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 ($H_2O_2$)
  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
Leukotriene Synthesis

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 +</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>
ARACHIDONIC ACID

LIPID OXYGENASE PATHWAY

5-HYDROPEROXYEICOSATETRAENOIC ACID (5-HPETE)
  ↓
LTA₄ (UNSTABLE)
  ↓
LTA₅ (UNSTABLE)
  ↓
LTB₂
  ↓
LTC₂

CYCLOOXYGENASE PATHWAY

PGG₂ → PGH₂
  ↓
PGI₂ (UNSTABLE)
  ↓
PGI₅ (UNSTABLE)
  ↓
TXA₂

PGE₂ + PGF₂
  ↓
5-Keto PGF₁₀₂
  ↓
TXB₂
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
- Mast cell activation
- Leukotrienes C,D,E (SRS-A)
- Causes smooth muscle contraction
- Increases vascular permeability

Chemotaxis
- 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
Production of Fever

Hypothalamus

Arachidonic Acid $\rightarrow$ Prostaglandin E2 $\rightarrow$ Temperature

(e.g. Interleukin-1)

Phagocytic leukocytes $\rightarrow$ Activated leukocytes $\rightarrow$ Endogenous pyrogen

Viruses
Bacteria
Toxins

Aspirin
NSAIDs

Shivering
Sweating
Vasomotor tone
Rheumatoid Arthritis distorts joints

Source: http://www.nih.gov/
Chemotactic Activity of LTB4

BY: Greg Luerman

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 (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 ACETYLATED 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

BY: Gretaz
GNU 1.2
Thrombus Formation

- Elastic Lamina
- Basement Membrane
- Endothelium
- Platelets
- 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.
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 E₂
Prostacyclin PGI₂

COX-1
Thromboxanes
TXB₂

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

Stimulus → Phospholipase

Phospholipids → Arachidonic acid

- **COX-1**
  - Prostaglandins
    - Prostaglandin E$_2$
    - Prostacyclin PGI$_2$
  - Thromboxanes
    - TXB$_2$

- **COX-1 + 2**

- **Lipoxygenases (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: Prostacyclin PGI$_2$

Platelets: 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

Prostacyclin PGI₂

Anti-thrombotic

Platelets

TXB₂

Pro-thrombotic

COX-2

Ibuprofen*

COX-1

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

Therapeutic targets

Endothelium

Platelets

COX-2

Vioxx®

COX-1

Prostacyclin PGI₂

TXB2

Anti-thrombotic

Pro-thrombotic
**Acute inflammation: lipid mediators**

**Endothelium**
- **Prostacyclin PGI$_2$**

**Platelets**
- **TXB2**
- **Aspirin inhibits COX-1 irreversibly**
- **Aspirin inhibits COX-2 irreversibly**

**Therapeutic targets**
- All cells but the platelet can resynthesize the enzymes
- Anti-thrombotic
- Pro-thrombotic
INFLAMMATORY MEDIATORS

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  Tumor Necrosis Factor
  Growth Factors