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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$_2^\cdot$)
  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

1. Lipoxygenase
   - Arachidonic Acid → 5-HPETE

2. Glutathione-S-transferase
   - 5-HPETE → Leukotriene A (LTA) → 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>
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<tr>
<td>Endothelial Cells</td>
<td>Prostacyclin</td>
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</tbody>
</table>
Biological Function

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:**

- **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
**Production of Fever**

- **Hypothalamus**
  - Viruses
  - Bacteria
  - Toxins
  - Phagocytic leukocytes
  - Activated leukocytes
  - Endogenous pyrogen
  - Arachidonic Acid
  - Prostaglandin E2
  - Temperature

- (e.g. Interleukin-1)

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

Source: http://www.nih.gov/
Immune Pathology of Rheumatoid Arthritis

Complement

Activated oxygen

(O₂, H₂O₂)

Chemotaxis

Lysosomal Enzymes

Collagenase Neutral Proteases Phospholipase

Nerve Sensitization Vasodilation

Nonsteroidal Anti-inflammatory Agents

Arachidonic Acid Prostaglandins

Cartilage

Subchondral bone plate

Source: Undetermined
Chemotactic Activity of LTB4

BY: Greg Luerman

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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 cysteinyI 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…….

Aspirin
THE HOMEOSTATIC BALANCE

PGI₂
ENDOTHELium

TXA₂
PLATELETS
Thrombus Formation

- Elastic Lamina
- Baseline 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 + Phospholipids → Arachidonic acid

Cell membrane Phospholipids

Arachidonic acid
Acute inflammation: lipid mediators

Stimulus

Phospholipase

Cell membrane
Phospholipids

Arachidonic acid

COX-1+2
Prostaglandins
Prostaglandin E₂
Prostacyclin PGI₂

COX-1
Thromboxanes
TXB₂

Lipooxigenases (5-LO)
Leukotrienes
LTB₄, LTC₄, LTD₄

COX-1
Acute inflammation: lipid mediators

Stimulus

+ Phospholipase

Cell membrane
Phospholipids

Arachidonic acid

COX-1+2
Prostaglandins
Prostaglandin E₂
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Lipooxigenases (5-LO)
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LTC₄, LTD₄

Acute inflammation: lipid mediators

An important role in vascular homeostasis

- **Endothelium**
  - Prostacyclin PGI$_2$
  - Anti-thrombotic

- **Platelets**
  - TXB2
  - Pro-thrombotic

Diagram illustrating the role of prostacyclin PGI$_2$ and TXB2 in vascular homeostasis, highlighting their anti-thrombotic and pro-thrombotic properties respectively.
Prostacyclin PGI\(_2\) and TXB2

Endothelium

Platelets

COX-2

Prostacyclin PGI\(_2\)

Anti-thrombotic

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

 Platelets

COX-2

 **Ibuprofen**

COX-1

Prostacyclin $\text{PGI}_2$

TXB2

Anti-thrombotic

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®
**Prostacyclin PGI\(_2\)**

**TXB2**

**Endothelium**

**Platelets**

Aspirin inhibits COX-1 irreversibly

All cells but the platelet can resynthesize the enzymes

Aspirin inhibits COX-2 irreversibly

**Pro-thrombotic**

**Anti-thrombotic**
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