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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
Phospholipid

Phospholipase A

Lysophospholipid + Arachidonic acid

Phospholipase C

Arachidonic acid + phosphoryl-R

Diacylglycerol

Diacylglyceride lipase

Arachidonic acid + HO-CH

Cyclooxygenase 1 + Lipooxygenase Products
Cyclooxygenase 2
Cell Membrane Phospholipids

Lipoxygenase Pathway

HETEs (mono & di) + LEUKOTRIENE (SRS-A)

Arachidonic Acid

PGG2 → PGH2

PGI2 unstable

6-Keto PGF1α

PGE2 + TXA2 unstable

PGF2α + TXB2
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>Thromboxoxane</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>Prostacyclin</td>
</tr>
</tbody>
</table>
ARACHIDONIC ACID

LIPOXYGENASE PATHWAY

5-HYDROPEROXIDEICOSATETRAENOIC ACID (5-HPETE)

- \( \text{LTA}_4 \) (UNSTABLE)
- \( \text{LTC}_4 \)
- \( \text{LTD}_4 \)
- \( \text{LTE}_4 \)

CYCLOOXYGENASE PATHWAY

- \( \text{PGG}_2 \) → \( \text{PGH}_2 \)
- \( \text{PGI}_2 \) (UNSTABLE)
- \( \text{PGE}_2 \)
- \( \text{PGF}_2 \)

- \( \text{TXA}_2 \) (UNSTABLE)
- \( \text{TXB}_2 \)

6-Keto PGF1α
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

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

Production of Fever

Viruses → Bacteria → Toxins → Activated leukocytes → Endogenous pyrogen → Arachidonic Acid → Prostaglandin E2 → Temperature

(e.g. Interleukin-1)

Phagocytic leukocytes

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 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

BY: Chaval Btasil
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THE HOMEOSTATIC BALANCE

PGI₂
ENDOTHELIUM

TXA₂
PLATELETS
Thrombus Formation

Elastic Lamina

Basement Membrane

Endothelium

platelets

Injury

ADP

Thromboxane

Collagen

Aggregation

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 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 E₂
Prostacyclin PGI₂

COX-1
Thromboxanes
TXB₂

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

Stimulus

Cell membrane
Phospholipids

$\text{Phospholipase} \rightarrow \text{Arachidonic acid}$

- 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

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

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

**Therapeutic targets**

NSAIDs inhibit both COX-1 and COX-2; COXIBs inhibit COX-2
Acute inflammation: lipid mediators

Therapeutic targets

Endothelium

COX-2

Prostacyclin PGI₂

Anti-thrombotic

Platelets

COX-1

TXB₂

Pro-thrombotic

Ibuprofen*

* 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
Prostacyclin PGI\textsubscript{2} and thromboxane TXB\textsubscript{2} are key lipid mediators in acute inflammation. Aspirin inhibits COX-1 irreversibly, targeting the endothelium, while COX-2 can be inhibited irreversibly, affecting platelets. Aspirin's dual targeting property makes it a pivotal therapeutic agent in anti-thrombotic treatments.
INFLAMMATORY MEDIATORS

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  Chemokines
  Interferons
  Tumor Necrosis Factor
  Growth Factors