SOME CLINICALLY RELEVANT EICOSANOIDs: An Overview

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What are Eicosanoids?

EICOSANOIDs:

• Group of compounds containing **20 Carbon atoms**;
• Derived from metabolism of **Eicosapolyenoic Fatty Acids**
  • Polyunsaturated fatty acids with 20 Carbons,
• Eicosanoids are **Paracrine** “Local hormones” (**Why?**)
  • They have specific effects on target cells very close to their site of biosynthesis,
    • They are rapidly degraded, thus cannot be transported to distal sites for action;
• Examples: Growth factors, clotting factors
What are the Clinically Relevant Eicosanoids? (Fig. 1)

• Prostaglandins (PGs):
  • Assumed to be produced in Prostate gland, but are produced in Seminal vesicles and many other tissues;

• Thromboxanes (TXs):
  • Assumed to be produced in Platelets (Thrombocytes);

• Leukotrienes (LTs):
  • Assumed to be produced in Leukocytes,

• Prostacyclins (PGIs),

• Lipoxins (LXs),

• PGs, TXs and PGIs are called PROSTANOIDS;
Fig. 1: Schematic diagrams of the structures of some Clinically relevant Eicosanoids

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
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<tbody>
<tr>
<td><img src="http://wcb.indstate.edu/thcme/mwking/lipid-synthesis.h" alt="Structure 1" /></td>
<td><strong>PGE$_2$</strong></td>
</tr>
<tr>
<td><img src="http://wcb.indstate.edu/thcme/mwking/lipid-synthesis.h" alt="Structure 2" /></td>
<td><strong>TXA$_2$</strong></td>
</tr>
<tr>
<td><img src="http://wcb.indstate.edu/thcme/mwking/lipid-synthesis.h" alt="Structure 3" /></td>
<td><strong>LTA$_4$</strong></td>
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What are the precursors for biosynthesis of Eicosanoids?

• **Principle Eicosanoids** are from **Arachidonic acid**
  - Arachidonic acid is \( \omega_6 \) Polyunsaturated fatty acid; \((\omega_6, 20:4)\);

• **Minor Eicosanoids** are from:
  - Dihomo-\( \gamma \)-Linoleic acid \((\omega_6)\),
  - Eicosapentaenoic acid \((\text{EPA}, \omega_3, 20:5)\);

• **Linoleic acid**: precursor for Eicosapentaenoic acid and Dihomo-\( \gamma \)-Linoleic acid;
What are the Essential Fatty Acids and why are they important?

• Dietary Essential Fatty Acids are **Omega** Fatty Acids:
  • \(\alpha\)-LINOLENIC ACID (\(\omega-3, 18:3\)),
  • LINOLEIC ACID (\(\omega-6, 18:2\)),
  • ARACHIDONIC ACID is semi-essential fatty acid;
    • Because it can be synthesize from Linoleic acid;

• Dietary deficiency of **LINOLEIC ACID** compromises ability of the body to synthesize **Eicosanoids**, 
What do you understand by “Omega” Fatty Acids?

Fig. 2: OMEGA NOMENCLATURE OF FATTY ACIDS
Examples of Omega fatty acids

- Eicosatrienoic acid (γ-Linolenic acid, ω6)
- Arachidonic acid (ω6)
- Eicosapentaenoic acid (ω3)
Dietary balance of the Omega fatty acids

• **ω6 and ω3** are not inter-convertible in humans,
• Diets rich in ω3 fatty acids result in high content in membrane phospholipids,
  • Recommended ratio: 1-4: 1 (ω6 : ω3)
  • Typical western diet: 14-25: 1 (ω6 : ω3)
• Individuals consuming diet rich in ω-6 FAs may shifts their physiological state to one that is pro-inflammatory, pro-thrombotic and proaggregatory which may lead to heart disease in susceptible individuals;
What are the major sources of Arachidonic acid?

• **Major source** is cellular stores,
  • It is predominantly located at **C-2** position of membrane Phospholipids:
    • Phosphatidyl-Inositol,
    • Phosphatidyl-Choline (Lecithin)
      • Phospholipase A$_2$ (PLA$_2$) catalyzes hydrolysis of membrane Phospholipids to produce Arachidonic acid (**Fig. 3**),
  • **Dietary source** of Arachidonic acid is Linoleic acid;
Fig. 3: Sites of action of Phospholipases on Phospholipid

Sites of action of the phospholipases $A_1$, $A_2$, $C$ and $D$. 

http://web.indstate.edu/thcme/mwking/lipid-synthesis.html
Dietary **Linoleic Acid** (C18:2, \(\omega 6\)) (plant oils)

\[ \text{Elongase} \]

\[ \text{Desaturase} \]

