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

LIPOXGENASE PATHWAY

5-HYDROPEROXYEICOSATETRAENOIC ACID (5-HPETE)

- LTA₄ (UNSTABLE)
- LTB₄
- LTC₄
- LTD₄
- LTE₄

CYCLOOXYGENASE PATHWAY

- PGG₂ → PGH₂
- PGI₂ (UNSTABLE)
- PGE₂ (UNSTABLE)
- TXA₂ (UNSTABLE)
- TxB₂
Cell Membrane
Phospholipids

\[ \text{PHOSPHOLIPASE A}_2 \]

\[ \text{Arachidonic Acid} \]

\[ \text{CYCLOOXYGENASE} \]

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

\[ \text{Les} \]

\[ \text{PI}_{2} \]

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

\[ \text{UNSTABLE} \]

\[ \text{PGE}_2 \]

\[ \text{TXA}_2 \]

\[ \text{UNSTABLE} \]

\[ \text{TXB}_2 \]

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

\[ \text{PGF}_{2\alpha} \]
Leukotriene Synthesis

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 +</td>
</tr>
<tr>
<td></td>
<td>Leukotrienes</td>
</tr>
<tr>
<td>Platelets</td>
<td>Thromboxoxane</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>Prostacyclin</td>
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</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>Leukotriene $B_4$</th>
<th>Neutrophil Activation</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>- degranulation</td>
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<th>Mast cell activation</th>
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<tr>
<th>Leukotriene C,D,E (SRS-A)</th>
<th>Causes smooth muscle contraction</th>
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<tbody>
<tr>
<td></td>
<td>Increases vascular permeability</td>
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</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 leukocytes
Endogenous pyrogen

Phagocytic leukocytes

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 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…….
THE HOMEOSTATIC BALANCE

PGI₂
ENDOTHELium

TXA₂
PLATELETS
Thrombus Formation

Elastic Lamina

Injury

ADP

Thromboxane

Collagen

Aggregation

Organization

Plaque

platelets

Endothelium

Basement Membrane

Thrombus
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.
Stimulus

Phospholipase

Cell membrane
Phospholipids

Arachidonic acid

lipid mediators of Inflammation
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$_4$
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 $\text{PGI}_2$

COX-2

Anti-thrombotic

Platelets

TXB2

Pro-thrombotic

COX-1

NSAIDs inhibit both COX-1 and COX-2; COXIBs inhibit COX-2

Therapeutic targets
Acute inflammation: lipid mediators

**Therapeutic targets**

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

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

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

Therapeutic targets

Endothelium

Prostacyclin PGI₂

COX-2

Vioxx®

Platelets

TXB2

COX-1

Anti-thrombotic

Pro-thrombotic
Prostacyclin PGI$_2$ and TXB2 are lipid mediators involved in acute inflammation. Aspirin inhibits COX-1 irreversibly, targeting platelets, while aspirin inhibits COX-2 irreversibly, affecting all cells except platelets. Prostacyclin PGI$_2$ is anti-thrombotic, while TXB2 is pro-thrombotic. Endothelium and platelets are the therapeutic targets for aspirin intervention.
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  Interferons
  Tumor Necrosis Factor
  Growth Factors