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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 + Lipooxygenase Products

Cyclooxygenase 2
Cell Membrane Phospholipids

Lipoxygenase Pathway
- HETEs [mono & di]
- Leukotriene (SRS-A)

Phospholipase A2

Arachidonic Acid

Cyclooxygenase

PGG2 → PGH2

PGI2 → PGE2

6-Keto PGF1α

TXA2 → TxB2

PGF2α
Leukotriene Synthesis

Arachidonic Acid → 5-HPETE → Leukotriene A (LTA) → Leukotriene B (LTB) → Leukotriene C (LTC) → Leukotriene D (LTD)

Lipoxygenase

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>Thromboxoxane</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>Prostacyclin</td>
</tr>
<tr>
<td>Biological Function</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td></td>
</tr>
</tbody>
</table>

**Cyclooxygenase-derived Products:**

<table>
<thead>
<tr>
<th>Prostaglandin E&lt;sub&gt;2&lt;/sub&gt;/Prostacyclin</th>
<th>Immunoregulatory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Inhibits immune cell activation</td>
</tr>
<tr>
<td></td>
<td>• Inhibits cytokine production</td>
</tr>
<tr>
<td></td>
<td>• Inhibits mast cell activation</td>
</tr>
<tr>
<td>Blocks platelet aggregation</td>
<td></td>
</tr>
<tr>
<td>Increases vasodilation</td>
<td></td>
</tr>
<tr>
<td>Stimulates adenylate cyclase</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thromboxoxane</th>
<th>Causes vasoconstriction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Induces platelet aggregation</td>
</tr>
</tbody>
</table>
## Biological Function

### Lipoxygenase-derived Products:

<table>
<thead>
<tr>
<th>Product</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukotriene B$_4$</td>
<td>Neutrophil Activation</td>
</tr>
<tr>
<td></td>
<td>- degranulation</td>
</tr>
<tr>
<td>Mast cell activation</td>
<td></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**

- **Arachidonic Acid**
  - Prostaglandin E2
  - Temperature

- Aspirin
- NSAIDs

(e.g. Interleukin-1)

- Shivering
- Sweating
- Vasomotor tone

**Production of Fever**

- Viruses
- Bacteria
- Toxins

- Phagocytic leukocytes
- Activated leukocytes
- Endogenous pyrogen

**Production of Fever**

- Viruses
- Bacteria
- Toxins
Rheumatoid Arthritis distorts joints

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

Complement

Fixation Activation

Phagolysosome

Activated oxygen

Lysosomal Enzymes

Collagenase Neutral Proteases Phospholipase

Cartilage

Subchondral bone plate

Nonsteroidal Anti-inflammatory Agents

Arachidonic acid Prostaglandins

Nerve Sensitization Vasodilation

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 cysteinyi 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 → Aggregation

Collagen

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.

- **Physiologic Stimuli** → **COX-1 (constitutive)**
  - \( \text{PG} \ E_2 \)
    - (Renal function)
  - Thromboxane \( A_2 \)
    - (Platelet function)
  - Prostacycline (PGI\(_2\))
    - (Gastric Protection)

- **COX-2 (inducible)** → **Pro-inflammatory PGs and other inflammatory mediators** → **Inflammation**

- **Inflammatory Stimuli**
lipid mediators of Inflammation

Stimulus

+ Phospholipase

Cell membrane
Phospholipids

Arachidonic acid
Acute inflammation: lipid mediators

Stimulus → 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

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

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

Endothelium
- Prostacyclin PGI$_2$
- Anti-thrombotic

Platelets
- TXB2
- Pro-thrombotic

COX-1
- COXIBs inhibit COX-2

COX-2
- NSAIDs inhibit both COX-1 and COX-2; COXIBs inhibit COX-2
Acute inflammation: lipid mediators

**Therapeutic targets**

- **Endothelium**
  - COX-2
  - Prostacyclin PGI$_2$
  - Anti-thrombotic

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

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

Therapeutic targets

Endothelium

Prostaglandin E2 (PGE2)

COX-2

Platelets

Prostaglandin I2 (PGI2)

TXB2

COX-1

Vioxx®

Anti-thrombotic

Pro-thrombotic
Prostaglandins (PG)

**Endothelium**

- **Prostacyclin (PGI₂)**
- **Aspirin** inhibits COX-2 irreversibly

**Platelets**

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

Therapeutic targets

**Anti-thrombotic**

**Pro-thrombotic**
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  cyclooxygenase-derived
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  Interleukins
  Chemokines
  Interferons
  Tumor Necrosis Factor
  Growth Factors