M1 - Immunology, Winter 2008

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http://hdl.handle.net/2027.42/64939
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 (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

Phospholipid

Phospholipase A

Lysophospholipid

Phospholipase C

Diacylglycerol

Diacylglyceride lipase

Cyclooxygenase 1 + Lipooxygenase Products
Cyclooxygenase 2
Cell Membrane Phospholipids → \[ \text{PHOSPHOLIPASE A}_2 \]

LIP OXYGENASE PATHWAY

- HETEs [mono & di]
- LEUKOTRIENE [SRS-A]

Arachidonic Acid → CYCLOOXYGENASE → \[ \text{PGG}_2 = \text{PGH}_2 \]

PGI\(_2\) UNSTABLE

\[ \text{PGF}_{2\alpha} \]

6-Keto PGF\(_{1\alpha}\)

TXA\(_2\) UNSTABLE

\[ \text{TXB}_2 \]
Leukotriene Synthesis

Lipoxygenase

Arachidonic Acid → 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 + 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 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 B₄**
  - Neutrophil Activation
  - degranulation

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

- **Mast cell activation**
  - degranulation
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

Phagocytic leukocytes

Activated leukocytes → Endogenous pyrogen

Arachidonic Acid → Prostaglandin E2 → Temperature

Aspirin
NSAIDs

(e.g. Interleukin-1)

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 cysteinyl leukotrienes
Non- Steroidal Anti-Inflammatory Compounds

- Aspirin (acetysalicylic 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

PGI₂
ENDOTHELium

TXA₂
PLATELETS

BY: Gretaz  GNU 1.2
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

Cell membrane

Arachidonic acid
Acute inflammation: lipid mediators

Stimulus

Phospholipase

Cell membrane
Phospholipids

Arachidonic acid

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

COX-1
Thromboxanes
TXB$_2$

Lipooxigenases (5-LO)
Leukotrienes
LTB$_4$
LTC$_4$, LTD$_4$

Prostaglandins
Thromboxanes
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Acute inflammation: lipid mediators

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COX-1+2

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Lipooxigenases (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

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

**Therapeutic targets**

- **Endothelium**
  - Prostaglandin PG\(\text{I}_2\)
  - Prostacyclin PG\(\text{I}_2\)
  - Anti-thrombotic

- **Platelets**
  - Thromboxane TXB\(\text{2}\)
  - Pro-thrombotic

- **COX-2**
  - Inhibits by **Ibuprofen**

- **COX-1**
  - Inhibits by **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

**Therapeutic targets**

**Endothelium**

- Prostacyclin PGI\(_2\)

**Platelets**

- TXB\(_2\)

**Aspirin** inhibits COX-1 irreversibly

**Aspirin** inhibits COX-2 irreversibly

All cells but the platelet can resynthesize the enzymes

Anti-thrombotic

Pro-thrombotic
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  Tumor Necrosis Factor
  Growth Factors