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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 (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
Arachidonic acid \( \rightarrow \) Phospholipid

- Phospholipase A: \( \rightarrow \) Lysophospholipid + Arachidonic acid

- Phospholipase C: \( \rightarrow \) Diacylglycerol + Arachidonic acid + phosphoryl-R

Diacylglycerol \( \rightarrow \) Diacylglyceride lipase

Arachidonic acid + HO-CH \( \rightarrow \) Cyclooxygenase 1 + Lipoxigenase Products

Cyclooxygenase 2
STIMULI

Cell Membrane Phospholipids

\[ \text{Lipoxigenase Pathway} \]

\[ \text{HETEs [mono & di]} \]

\[ \text{Leukotriene [SRS-A]} \]

\[ \text{Arachidonic Acid} \]

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

\[ \text{Cyclooxygenase} \]

\[ \text{PGI}_{2 \text{U}} \]

\[ \text{PGE}_2 \]

\[ \text{TXA}_2 \]

\[ \text{TXB}_2 \]

\[ \text{6-Keto PGF}_{1\alpha} \]
Leukotriene Synthesis

Lipoxygenase

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

Glutathione-S-transferase

Leukotriene B (LTB) → Leukotriene C (LTC) → Leukotriene D (LTD)
<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>Prostacycllin</td>
</tr>
</tbody>
</table>
## Biological Function

**Cyclooxygenase-derived Products:**

<table>
<thead>
<tr>
<th>Product</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin E₂/Prostacyclin</td>
<td><strong>Immunoregulatory</strong></td>
</tr>
<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></td>
<td>Blocks platelet aggregation</td>
</tr>
<tr>
<td></td>
<td>Increases vasodilation</td>
</tr>
<tr>
<td></td>
<td>Stimulates adenylate cyclase</td>
</tr>
<tr>
<td>Thromboxoxane</td>
<td><strong>Causes vasoconstriction</strong></td>
</tr>
<tr>
<td></td>
<td>Induces platelet aggregation</td>
</tr>
</tbody>
</table>
# Biological Function

**Lipoxygenase-derived Products:**

<table>
<thead>
<tr>
<th>Leukotriene $\text{B}_4$</th>
<th>Neutrophil Activation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- degranulation</td>
</tr>
<tr>
<td></td>
<td><strong>Mast cell activation</strong></td>
</tr>
<tr>
<td></td>
<td>- degranulation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Leukotriene $\text{C, D, E}$ (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

Viruses
Bacteria
Toxins

Activated leukocytes
Endogenous pyrogen

Phagocytic leukocytes

Arachidonic Acid
Prostaglandin E2
Temperature

Aspirin
NSAIDs

Shivering
Sweating
Vasomotor tone

(e.g. Interleukin-1)
Rheumatoid Arthritis distorts joints

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

- Complement
- Fixation Activation
- Chemotaxis
- Lysosomal Enzymes
  - Collagenase
  - Neutral Proteases
  - Phospholipase

- Activated oxygen ($O_2, H_2O_2$)

- 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 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 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
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.

Physiologic Stimuli → COX-1 (constitutive) → PG E2 (Renal function), Thromboxane A2 (Platelet function), Prostacycline (PGL2) (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

Cell membrane
Phospholipids

Arachidonic acid

COX-1+2
Prostaglandins
Prostaglandin E$_2$
Prostacyclin PGI$_2$

COX-1
Thromboxanes
TXB$_2$

Lipoxygenases (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

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 PGI$_2$

- Anti-thrombotic

Platelets

- COX-1

- TXB2

- Pro-thrombotic

Ibuprofen*

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

Endothelium

COX-2

Prostacyclin PGI$_2$

Anti-thrombotic

Platelets

COX-1

TXB2

Pro-thrombotic

Therapeutic targets

Vioxx®
Acute inflammation: lipid mediators

Therapeutic targets

Aspirin inhibits COX-2 irreversibly

Prostacyclin PGI₂

Aspirin inhibits COX-1 irreversibly

TXB₂

Endothelium

Platelets

All cells but the platelet can resynthesize the enzymes

Anti-thrombotic

Pro-thrombotic
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