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Viewer discretion advised: Material may contain medical images that may be disturbing to some viewers.
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

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

Lipoxygenase

Leukotriene A (LTA) → 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 + Leukotrienes</td>
</tr>
<tr>
<td>Platelets</td>
<td>Thromboxxane</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>Prostacyclin</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:

<table>
<thead>
<tr>
<th>Product</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukotriene B&lt;sub&gt;4&lt;/sub&gt;</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
The production of fever involves several factors, including:

- Viruses, Bacteria, Toxins
  - Activated leukocytes
  - Endogenous pyrogen
  - Phagocytic leukocytes

In the hypothalamus, Arachidonic Acid leads to Prostaglandin E2, which affects Temperature, Shivering, Sweating, Vasomotor tone, and Aspirin/NSAIDs (e.g., Interleukin-1).
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

<table>
<thead>
<tr>
<th>Osteoarthritis</th>
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<tbody>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Primary dysmenorrhea</td>
</tr>
<tr>
<td>Pain management</td>
</tr>
<tr>
<td>Complications!!</td>
</tr>
</tbody>
</table>
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.
INDOMETHACIN

IBUPROFEN

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……
Thrombus Formation

- Elastic Lamina
- Platelets
- Basement Membrane
- Endothelium
- 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.
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 E₂
Prostacyclin PGI₂

COX-1

Thromboxanes

TXB₂

Lipooxigenases (5-LO)

Leukotrienes

LTB₄
LTC₄, LTD₄
Acute inflammation: lipid mediators

Stimulus

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Lipooxigenases (5-LO)
Leukotrienes
LTB₄
LTC₄, LTD₄

Acute inflammation: lipid mediators

An important role in vascular homeostasis

- **Endothelium**
  - Prostacyclin (PGI₂)
  - Anti-thrombotic

- **Platelets**
  - TXB₂
  - Pro-thrombotic

Prostaglandin E₃ (PGE₃)
Acute inflammation: lipid mediators

Therapeutic targets

Endothelium

COX-2
Prostacyclin $\text{PGI}_2$
Anti-thrombotic

Platelets

COX-1
$\text{TXB}_2$
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**

**Therapeutic targets**

- Endothelium
  - COX-2
  - Prostacyclin \( \text{PGI}_2 \)
  - Anti-thrombotic

- Platelets
  - COX-1
  - TXB2
  - Pro-thrombotic

**Vioxx®**
Acute inflammation: lipid mediators

**Endothelium**
- Prostacyclin PGI$_2$

**Platelets**
- TXB2

**Aspirin**
- Inhibits COX-2 irreversibly
- Inhibits COX-1 irreversibly

**Therapeutic targets**
- All cells but the platelet can resynthesize the enzymes

**Anti-thrombotic**

**Pro-thrombotic**
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  Growth Factors