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How many take aspirin, ibuprofen, tylenol, naproxen?

Why???
INFLAMMATORY MEDIATORS

PLASMA DERIVED

• COMPLEMENT CASCADE
  C3a, C5a

• COAGULATION CASCADE
  Thrombin, plasmin

CELL-DERIVED

• VASOACTIVE AMINES
  histamine, serotonin

• OXYGEN METABOLITES
  hydrogen peroxide (H₂O₂)
  superoxide anion (O₂⁻)
  hypochlorous acid (HOCl⁻)

• ARACHIDONIC ACID METABOLITES
  cyclooxygenase-derived
  lipoxygenase-derived

• CYTOKINES
  Interleukins
  Chemokines
  Interferons
  Growth Factors
  Tumor Necrosis Factor
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.
What is Arachidonic Acid?
How And Where Is Arachidonic Acid Generated?
Lipid Mediators of Inflammation

Stimulus

+ Phospholipase

Cell membrane Phospholipids

Arachidonic acid

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What are the primary products derived from arachidonic acid?

- Cyclooxygenase (COX)
- Lipoxygenase (LO)
Acute inflammation: lipid mediators

Stimulus

Cell membrane
Phospholipids

\[ \text{Arachidonic acid} \]

+ Phospholipase

\[ \text{COX-1+2} \]

Prostaglandins

\[ \text{Prostaglandin E}_2 \]

\[ \text{Prostaglandin PGI}_2 \]

\[ \text{COX-1} \]

Thromboxanes

\[ \text{TXB}_2 \]

\[ \text{Lipooxygenases (5-LO)} \]

Leukotrienes

\[ \text{LTB}_4 \]

\[ \text{LTC}_4, \text{LTD}_4 \]

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<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>
In Vivo Effects of Arachidonic Acid Derived Products: Regulates

- Thermostatic Set Point (Fever)
- Pain (Interacts with pain receptors)
- Blood Flow
- Leukocyte Activity
- Platelet Function
Biological Function of Arachidonic Acid Products

Cyclooxygenase-derived Products:

Prostaglandin E$_2$/Prostacycllin  
- Inhibits immune cell activation  
- Inhibits cytokine production  
- Inhibits mast cell activation  
Blocks platelet aggregation  
Increases vasodilation

Thromboxane  
Causes vasoconstriction  
Induces platelet aggregation
The Homeostatic Balance

Endothelium
PGI$_2$

Platelets
TXA$_2$
Production of Fever

Hypothalamus Thermoregulatory Area

Endogenous pyrogens (Interleukins -1,-6)

Exogenous pyrogens (bacterial products)

Arachidonic acid

Prostaglandins

Increase temp set-point

COX inhibitors (aspirin)
## Biological Function

### Lipoxygenase-derived Products:

<table>
<thead>
<tr>
<th>Component</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukotriene B&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Neutrophil Activation</td>
</tr>
<tr>
<td></td>
<td>- chemotaxis</td>
</tr>
<tr>
<td></td>
<td>- degranulation</td>
</tr>
<tr>
<td>Mast cell activation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- degranulation</td>
</tr>
<tr>
<td>Leukotriene C,D,E (SRS-A)</td>
<td>Smooth muscle contraction</td>
</tr>
<tr>
<td></td>
<td>Increase vascular permeability</td>
</tr>
</tbody>
</table>
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

• Cyclooxygenase Activity:
  – Blocks Cyclooxygenase-derived products
  – COX-1 and COX-2 inhibitors

• Specific enzymes down-stream from COX:
  – Thromboxane synthetase inhibitors

• Lipoxygenase activity:
  – Block 5-lipoxygenase enzyme
  – Small molecule receptor antagonists for cysteinyI leukotrienes
Non-Steroidal Anti-Inflammatory Compounds; NSAIDS

• 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
Aspirin

• Irreversible inhibition of cyclooxygenase
• Acetylates active site of enzyme
• Decreased production of products (e.g. prostaglandins, prostacyclins & thromboxanes)
NSAIDS: Inhibit cyclooxygenase: reversible binding to active site of enzyme
About 80 million aspirin tablets are consumed daily in the USA. Of those:

72% are taken for disease prevention

28% are taken for pain
The Homeostatic Balance

Endothelium
PGI₂

Platelets
TXA₂
Aspirin Anti-thrombogenic Activity

- Inhibits platelet aggregation; blocks platelet-derived thromboxane production

- Blocks platelet cyclooxygenase for the life of the platelet; no new protein synthesis

- 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
Acute inflammation: lipid mediators

An important role in vascular homeostasis

- Endothelium
- Platelets

Prostacyclin PGI$_2$ <-> TXB2

Anti-thrombotic <-> Pro-thrombotic
Acute inflammation: lipid mediators

Therapeutic targets

Endothelium

- Aspirin inhibits COX-2 irreversibly

Platelets

- Aspirin inhibits COX-1 irreversibly

Prostacyclin PGI₂

- All cells but the platelet can resynthesize the enzymes

TXB₂

Anti-thrombotic

Pro-thrombotic
Acute inflammation: lipid mediators

Prostacyclin PGI\(_2\)  TXB2

Endothelium  Platelets

COX-2  COX-1

Prostacyclin PGI\(_2\)  TXB2

Anti-thrombotic  Pro-thrombotic

NSAIDs inhibit both COX-1 and COX-2; COXIBs inhibit COX-2

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Acute inflammation: lipid mediators

**Therapeutic targets**

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

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

Ibuprofen* inhibits both COX enzymes (COX-1 and COX-2).

* Classical NSAID, it inhibits both COX enzymes.
COX-2 inhibitors work by blocking COX-2 enzyme which is involved in gastrointestinal toxicity is reduced the inflammation pathway. By sparing COX-1
Acute inflammation: lipid mediators

Therapeutic targets

Endothelium

- Prostacyclin (PGI$_2$)

Platelets

- TXB2

COX-2

COX-1

Vioxx®

Anti-thrombotic

Pro-thrombotic

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Fish Oil: Protective Effects

Eicosapentaenoic Acid

Arachidonic Acid

Omega-3

Omega-6

Source Undetermined

Source Undetermined
Acute inflammation: lipid mediators

Stimulus

Cell membrane
Phospholipids

Phospholipase

Arachidonic acid

COX-1+2

Prostaglandins

Prostaglandin E₂
Prostacyclin PGI₂

COX-1

Thromboxananes

TXB₂

Lipooxigenases (5-LO)

Leukotrienes

LTB₄
LTC₄, LTD₄


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