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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$_2$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
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:

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:**

- **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 cysteinyll 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!!
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  

CH₂CO₂H  

CH₃  

Cl  

C = O  

IBUPROFEN  

CH₃  

CH₃CH₂  

CH₃  

CH₃  

CHCOOH  

CH

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

PG\textsubscript{I}\textsubscript{2}  
ENDOTHELium

TXA\textsubscript{2}  
PLATELETS

BY: Gretaz

GNU 1.2
Thrombus Formation

- 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 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

Phospholipase

Arachidonic acid

Cell membrane
Phospholipids

COX-1+2
Prostaglandins
Prostaglandin E₂
Prostacyclin PGI₂

COX-1
Thromboxanes
TXB₂

Lipoxygenases (5-LO)
Leukotrienes
LTB₄
LTC₄, LTD₄

PGE₂
Acute inflammation: lipid mediators

Stimulus

Cell membrane
Phospholipids

Phospholipase

Arachidonic acid

COX-1+2
Prostaglandins
Prostaglandin E\(_2\)
Prostacyclin PGI\(_2\)

COX-1
Thromboxanases
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

Platelets

Prostacyclin PGI₂

TXB₂

Anti-thrombotic

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

COX-1

TXB₂

Pro-thrombotic

Ibuprofen*

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

Therapeutic targets

Endothelium

- COX-2
- Prostacyclin PGI$_2$

Platelets

- COX-1
- TXB2

Anti-thrombotic

Pro-thrombotic

Vioxx®
Acute inflammation: lipid mediators

**Endothelium**
- Prostacyclin $\text{PGI}_2$
- Aspirin inhibits COX-2 irreversibly

**Platelets**
- TXB2
- Aspirin inhibits COX-1 irreversibly

**Therapeutic targets**
- All cells but the platelet can resynthesize the enzymes

**Anti-thrombotic**
- Prostaglandin $\text{PGI}_2$

**Pro-thrombotic**
- TXB2
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