynthesize the enzymes
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  Chemokines
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  Tumor Necrosis Factor
  Growth Factors