2008-09

M1 - Immunology, Winter 2008

Fantone, J.; Pietropaolo, M. T.

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 (HOCI$^-$)
• 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
Cell Membrane Phospholipids

\[ \text{Phospholipase A}_2 \]

\[ \rightarrow \text{Arachidonic Acid} \]

\[ \rightarrow \text{Cyclooxygenase} \]

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

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

\[ \rightarrow \text{6-Keto PGF}_1\alpha \]

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

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

Arachidonic Acid

Lipoxygenase

5-HPETE

Leukotriene A (LTA)

Glutathione-S-transferase

Leukotriene B (LTB)

Leukotriene C (LTC)

Leukotriene D (LTD)
<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 +</td>
</tr>
<tr>
<td></td>
<td>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>Prostaglandin E₂/Prostacyclin</th>
<th>Immunoregulatory</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thromboxane</th>
<th>Causes vasoconstriction</th>
</tr>
</thead>
<tbody>
<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>- degranulation</td>
</tr>
<tr>
<td>Leukotriene C,D,E (SRS-A)</td>
<td>Causes smooth muscle contraction</td>
</tr>
<tr>
<td></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 → Arachidonic Acid → Prostaglandin E2 → Temperature

(e.g. Interleukin-1)

Phagocytic leukocytes

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 cysteinyI 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
THE HOMEOSTATIC BALANCE

PGI₂
ENDOTHELium

TXA₂
PLATELETs

BY: Gretaz
GNU 1.2
Thrombus Formation

Thrombus

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 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.

Physiologic Stimuli → COX-1 (constitutive) → PG E_2 (Renal function) → Thromboxane A_2 (Platelet function) → Prostacycline (PGI_2) (Gastric Protection) → COX-2 (inducible) → Pro-inflammatory PGs and other inflammatory mediators → Inflammation

Inflammatory Stimuli
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

Lipooxigenases (5-LO)
Leukotrienes
LTB₄
LTC₄, LTD₄
Acute inflammation: lipid mediators

Stimulus

+ Phospholipase

Cell membrane
Phospholipids

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COX-1+2
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Lipooxigenases (5-LO)
Leukotrienes
LTB₄
LTC₄, LTD₄

Vasodilation  Increase vascular permeability  Control platelet aggregation  Chemotaxis  Pain  Fever
Acute inflammation: lipid mediators

An important role in vascular homeostasis

Endothelium

Prostacyclin PGI₂

Anti-thrombotic

Platelets

TXB2

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**

- COX-2
- Prostacyclin PGI\(_2\)
- Anti-thrombotic

**Platelets**

- COX-1
- TXB2
- Pro-thrombotic

**Ibuprofen**

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

Therapeutic targets

Endothelium

- COX-2
- Prostacyclin PGI₂

Platelets

- COX-1
- TXB2

Anti-thrombotic

Pro-thrombotic
Prostacyclin PGI_2

Endothelium

Aspirin inhibits COX-2 irreversibly

All cells but the platelet can resynthesize the enzymes

Prostacyclin PGI_2

Platelets

Aspirin inhibits COX-1 irreversibly

TXB2

Anti-thrombotic

Pro-thrombotic

Therapeutic targets
INFLAMMATORY MEDIATORS

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