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 ($\text{H}_2\text{O}_2$)
  - superoxide anion ($\text{O}_2^-$)
  - hypochlorous acid ($\text{HOCl}^-$)
- **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

Phospholipase C

Lysophospholipid

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)

Lipoxygenase

Glutathione-S-transferase
<table>
<thead>
<tr>
<th>CELL</th>
<th>PRODUCT</th>
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<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 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>
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<tbody>
<tr>
<td></td>
<td>- degranulation</td>
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<th>Mast cell activation</th>
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<td>- degranulation</td>
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<tr>
<th>Leukotriene C,D,E (SRS-A)</th>
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<tr>
<th>Causes smooth muscle contraction</th>
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<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
**Production of Fever**

Viroles, Bacteria, Toxins → Activated leukocytes → Endogenous pyrogen → Aspirin, NSAIDs, interleukin-1 → Arachidonic Acid → Prostaglandin E2 → Temperature

Hypothalamus

- Shivering
- Sweating
- Vasomotor tone
Rheumatoid Arthritis distorts joints

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

- Complement
  - Anti-altered IgG
  - Altered IgG
- Chemotaxis
- Fixation Activation
- Granules
  - Phagolysosome
  - Lysosomal Enzymes
  - Collagenase
  - Neutral Proteases
  - Phospholipase
- Nonsteroidal Anti-inflammatory Agents
  - Arachidonic acid
  - Prostaglandins
  - Nerve Sensitization
  - Vasodilation
  - Cartilage
  - Activated oxygen
    - $\text{O}_2$, $\text{H}_2\text{O}_2$
  - Subchondral bone plate

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 (Acetominophen)
- 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
ENDOTHELium

TXA₂
PLATELETS
Thrombus Formation

1. Elastic Lamina
2. Basement Membrane
3. Endothelium
4. Platelets
5. Injury
6. ADP
7. Thromboxane
8. Collagen
9. Aggregation
10. Organization
11. 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

Cell membrane
Phospholipids

Phospholipase

Arachidonic acid

**COX-1+2**
Prostaglandins
Prostaglandin E₂
Prostacyclin PGI₂

**COX-1**
Thromboxanen
TXB₂

**Lipoxygenases (5-LO)**
Leukotrienes
LTB₄
LTC₄, LTD₄

**COX-1**

**Stimulus**

**Phospholipase**

**Arachidonic acid**

**Prostaglandins**
Prostaglandin E₂
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**Leukotrienes**
LTB₄
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Acute inflammation: lipid mediators

Stimulus

Cell membrane Phospholipids

Phospholipase

Arachidonic acid

COX-1+2

Prostaglandins

Prostaglandin E\textsubscript{2}

Prostacyclin PGI\textsubscript{2}

COX-1

Thromboxanes

TXB\textsubscript{2}

Lipooxigenases (5-LO)

Leukotrienes

LTB\textsubscript{4}

LTC\textsubscript{4, LTD}\textsubscript{4}

Acute inflammation: lipid mediators

An important role in vascular homeostasis

Endothelium

Prostacyclin $\text{PGI}_2$

Anti-thrombotic

Platelets

TXB2

Pro-thrombotic
Acute inflammation: lipid mediators

Endothelium

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

Platelets

- COX-1
- TXB2
- Pro-thrombotic

Therapeutic targets

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

Therapeutic targets

Endothelium

Platelets

COX-2

Ibuprofen*

COX-1

Prostacyclin PGI₂

TXB₂

Anti-thrombotic

Pro-thrombotic

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

Therapeutic targets

Endothelium

COX-2

Prostacyclin PGI$_2$

Anti-thrombotic

Platelets

COX-1

TXB2

Pro-thrombotic

Vioxx®
Acute inflammation: lipid mediators

**Therapeutic targets**

- **Endothelium**
  - **Prostacyclin PGI₂**
  - **Aspirin inhibits COX-2 irreversibly**

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

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

**Anti-thrombotic**

**Pro-thrombotic**
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