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
STIMULI

Cell Membrane Phospholipids

PHOSPHOLIPASE A2

LIPOXGENASE PATHWAY

HETEs [mono & di]

LEUKOTRIENE [SRS-A]

Arachidonic Acid

CYCLOOXYGENASE

$\text{PGG}_2 \rightarrow \text{PGH}_2$

$\text{PGI}_2$ UNSTABLE

$\text{PGE}_2$

+ $\text{PGF}_{2\alpha}$

$\text{TXA}_2$ UNSTABLE

$\text{TXB}_2$
Leukotriene Synthesis

1. Arachidonic Acid
   \[
   \text{Lipoxygenase} \rightarrow \text{5-HPETE}
   \]
   \[
   \text{Leukotriene A (LTA)}
   \]
   \[
   \text{Leukotriene B (LTB)} \rightarrow \text{Leukotriene C (LTC)} \rightarrow \text{Leukotriene D (LTD)}
   \]

2. Glutathione-S-transferase

Chemical structures and reactions are shown in the diagram.
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>Prostacycllin</td>
</tr>
</tbody>
</table>
ARACHIDONIC ACID

LIPOXGENASE PATHWAY

5-HYDROPEROXEOICOSATETRAENOIC ACID (5-HPETE)

\[
\text{LTA}_4 \quad \text{(UNSTABLE)}
\]

\[
\text{LTC}_2
\]

\[
\text{LTB}_2
\]

\[
\text{LTD}_4
\]

\[
\text{LTE}_4
\]

CYCLOOXYGENASE PATHWAY

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

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

\[
\text{PGE}_2
\]

\[
\text{PGF}_2^+)
\]

\[
\text{5-Keto PGF}_1^2
\]

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

\[
\text{TXB}_2
\]
# Biological Function

**Cyclooxygenase-derived Products:**

<table>
<thead>
<tr>
<th>Product</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin E$_2$/Prostacyclin</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>Thromboxxane</td>
<td>Causes vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Induces platelet aggregation</td>
</tr>
</tbody>
</table>
Biological Function

Lipoxygenase-derived Products:

Leukotriene $B_4$  Neutrophil Activation
- degranulation

Mast cell activation
- degranulation

Leukotriene C,D,E (SRS-A)  Causes smooth muscle contraction
Increases vascular permeability
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

Aspirin
NSAIDs

(e.g. Interleukin-1)

Shivering
Sweating
Vasomotor tone
Rheumatoid Arthritis distorts joints

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

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

Chemotaxis

- Anti-altered IgG
- Altered IgG

Cartilage

- Subchondral bone plate

Nonsteroidal Anti-inflammatory Agents

- Arachidonic acid
- Prostaglandins

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 (acetysalicylic 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.
INDOMETHACIN

IBUPROFEN

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

PGI<sub>2</sub>
ENDOTHELIUM

TXA<sub>2</sub>
PLATELETS

BY: Gretaz
GNU 1.2
Thrombus Formation

- Elastic Lamina
- Platelets
- Basement Membrane
- Endothelium
- Injury
- Thromboxane
- ADP
- Collagen
- Aggregation
- 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.
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 E₂
Prostacyclin PGI₂

COX-1
Thromboxanes
TXB₂

Lipooxygenases (5-LO)
Leukotrienes
LTB₄
LTC₄, LTD₄
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

An important role in vascular homeostasis

Endothelium

Prostacyclin $\text{PGI}_2$

Anti-thrombotic

Platelets

$\text{TXB}_2$

Pro-thrombotic
Acute inflammation: lipid mediators

Therapeutic targets

- 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**
  - Prostaglandin E2 (PGE2)
  - Prostacyclin (PGI2)

- **Platelets**
  - Thromboxane A2 (TXA2)
  - Thromboxane B2 (TXB2)

**Pathways**

- **COX-2**
  - Prostacyclin (PGI2)
  - Pro-thrombotic

- **Ibuprofen**
  - COX-2 inhibition

- **COX-1**
  - Thromboxane B2 (TXB2)
  - Anti-thrombotic

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

Therapeutic targets

Endothelium

COX-2

Prostacyclin PGI₂

Platelets

COX-1

TXB₂

Vioxx®

Anti-thrombotic

Pro-thrombotic
Acute inflammation: lipid mediators

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

**Platelets**
- All cells but the platelet can resynthesize the enzymes
- **Aspirin** inhibits COX-1 irreversibly
- TXB₂

Therapeutic targets

Anti-thrombotic

Pro-thrombotic
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  Interferons
  Tumor Necrosis Factor
  Growth Factors