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
STIMULI

Cell Membrane Phospholipids

\[ \text{Lipoxygenase Pathway} \]

HETEs
[mono & di]

Leukotriene
[SRS-A]

Arachidonic Acid

\[ \text{Cyclooxygenase} \]

PGG\(_2\) \rightarrow PGH\(_2\)

PGI\(_2\) Unstable

PGF\(_{2\alpha}\)

6-Keto PGF\(_{1\alpha}\)

TXA\(_2\) Unstable

TXB\(_2\)

\[ \text{COOH} \]

\[ \text{COOH} \]

\[ \text{COOH} \]
Leukotriene Synthesis

Arachidonic Acid

Lipoxygenase → 5-HPETE

Leukotriene A (LTA)

Glutathione-S-transferase

Leukotriene B (LTB) → Leukotriene C (LTC) → Leukotriene D (LTD)
## 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>Thromboxxane</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>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin E₂/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:

<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></td>
<td>Mast cell activation</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
Production of Fever

Hypothalamus

Viruses
Bacteria
Toxins

Phagocytic leukocytes

Activated leukocytes
Endogenous pyrogen

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

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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 cysteinyl 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
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.
l lipid mediators of Inflammation

Stimulus

+ Phospholipase

Cell membrane
Phospholipids

Arachidonic acid
Acute inflammation: lipid mediators

Stimulus

Cell membrane
Phospholipids

Arachidonic acid

\[ \text{Stimulus} \rightarrow \text{Phospholipase} \rightarrow \text{Arachidonic acid} \]

\[ \text{Arachidonic acid} \rightarrow \text{COX-1+2} \rightarrow \text{Prostaglandins} \]

\[ \text{COX-1} \rightarrow \text{Thromboxanes} \]

\[ \text{Lipoxygenases (5-LO)} \rightarrow \text{Leukotrienes} \]

\[ \text{Prostaglandin E}_2, \text{Prostacyclin PGI}_2 \]

\[ \text{Thromboxane B}_2 \]

\[ \text{LTB}_4, \text{LTC}_4, \text{LTD}_4 \]
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

An important role in vascular homeostasis

- Prostacyclin (PGI₂)
- TXB₂

Endothelium → Prostacyclin (PGI₂) → Anti-thrombotic

Platelets → TXB₂ → Pro-thrombotic
Acute inflammation: lipid mediators

Therapeutic targets

Endothelium

COX-2

Prostacyclin $\text{PGI}_2$

Anti-thrombotic

Platelets

COX-1

$\text{TXB}_2$

Pro-thrombotic

NSAIDs inhibit both COX-1 and COX-2; COXIBs inhibit COX-2
Prostacyclin PGI$_2$  
TXB$_2$  

Anti-thrombotic  Pro-thrombotic

Endothelium  Platelets

COX-2  COX-1

Prostaglandin PGI$_2$  TXB$_2$

Ibuprofen*  * Classical NSAID, it inhibits both COX enzymes

Therapeutic targets
Acute inflammation: lipid mediators

Endothelium

Prostacyclin PGI$_2$

COX-2

Platelets

TXB2

COX-1

Anti-thrombotic

Pro-thrombotic

Therapeutic targets

Vioxx®
Prostacyclin $\text{PGI}_2$

Endothelium

Aspirin inhibits COX-2 irreversibly

All cells but the platelet can resynthesize the enzymes

Prostacyclin $\text{PGI}_2$

Platelets

Aspirin inhibits COX-1 irreversibly

$\text{TXB}_2$

Therapeutic targets

Anti-thrombotic

Pro-thrombotic
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  Interferons
  Tumor Necrosis Factor
  Growth Factors