2008-09

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
Arachidonic acid \(-\text{CH}\) \(-\text{CH}_2\text{O}-\text{P-O-R}\) \(\text{CH}_2\text{O}\) \(\text{HO-CH}\) \(\text{CH}_2\text{O}-\text{P-O-R}\) Lysophospholipid

Phospholipid

Phospholipase A

Arachidonic acid \(-\text{CH}\) \(\text{CH}_2\text{O}\) \(\text{HO-CH}\) \(\text{CH}_2\text{OH}\) Diacylglycerol

Phospholipase C

Arachidonic acid \(-\text{CH}\) \(\text{CH}_2\text{OH}\) Diacylglyceride lipase

Cyclooxygenase 1 + Lipoxigenase Products

Cyclooxygenase 2
Cell Membrane Phospholipids

Lipoxygenase Pathway

HETEs (mono & di)

Leukotriene (SRS-A)

Arachidonic Acid

PGG$_2$ → PGH$_2$

PGI$_2$ → Unstable

6-Keto PGF$_{1\alpha}$

PGE$_2$

PGF$_{2\alpha}$

TXA$_2$ → Unstable

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>Thromboxoxane</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>Prostacycllin</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>
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</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:

- Leukotriene B\(_4\)  
  - 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  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 (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......
THE HOMEOSTATIC BALANCE

PGI$_2$ ENDOTHELium

TXA$_2$ PLATELETS

BY: Gretaz

GNU 1.2
Thrombus Formation

- Elastic Lamina
- Platelets
- Basement Membrane
- Endothelium
- Injury
- ADP
- Thromboxane
- Collagen
- Aggregation
- Organization
- Plaque

THROMBUS
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

Cell membrane
Phospholipids

Arachidonic acid

Phospholipase

COX-1+2
Prostaglandins
Prostaglandin E₂
Prostacyclin PGI₂

COX-1
Thromboxanes
TXB₂

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

Stimulus

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COX-1+2
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Prostaglandin E\(_2\)
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COX-1
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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
Prostacyclin $\text{PGI}_2$

COX-2

Endothelium

TXB2

COX-1

Platelets

Pro-thrombotic

Anti-thrombotic

NSAIDs inhibit both COX-1 and COX-2; COXIBs inhibit COX-2
Acute inflammation: lipid mediators

Therapeutic targets

Endothelium → COX-2 → Prostacyclin PGI₂

Platelets → COX-1 → TXB2

Ibuprofen* inhibits COX-2

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

**Therapeutic targets**

- COX-2
  - Prostacyclin PGI$_2$
  - Anti-thrombotic
- COX-1
  - TXB2
  - Pro-thrombotic

**Endothelium**

- Prostacyclin PGI$_2$

**Platelets**

- TXB2

**Vioxx®**

- Inhibits COX-2

- Reduces thrombotic effects
Acute inflammation: lipid mediators

**Therapeutic targets**

- **Prostacyclin PGI$_2$**
- **TXB2**

**Endothelium**

- Aspirin inhibits COX-2 irreversibly
- Prostacyclin PGI$_2$

**Platelets**

- Aspirin inhibits COX-1 irreversibly
- All cells but the platelet can resynthesize the enzymes
- TXB2

**Antithrombotic**

**Pro-thrombotic**
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