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 ($H_2O_2$)
  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
Phospholipid

Arachidonic acid

CH₂O

CH₂-O-P-O-R

Lysophospholipid

Phospholipase A

+ Arachidonic acid

CH₂O

HO-CH

CH₂-O-P-O-R

Diacylglycerol

Phospholipase C

Arachidonic acid

CH₂O

CH₂-OH

+ phosphoryl-R

Diacylglyceride lipase

Arachidonic acid

CH₂O

HO-CH

CH₂-OH

Cyclooxygenase 1 + Lipooxygenase Products

Cyclooxygenase 2
Cell Membrane Phospholipids

Lipoxygenase Pathway
HETEs (mono & di)
Leukotriene (SRS-A)

Arachidonic Acid

PGG2 → PGH2

PGI2 unstable

PGE2 + TXA2 unstable

6-Keto PGF1α
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>Thromboxane</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>Prostacyclin</td>
</tr>
<tr>
<td>Biological Function</td>
<td>Cyclooxygenase-derived Products:</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td></td>
<td>Prostaglandin $E_2$/Prostacyclin</td>
</tr>
<tr>
<td></td>
<td>Immuno regulatory</td>
</tr>
<tr>
<td></td>
<td>• Inhibits Immune cell activation</td>
</tr>
<tr>
<td></td>
<td>• Inhibits cytokine production</td>
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<tr>
<td></td>
<td>• Inhibits mast cell activation</td>
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<tr>
<td></td>
<td>Blocks platelet aggregation</td>
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<tr>
<td></td>
<td>Increases vasodilation</td>
</tr>
<tr>
<td></td>
<td>Stimulates adenylate cyclase</td>
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<tr>
<td></td>
<td>Thromboxane</td>
</tr>
<tr>
<td></td>
<td>Causes vasoconstriction</td>
</tr>
<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&lt;sub&gt;4&lt;/sub&gt;</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
Production of Fever

Hypothalamus

- Arachidonic Acid
- Prostaglandin E2
- Temperature
- (e.g. Interleukin-1)

- Aspirin
- NSAIDs
- Shivering
- Sweating
- Vasomotor tone
Rheumatoid Arthritis distorts joints

Source: http://www.nih.gov/
Immunopathology of Rheumatoid Arthritis

- Complement
- Fixation Activation
- Chemotaxis
- Lysosomal Enzymes
- Collagenase Neutral Proteases Phospholipase
- Nonsteroidal Anti-inflammatory Agents
- Arachidonic acid Prostaglandins
- Nerve Sensitization Vasodilation
- Activated oxygen ($O_2$, $H_2O_2$)
- Cartilage
- Subchondral bone plate

Source: Undetermined
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!!
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.
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
ENDOTHELium

TXA₂
PLATELETS

BY: Gretaz
GNU 1.2
Thrombus Formation

- Elastic Lamina
- Basement Membrane
- Endothelium
- platelets
- Thrombus
- ADP
- Thromboxane
- Collagen
- Aggregation
- Injury
- 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) → Prostaglandin E₂ (Renal function) → Thromboxane A₂ (Platelet function) → Prostacycline (PGL₂) (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 E\textsubscript{2}
Prostacyclin PGI\textsubscript{2}

COX-1
Thromboxanes
TXB\textsubscript{2}

Lipooxigenases (5-LO)
Leukotrienes
LTB\textsubscript{4}
LTC\textsubscript{4}, LTD\textsubscript{4}
Acute inflammation: lipid mediators

Stimulus

Cell membrane
Phospholipids

+ Phospholipase

Arachidonic acid

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

COX-1
- Thromboxanes
  - TXB$_2$

Lipooxygenases (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

**Endothelium**

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

**Endothelium**

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

**Platelets**

- COX-1
- TXB2
- Pro-thrombotic

Ibuprofen* inhibits both COX enzymes.

*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**

- **Aspirin** inhibits COX-2 irreversibly
- All cells but the platelet can resynthesize the enzymes
- **Prostaglandin E1 (PGE1)**
- **Thromboxane A2 (TXA2)**

**Endothelium**

**Platelets**

**Anti-thrombotic**

**Pro-thrombotic**

**Aspirin** inhibits COX-1 irreversibly
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  Tumor Necrosis Factor
  Growth Factors