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
Phospholipid

- Phospholipase A
  - Lysophospholipid + Arachidonic acid

- Phospholipase C
  - Arachidonic acid + phosphoryl-R
    - Diacylglycerol
      - Diacylglyceride lipase
      - Arachidonic acid + HO-CH

Cyclooxygenase 1 + Lipooxygenase Products:
Cyclooxygenase 2
Cell Membrane Phospholipids

- PHOSPHOLIPASE A₂

Lipoxygenase Pathway

- HETEs (mono & di)
- LEUKOTRIENE (SRS-A)

Arachidonic Acid

- CYCLOOXYGENASE

PGG₂ → PGH₂

PGI₂ → PGE₂

TXA₂ → TXB₂

6-Keto PGF₁α
### 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>
Cyclooxygenase-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:

<table>
<thead>
<tr>
<th>Product</th>
<th>Function</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

- Arachidonic Acid
- Prostaglandin E2
- Temperature

Activation of leukocytes leads to endogenous pyrogen formation.

Phagocytic leukocytes

(e.g. Interleukin-1)

Viruses, Bacteria, Toxins

Activated leukocytes

Aspirin
NSAIDs

Shivering
Sweating
Vasomotor tone
Rheumatoid Arthritis distorts joints

Source: http://www.nih.gov/
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 (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!!
ASPIRIN

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 and 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

PGI₂
ENDOTHELUM

TXA₂
PLATELETS

BY: Gretaz
GNU 1.2
Source: Undetermined
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
Arachidonic acid

Cell membrane
Phospholipids

Phospholipase

Arachidonic acid

Stimulus

COX-1+2
Prostaglandins
Prostaglandin E₂
Prostacyclin PGI₂

COX-1
Thromboxanes
TXB₂

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

Stimulus

Cell membrane
Phospholipids

Phospholipase

Arachidonic acid

COX-1+2
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Lipooxigenases (5-LO)
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Vasodilation, Increase vascular permeability, Control platelet aggregation, Chemotaxis, Pain, Fever
Acute inflammation: lipid mediators

An important role in vascular homeostasis

[Diagram:]

Endothelium → Prostacyclin PGI$_2$ → Anti-thrombotic

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

**Therapeutic targets**

- **Endothelium**
  - COX-2
  - Prostacyclin PGI$_2$
  - 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 PGI₂

Anti-thrombotic

Platelets

Ibuprofen*

COX-1

TXB2

Pro-thrombotic

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

**Therapeutic targets**

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

- Platelets
  - COX-1
  - TXB2
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**Vioxx®**
Acute inflammation: lipid mediators

Therapeutic targets

Endothelium

Platelets

Prostacyclin PGI$_2$

TXB2

Aspirin inhibits COX-2 irreversibly

Aspirin inhibits COX-1 irreversibly

All cells but the platelet can resynthesize the enzymes

Antithrombotic

Pro-thrombotic

The image describes the actions of aspirin on COX-1 and COX-2 enzymes, affecting prostacyclin PGI$_2$ and TXB2 production in endothelial and platelet cells, respectively. Aspirin irreversibly inhibits COX-2 in all cells except platelets, which can resynthesize the enzymes. In platelets, aspirin irreversibly inhibits COX-1.
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