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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 ($H_2O_2$)
  - 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
Arachidonic acid

Phospholipid

Phospholipase A

Lysophospholipid

Phospholipase C

Diacylglycerol

Diacylglyceride lipase

Cyclooxygenase 1 + Lipoxygenase Products

Cyclooxygenase 2
Leukotriene Synthesis

Arachidonic Acid → 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>
</tbody>
</table>
| Macrophage/Monocyte | Prostaglandins +
|                  | Leukotrienes             |
| Platelets        | Thromboxxane             |
| Endothelial Cells | Prostacyclin             |
Biological Function

Cyclooxygenase-derived Products:

Prostaglandin $E_2$/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>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 (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

Phagocytic
leukocytes

Arachidonic
Acid

Prostaglandin E2

Temperature

Aspirin
NSAIDs

Shivering
Sweating
Vasomotor tone

(e.g. Interleukin-1)
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 (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
THE HOMEOSTATIC BALANCE

PGI₂
ENDOTHELIUM

TXA₂
PLATELETS
Thrombus Formation

- Elastic Lamina
- Platelets
- Basement Membrane
- Endothelium
- Injury
- ADP
- Thromboxane
- Collagen
- Aggregation
- Thrombus
- 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 → Arachidonic acid

Cell membrane
Phospholipids
Acute inflammation: lipid mediators

- Stimulus

Phospholipase → 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 → Phospholipids → Arachidonic acid

- COX-1+2
  - Prostaglandins
    - Prostaglandin E$_2$
    - Prostacyclin PGI$_2$

- COX-1
  - Thromboxanes
    - TXB$_2$

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

Vasodilation, increase vascular permeability, control platelet aggregation, chemotaxis, pain, fever
Acute inflammation: lipid mediators

An important role in vascular homeostasis

Endothelium

Prostacyclin PGI$_2$

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 PGI₂
  - Anti-thrombotic

- **Platelets**
  - COX-1
  - TXB2
  - Pro-thrombotic

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

Therapeutic targets

Endothelium
- COX-2
- Prostacyclin PGI₂
- Anti-thrombotic

Platelets
- COX-1
- TXB2
- Pro-thrombotic

Vioxx®
Acute inflammation: lipid mediators

**Therapeutic targets**

Endothelium

Prostacyclin PGI2

Aspirin inhibits COX-2 irreversibly

All cells but the platelet can resynthesize the enzymes

Platelets

TXB2

Aspirin inhibits COX-1 irreversibly

Anti-thrombotic

Pro-thrombotic
INFLAMMATORY MEDIATORS

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  Chemokines
  Interferons
  Tumor Necrosis Factor
  Growth Factors