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
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 + 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\textsubscript{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

- **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
Hypothalamus

Viruses
Bacteria
Toxins

Phagocytic leukocytes

Activated leukocytes
Endogenous pyrogen

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
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 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
ENDOTHELUM

TXA₂
PLATELETS

BY: Gretaz
GNU 1.2
Thrombus Formation

Elastic Lamina

Injury

ADP

Thromboxane

Aggregation

Collagen

platelets

Endothelium

Basement Membrane

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)
- Inflammatory Stimuli

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

- PG E₂ (Renal function)
- Thromboxane A₂ (Platelet function)
- Prostacycline (PGL₂) (Gastric Protection)
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$_4$

PGI$_2$
TXB$_2$
Arachidonic acid

Stimulus

Phospholipase

Cell membrane
Phospholipids

Arachidonic acid

COX-1+2

Prostaglandins

Prostaglandin E₂
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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 PGI$_2$ ➔ 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

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* Classical NSAID, it inhibits both COX enzymes

* Ibuprofen

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**COX-2**

**COX-1**
Acute inflammation: lipid mediators

Therapeutic targets

Endothelium
- COX-2
- Prostacyclin PGI₂
  - Anti-thrombotic

Platelets
- COX-1
- TXB2
  - Pro-thrombotic

COX-2

Vioxx®
Prostacyclin PGI$_2$

Endothelium

Aspirin inhibits COX-2 irreversibly

Prostacyclin PGI$_2$

Anti-thrombotic

Therapeutic targets

Aspirin inhibits COX-1 irreversibly

TXB2

Pro-thrombotic

Platelets

All cells but the platelet can resynthesize the enzymes
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  Growth Factors