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 ($H_2O_2$)
  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

LIPOXYGENASE PATHWAY

5-HYDROPEROXYEICOSATETRAENOIC ACID (5-HPETE)

LTA₄ (UNSTABLE)

LTC₄

LTB₄

LTD₄

LTE₄

CYCLOOXYGENASE PATHWAY

PGG₂ - PGH₂

PGI₂ (UNSTABLE)

PGE₂

PGF₂α

5-Keto PGF₁α

TXA₂ (UNSTABLE)

TXB₂
Cell Membrane Phospholipids

Lipoxygenase Pathway
HetES [mono & di] + Leukotriene [SRS-A]

Arachidonic Acid

PGG₂ → PGH₂ → Cyclooxygenase

PGI₂ Unstable

PGE₂ → TXA₂ Unstable

6-Keto PGF₁α

PGF₂α + TXB₂
Leukotriene Synthesis

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

Leukotriene A (LTA) → Leukotriene B (LTB) → Glutathione-S-transferase

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:

<table>
<thead>
<tr>
<th>Product</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin E₂/Prostacyclin</td>
<td><strong>Immunoregulatory</strong>&lt;br&gt;• Inhibits immune cell activation&lt;br&gt;• Inhibits cytokine production&lt;br&gt;• Inhibits mast cell activation&lt;br&gt;Blocks platelet aggregation&lt;br&gt;Increases vasodilation&lt;br&gt;Stimulates adenylate cyclase</td>
</tr>
<tr>
<td>Thromboxane</td>
<td><strong>Causes vasoconstriction</strong>&lt;br&gt;Induces platelet aggregation</td>
</tr>
</tbody>
</table>
**Biological Function**

Lipoxygenase-derived Products:

<table>
<thead>
<tr>
<th>Leukotriene B&lt;sub&gt;4&lt;/sub&gt;</th>
<th>Neutrophil Activation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- degranulation</td>
</tr>
<tr>
<td></td>
<td>Mast cell activation</td>
</tr>
<tr>
<td></td>
<td>- degranulation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Leukotriene C,D,E (SRS-A)</th>
<th>Causes smooth muscle contraction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increases vascular permeability</td>
</tr>
</tbody>
</table>
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
- Prostaglandin E2
- Temperature

(e.g. Interleukin-1)

- Aspirin
- NSAIDs

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 cysteinyi 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
ENDOTHELIUM

TXA₂
PLATELETS
Thrombus Formation

Elastic Lamina

Injury

ADP

Thromboxane

Collagen

Aggregation

THROMBUS

Organization

Plaque

platelets

Basement Membrane

Endothelium

Signal for platelet aggregation
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 generate 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 E\(_2\)
Prostacyclin PGI\(_2\)

COX-1

Thromboxanes

TXB\(_2\)

Lipooxigenases (5-LO)

Leukotrienes

LTB\(_4\)
LTC\(_4\), LTD\(_4\)
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$_4$

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

- Platelets
  - TXB2
  - COX-1
  - 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

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

**Therapeutic targets**

- Prostacyclin (PGI$_2$)
- Thromboxane (TXB$_2$)

**Endothelium**

- COX-2
- Prostacyclin (PGI$_2$)

**Platelets**

- COX-1
- Thromboxane (TXB$_2$)

- Vioxx®

**Anti-thrombotic**

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

Therapeutic targets

Endothelium

Aspirin inhibits COX-2 irreversibly

Prostacyclin PGI$_2$

All cells but the platelet can resynthesize the enzymes

TXB2

Platelets

Aspirin inhibits COX-1 irreversibly

Anti-thrombotic

Pro-thrombotic
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  - histamine, serotonin
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  - superoxide anion ($O_2^-$)
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  - cyclooxygenase-derived
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- **CYTOKINES**
  - Interleukins
  - Chemokines
  - Interferons
  - Tumor Necrosis Factor
  - Growth Factors