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M1 - Immunology, Winter 2008

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Viewer discretion advised: Material may contain medical images that may be disturbing to some viewers.
Arachidonic Acid Metabolites and Inflammation

Joseph Fantone, M.D.
Host Defense 2/12  10-11:00am
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
Phospholipid

Phospholipase A

Lysophospholipid

+ Arachidonic acid

Arachidonic acid - CH

CH₂O-P-O-R

Diacylglycerol

+ phosphoryl-R

Diacylglyceride lipase

Arachidonic acid + HO-CH

CH₂-OH

Cyclooxygenase 1 + Lipoxygenase Products

Cyclooxygenase 2
Cell Membrane Phospholipids → PHOSPHOLIPASE A2

LIPID PATHWAY

HETEs
[mono & di]

LEUKOTRIENE (SRS-A)

Arachidonic Acid → CYCLOOXYGENASE

PGG2 → PGH2

PGI2 UNSTABLE

PGE2

6-Keto PGF1α

PGF2α

TXA2 UNSTABLE

+ TXB2
Leukotriene Synthesis

1. Arachidonic Acid
2. 5-HPETE
3. Leukotriene A (LTA)
4. Leukotriene B (LTB)
5. Leukotriene C (LTC)
6. Leukotriene D (LTD)

Reactions:
- Lipoxygenase
- Glutathione-S-transferase
<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>
Biological Function

Cyclooxygenase-derived Products:

Prostaglandin E₂/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 $\text{B}_4$  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

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

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 ENDOTHELUM

TXA₂ PLATELETS

BY: Gretaz
GNU 1.2
Thrombus Formation

- Elastic Lamina
- Platelets
- Basement Membrane
- Endothelium

Injury → ADP → Thromboxane → 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 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

Phospholipids

Arachidonic acid

Cell membrane

COX-1+2

Prostaglandins

Prostaglandin E₂
Prostacyclin PGI₂

COX-1

Thromboxanes

TXB₂

Lipooxygenases (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 PGI<sub>2</sub>
    - 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 PGI$_2$

**Platelets**
- TXB2

- COX-2
- Ibuprofen*
- COX-1

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

**Therapeutic targets**

- **Prostacyclin PGI_2**
- **TXB2**

**COX-1**

**COX-2**

**Endothelium**

**Platelets**

**Vioxx®**

**Anti-thrombotic**

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

**Therapeutic targets**

- **Endothelium**
  - Prostacyclin $\text{PGI}_2$
  - Aspirin inhibits COX-2 irreversibly

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

- All cells but the platelet can resynthesize the enzymes

- Anti-thrombotic
- Pro-thrombotic

*Aspirin* inhibits COX-2 irreversibly.
INFLAMMATORY MEDIATORS

PLASMA DERIVED
  • COMPLEMENT CASCADE
    C3a, C5a
  • COAGULATION CASCADE
    Thrombin, plasmin

CELL-DERIVED
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    Interferons
    Tumor Necrosis Factor
    Growth Factors