Arachidonic Acid Metabolites and Inflammation

Joseph Fantone, M.D.
Host Defense 2/12  10-11:00am
<table>
<thead>
<tr>
<th>INFLAMMATORY MEDIATORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLASMA DERIVED</td>
</tr>
<tr>
<td>• COMPLEMENT CASCADE</td>
</tr>
<tr>
<td>C3a, C5a</td>
</tr>
<tr>
<td>• COAGULATION CASCADE</td>
</tr>
<tr>
<td>Thrombin, plasmin</td>
</tr>
<tr>
<td>CELL-DERIVED</td>
</tr>
<tr>
<td>• VASOACTIVE AMINES</td>
</tr>
<tr>
<td>histamine, serotonin</td>
</tr>
<tr>
<td>• OXYGEN METABOLITES</td>
</tr>
<tr>
<td>hydrogen peroxide (H₂O₂)</td>
</tr>
<tr>
<td>superoxide anion (O₂⁻)</td>
</tr>
<tr>
<td>hypochlorous acid (HOCl⁻)</td>
</tr>
<tr>
<td>• ARACHIDONIC ACID METABOLITES</td>
</tr>
<tr>
<td>cyclooxygenase-derived</td>
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<tr>
<td>lipoxygenase-derived</td>
</tr>
<tr>
<td>• CYTOKINES</td>
</tr>
<tr>
<td>Interleukins</td>
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<tr>
<td>Chemokines</td>
</tr>
<tr>
<td>Interferons</td>
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<tr>
<td>Tumor Necrosis Factor</td>
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<tr>
<td>Growth Factors</td>
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</tbody>
</table>
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 + phospholyl-R

Diacylglycerol

Diacylglyceride lipase

Arachidonic acid + HO-CH

Cyclooxygenase 1 + Lipoxygenase Products

Cyclooxygenase 2
STIMULI

Cell Membrane Phospolipids

PHOSPHOLIPASE A2

LIPoxyGENASE PATHWAY

HETEs [mono & di]

LEUKOTRIENE (SRS-A)

Arachidonic Acid

CYCLOOXYGENASE

PGG2 → PGH2

PGI2 UNSTABLE

PGE2

TXA2 UNSTABLE

6-Keto PGF1α

PGF2α

TXB2
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 + Leukotrienes</td>
</tr>
<tr>
<td>Platelets</td>
<td>Thromboxane</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>Prostacyclin</td>
</tr>
</tbody>
</table>
Biological Function

Cycloxygenase-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:**

| Leukotriene B₄ | 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

(e.g. Interleukin-1)

Arachidonic Acid → Prostaglandin E2 → Temperature

Aspirin
NSAIDs

Shivering
Sweating
Vasomotor tone
Rheumatoid Arthritis distorts joints

Source: http://www.nih.gov/
Chemotactic Activity of LTB4

BY: Greg Luerman
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.

\[
\begin{align*}
\text{COOH} & \quad \text{OCCH}_3 \\
+ & \quad \text{H}_2\text{N-ENZYME} \quad \rightarrow \quad \text{COOH} & \quad \text{OH} & \quad \text{CH}_3\text{C}^\text{--H}_2\text{N-ENZYME} \\
\text{(INACTIVE)}
\end{align*}
\]
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
THE HOMEOSTATIC BALANCE

PGI₂
ENDOTHELIIUM

TXA₂
PLATELETS

BY: Gretaz
GNU 1.2
Thrombus Formation

- Elastic Lamina
- Basement Membrane
- Endothelium

Platelets

Injury

- ADP
- Thromboxane
- 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 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.
lipid mediators of Inflammation

Stimulus

+ Phospholipase

Cell membrane Phospholipids

Arachidonic acid
Acute inflammation: lipid mediators

Stimulus

Phospholipase

Arachidonic acid

Cell membrane
Phospholipids

Prostaglandins
Thromboxanes
Leukotrienes

Prostaglandin E\(_2\)
Prostacyclin PGI\(_2\)

COX-1+2

COX-1

Lipoxygenases (5-LO)

Prostaglandins
Thromboxanes
Leukotrienes

LTB\(_4\)
LTC\(_4\), LTD\(_4\)
Acute inflammation: lipid mediators

Stimulus

Phospholipase

Cell membrane
Phospholipids

Arachidonic acid

COX-1+2
Prostaglandins
Prostaglandin E$_2$
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COX-1
Thromboxanes
TXB$_2$

Lipooxigenases (5-LO)
Leukotrienes
LTB$_4$
LTC$_4$, LTD$_4$

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

COX-2

Prostacyclin PGI₂

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**

- Prostacyclin PGI$_2$
- TXB2

**Endothelium**

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

**Platelets**

- COX-1
- TXB2
- Pro-thrombotic

* Classical NSAID, it inhibits both COX enzymes

Ibuprofen* inhibits both COX-1 and COX-2 enzymes.
Acute inflammation: lipid mediators

Therapeutic targets

Endothelium

- COX-2
- Prostacyclin PGI₂
- Anti-thrombotic

Platelets

- COX-1
- TXB2
- Pro-thrombotic

Vioxx®
Prostacyclin PGI\textsubscript{2}  

Endothelium  

Aspirin inhibits COX-2 irreversibly  

All cells but the platelet can resynthesize the enzymes  

Prostacyclin PGI\textsubscript{2}  

Aspirin inhibits COX-1 irreversibly  

TXB\textsubscript{2}  

Platelets  

Therapeutic targets  

Anti-thrombotic  

Pro-thrombotic
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  Tumor Necrosis Factor
  Growth Factors