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
Cell Membrane Phospholipids → PHOSPHOLIPASE A2 → Arachidonic Acid → CYCLOOXYGENASE → PGG_2 → PGH_2 → Leukotriene (SRS-A) → PGI_2 → 6-Keto PGF_1α → TXA_2 → TxB_2 → PGE_2 → PGF_2α
Leukotriene Synthesis

Arachidonic Acid → 5-HPETE → Leukotriene A (LTA)

Leukotriene B (LTB) → Leukotriene C (LTC) → Leukotriene D (LTD)
## Cell Dependent End-Product Specificity of Arachidonic Acid-Derived Products

<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 + Leukotrienes</td>
</tr>
<tr>
<td>Platelets</td>
<td>Thromboxane</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>Prostacyclin</td>
</tr>
</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
  - Mast cell activation
  - Degranulation

- Leukotriene C,D,E
  - Causes smooth muscle contraction
  - Increases vascular permeability
  (SRS-A)
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

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 (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.

\[
\text{COOH} \quad \text{O} \quad \text{OCCH}_3
\]

\[
\text{COOH} \quad \text{O} \quad \text{OCCH}_3 + \text{H}_2\text{N-ENZYME} \rightarrow \text{COOH} \quad \text{OH} \quad \text{O} \quad \text{CH}_3\text{C}--\text{H}_2\text{N-ENZYME} \quad \text{(INACTIVE)}
\]
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

BY: Chaval Btasil
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THE HOMEOSTATIC BALANCE

PGI₂
ENDOTHELUM

TXA₂
PLATELETS

BY: Gretaz
GNU 1.2
Thrombus Formation

- Elastic Lamina
- Baseline Membrane
- Endothelium
- Platelets

Injury → ADP → Thromboxane → 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.

Physiologic Stimuli → COX-1 (constitutive) → PG E₂ (Renal function) → Inflammatory Stimuli

Thromboxane A₂ (Platelet function)

Prostacycline (PGL₂) (Gastric Protection)

COX-2 (inducible) → Pro-inflammatory PGs and other inflammatory mediators → Inflammation
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

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

Stimulus

Phospholipase

Cell membrane
Phospholipids

Arachidonic acid

COX-1+2
Prostaglandins
Prostaglandin E₂
Prostacyclin PGI₂

COX-1
Thromboxanes
TXB₂

Lipoxygenases (5-LO)
Leukotrienes
LTB₄
LTC₄, LTD₄

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 PGI$_2$
  - Anti-thrombotic

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

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** 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 PGI$_2$

Anti-thrombotic

Platelets

COX-1

TXB2

Pro-thrombotic

Vioxx®
Prostacyclin PGI_2

Endothelium

Aspirin inhibits COX-2 irreversibly

All cells but the platelet can resynthesize the enzymes

Prostacyclin PGI_2

TXB2

Platelets

Aspirin inhibits COX-1 irreversibly

Anti-thrombotic

Pro-thrombotic
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