M1 - Immunology, Winter 2008

Fantone, J.; Pietropaolo, M. T.

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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 (H₂O₂)
  superoxide anion (O₂⁻)
  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

Phospholipase C

Lysophospholipid

+ Arachidonic acid

Arachidonic acid + HO-CH

Diacylglyceride

Diacylglyceride lipase

Cyclooxygenase 1 + Lipooxygenase Products

Cyclooxygenase 2
Leukotriene Synthesis

Arachidonic Acid

Lipoxygenase

5-HPETE

Leukotriene A (LTA)

Glutathione-S-transferase

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 +</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

- 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

\[ \text{Activated leukocytes} \rightarrow \text{Endogenous pyrogen} \]

(e.g. Interleukin-1)

- Phagocytic leukocytes

\[ \text{Arachidonic Acid} \rightarrow \text{Prostaglandin E2} \rightarrow \text{Temperature} \]

- Aspirin
- NSAIDs

- Shivering
- Sweating
- Vasomotor tone
Rheumatoid Arthritis distorts joints

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

Complement

Anti-altered IgG

Fixation
Activation

Altered IgG

Chemotaxis

Lysosomal Enzymes

Collagenase
Neutral Proteases
Phospholipase

Nonsteroidal
Anti-inflammatory
Agents

Arachidonic acid

Prostaglandins

Nerve Sensitization

Vasodilation

Activated oxygen

O₂, H₂O₂

Cartilage

Subchondral bone plate

Source: Undetermined
Chemotactic Activity of LTB4

PMN

Vascular endothelium

LTB4
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!!
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  

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

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THE HOMEOSTATIC BALANCE

PGI₂
ENDOTHELIUM

TXA₂
PLATELETS
Thrombus Formation

- Elastic Lamina
- Platelets
- Basement Membrane
- Endothelium
- Injury
- ADP
- Thromboxane
- Collagen
- Aggregation
- Thrombus

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)
  - 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\(_2\)
Prostacyclin PGI\(_2\)

COX-1
Thromboxanes
TXB\(_2\)

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

Lipooxigenases (5-LO)
Acute inflammation: lipid mediators

Stimulus + Phospholipase → Phospholipids → Arachidonic acid

Cell membrane

COX-1+2
- Prostaglandins
  - Prostaglandin E₂
  - Prostacyclin PGI₂

COX-1
- Thromboxanes
  - TXB₂

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

Vasodilation, increase vascular permeability, control platelet aggregation, chemotaxis, pain, fever
Acute inflammation: lipid mediators

An important role in vascular homeostasis

- Endothelium
  - Prostacyclin PGI₂
  - Anti-thrombotic

- Platelets
  - TXB2
  - Pro-thrombotic
Acute inflammation: lipid mediators

**Therapeutic targets**

- **Endothelium**
  - COX-2
  - Prostacyclin $\text{PGI}_2$
  - 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 PGI$_2$
  - Anti-thrombotic

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

**Ibuprofen**

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

Endothelium

Prostacyclin PGI₂

Anti-thrombotic

Platelets

TXB2

Pro-thrombotic

COX-2

COX-1

Vioxx®

Therapeutic targets
Acute inflammation: lipid mediators

**Endothelium**

- **Prostacyclin PGI₂**
- **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**
- **Pro-thrombotic**

**Key Mediators**

- **Endothelium**
- **Platelets**
- **Prostacyclin PGI₂**
- **TXB2**
- **Aspirin**

**Enzymes**

- COX-1
- COX-2
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  Chemokines
  Interferons
  Tumor Necrosis Factor
  Growth Factors