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
Cell Membrane Phospholipids

LIP氧化GENASE PATHWAY
HETEs [mono & di] + LEUKOTRIENE (SRS-A)

Arachidonic Acid

PGG₂ → PGH₂

PGI₂ UNSTABLE

6-Keto PGF₁α

PGE₂

TXA₂ UNSTABLE

PGF₂α

TXB₂
<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>
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</tbody>
</table>
## Biological Function

### Cyclooxygenase-derived Products:

<table>
<thead>
<tr>
<th>Prostaglandin E$_2$/Prostacyclin</th>
<th>Immunoregulatory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Inhibits immune cell activation</td>
</tr>
<tr>
<td></td>
<td>• Inhibits cytokine production</td>
</tr>
<tr>
<td></td>
<td>• Inhibits mast cell activation</td>
</tr>
<tr>
<td></td>
<td>Blocks platelet aggregation</td>
</tr>
<tr>
<td></td>
<td>Increases vasodilation</td>
</tr>
<tr>
<td></td>
<td>Stimulates adenylate cyclase</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Thromboxane</th>
<th>Causes vasoconstriction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Induces platelet aggregation</td>
</tr>
</tbody>
</table>
# Biological Function

**Lipoxygenase-derived Products:**

<table>
<thead>
<tr>
<th>Leukotriene B₄</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
Hypothalamus

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

PMN

Vascular endothelium

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 ACETYLATED 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

BY: Chaval Btasil
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THE HOMEOSTATIC BALANCE

PGI₂
ENDOTHELIUM

TXA₂
PLATELETS

BY: Gretaz
GNU 1.2
Thrombus Formation

Thrombus Formation involves the interaction of various components in the blood vessel wall and the blood stream. It begins with injury to the endothelium, which triggers the release of ADP and collagen. ADP attracts platelets to the site of injury, causing them to aggregate. Thromboxane, another product of the injured endothelium, amplifies this process.

The aggregation of platelets leads to the formation of a thrombus, which is a clump of platelets and fibrin. This thrombus can block blood flow, leading to tissue ischemia and potential organ damage.

After the initial thrombus forms, it undergoes organization, which involves the deposition of fibrin and the formation of a more stable structure. This process results in the formation of a plaque, which can progress to atheroma, a condition associated with arterial disease.

Components involved in thrombus formation include:
- Elastic Lamina
- Basement Membrane
- Platelets
- Endothelium
- ADP
- Thromboxane
- Collagen

The process is an essential part of the body's response to injury and a critical factor in the development of arterial diseases.
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.

- 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
lipid mediators of Inflammation

Stimulus

+ Phospholipase

Cell membrane
Phospholipids

Arachidonic acid
Acute inflammation: lipid mediators

Stimulus

Phospholipase

Phospholipids

Arachidonic acid

Cell membrane

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

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TXB$_2$

Lipooxygenases (5-LO)

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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**
  - 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<sub>2</sub>
- Anti-thrombotic

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

*Ibuprofen*

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

**Therapeutic targets**

- **Endothelium**
  - COX-2
  - Prostacyclin PGI$_2$

- **Platelets**
  - COX-1
  - TXB2

**COX-2 inhibitors**

- **Vioxx®**
Acute inflammation: lipid mediators

**Therapeutic targets**

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

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

All cells but the platelet can resynthesize the enzymes.

Anti-thrombotic → Pro-thrombotic
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- CYTOKINES
  - Interleukins
  - Chemokines
  - Interferons
  - Tumor Necrosis Factor
  - Growth Factors