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

Cyclooxygenase 1 + Lipoygenase Products
Cyclooxygenase 2
ARACHIDONIC ACID

LIPOXYGENASE PATHWAY

5-HYDROPEROXIDEICOSATETRAENOIC ACID (5-HPETE)

\[ \rightarrow \text{LTA}_4 \]

\( \text{LTA}_4 \) (UNSTABLE)

\[ \rightarrow \text{LTB}_4 \]

\[ \rightarrow \text{LTC}_4 \]

\[ \rightarrow \text{LTD}_4 \]

\[ \rightarrow \text{LTE}_4 \]

CYCLOOXYGENASE PATHWAY

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

\[ \rightarrow \text{PGI}_2 \] (UNSTABLE)

\[ \rightarrow \text{PGE}_2 \]

\[ \rightarrow \text{TXA}_2 \] (UNSTABLE)

\[ \rightarrow \text{TXB}_2 \]

\[ \text{5-Keto PGF}_{1\alpha} \]
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>
</tbody>
</table>
**Biological Function**

**Cyclooxygenase-derived Products:**

<table>
<thead>
<tr>
<th>Product</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin $E_2$</td>
<td>Immunoregulatory</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>Thromboxane</td>
<td>Causes vasoconstriction</td>
</tr>
<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</td>
<td>Causes smooth muscle contraction</td>
</tr>
<tr>
<td>(SRS-A)</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

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/
Immunopathology of Rheumatoid Arthritis

- Complement
- Anti-altered IgG
- Altered IgG
- Chemotaxis
- Lysosomal Enzymes
  - Collagenase
  - Neutral Proteases
  - Phospholipase
- Arachidonic acid
  - Prostaglandins
- Nerve Sensitization
- Vasodilation

Activated oxygen ($O_2$, $H_2O_2$)

Cartilage

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

BY: Chaval Btasil
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THE HOMEOSTATIC BALANCE

PGI₂
ENDOTHELİUM

TXA₂
PLATELETS

BY: Gretaz  GNU 1.2
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 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

Stimulus

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Cell membrane
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Prostaglandins
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Lipooxigenases (5-LO)
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- LTB$_4$
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Vasodilation, Increase vascular permeability, Control platelet aggregation, Chemotaxis, Pain, Fever
Acute inflammation: lipid mediators

An important role in vascular homeostasis

Endothelium

Prostacyclin PGI$_2$

Platelets

TXB2

Pro-thrombotic

Anti-thrombotic

Red arrows indicate the direction of the effect from the left side to the right side.
Acute inflammation: lipid mediators

Endothelium

COX-2

Prostacyclin PGI₂

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

Platelets

COX-2

Ibuprofen*

COX-1

Prostacyclin PGI₂

TXB2

Anti-thrombotic

Pro-thrombotic

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

Endothelium

COX-2

Prostacyclin PGI₂

Anti-thrombotic

Platelets

COX-1

TXB2

Pro-thrombotic

Therapeutic targets

Vioxx®
Prostacyclin $\text{PGI}_2$

Endothelium

Platelets

Aspirin inhibits COX-1 irreversibly

$\text{TXB}_2$

All cells but the platelet can resynthesize the enzymes

Therapeutic targets

Aspirin inhibits COX-2 irreversibly

Pro-thrombotic

Anti-thrombotic
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  Tumor Necrosis Factor
  Growth Factors