**Arachidonic Acid** (C20: 4, \(\omega 6\))
How is Arachidonic acid release from membrane lipids

Stimulus: Bradykinin, Epinephrine or Thrombin
General pathways for biosynthesis of Eicosanoids

[Diagram showing the pathways from Phospholipids to Leukotrienes, Prostaglandin H2 (PGH2), Prostacyclin, Other Prostaglandins, and Thromboxanes, involving enzymes like PLA2, Lipoxygenases, DG lipase, and synthases.]
CYCLIC PATHWAY for biosynthesis of PGs and TXs

- Eicosanoids are produced in all cells except RBC,
  - Fig. 4: Cyclic Pathway for biosynthesis of Prostaglandins & Thromboxanes;
- Bradykinin, Epinephrine or Thrombin activate Phospholipase A\(_2\) (PLA\(_2\)),
• Major enzymes in Cyclic Pathway:
  • PROSTAGLANDIN ENDO-PEROXIDE SYNTHASE made up of 2 enzymes:
    • CYCLOOXYGENASE (COX),
    • PEROXIDASE;
• IMPORTANT TO NOTE:

• **Nitric Oxide (NO) initiates** the biosynthesis of Prostaglandins,

• **Inhibitors of Nitric Oxide Synthase can inhibit** biosynthesis of Prostaglandins;
Fig. 4: Cyclic Pathway for biosynthesis of Prostaglandins, Prostacyclins and Thromboxanes
Why is Cyclooxygenase (COX) called “Suicide Enzyme”? 

• **COX** can **“Switch off”** Prostaglandin biosynthesis by self-catalyzed destruction (**Enzyme Suicide**),

• Self destruction may be due to presence in tissues of specific enzyme: **15-Hydroxy-Prostaglandin Dehydrogenase** (15 HPD),

• Blocking the action of **15 HPD** (with **Sulfa-Salazine** or **Indomethacin**) can prolong the half-life of Prostaglandins,
Linear pathway for biosynthesis of Leukotrienes (Fig. 5)

- $\text{PLA}_2$ hydrolyzes Phospholipids to produce Arachidonic acid, substrate for Linear Pathway,

- 5-Lipoxygenase is activated by membrane protein FLAP (5-Lipoxygenase-Activating Protein);
  - FLAP binds Arachidonic acid, facilitating its interaction with 5-Lipoxygenase;
Fig. 5: Linear pathway for biosynthesis of some Leukotrienes

MEMBRANE PHOSPHOLIPIDS

Inhibitors:
Anti-inflammatory Corticosteroids

PHOSPHOLIPASE A₂ (PLA₂)

ARACHIDONIC ACID

LYSOPHOSPHOLIPID

5-LIPOXYGENASE +
5-Lipoxygenase Activating Protein (FLAP)

LEUKOTRIENE (LTA₄)

LTB₄

2 GSH

GSSG

LTC₄

Other Leukotrienes
How do Eicosanoids interact with receptors in target cells?

- Eicosanoids acts via **Receptor-Mediated G-proteins** Linked to signaling pathways,
  - Metabotropic Receptors or 2\textsuperscript{nd} Messenger system
- Depending on cell type, activated G-protein may:
  - Stimulate formation of Cyclic-AMP,
  - Inhibit formation of Cyclic-AMP,
  - Activate Phosphatidyl-Inositol Signal pathway leading to Intracellular Ca\textsuperscript{++} release,
Some general functions of Eicosanoids:

• Induction of inflammation,
• Mediation of pain signals,
• Induction of fever,
• Smooth muscle contraction (including uterus),
• Smooth muscle relaxation,
• Protection of stomach lining,
• Simulation of platelet aggregation,
• Inhibition of platelet aggregation,
• Sodium and water retention,
State some general functions of Eicosanoids

- **Prostaglandins** have wide range of functions:
  - Cause pain, Inflammation and Fever,
  - Cause contraction of smooth muscle,
  - Involved in Reproductive functions,
  - Involved in Blood Pressure Control,
  - Suppress acid secretion in stomach, etc

- **Thromboxanones** affect Platelet aggregation and blood clotting,
Prostaglandins (PGE\textsubscript{2} and PGE\textsubscript{1}) can induce:

- Signs of inflammation, Redness and Heat (due to Arteriolar Vasodilatation),
- Swelling and Edema resulting from increasing capillary permeability,
• Bradykinin and Histamine can activate biosynthesis of PGE$_2$ in region of Hypothalamus where body temperature is regulated, causing increase body temperature or fever (Pyrogenic effect of Prostaglandins);
• Interleukin-1 (IL-1α) acts on Hypothalamus to cause increase production of Prostaglandins, thereby increasing body temperature,

• Prostaglandins (PGE, PGA) and Prostacyclin (PGI₂) are Vasodilators,
  • They lower systemic arterial pressure, thereby increasing local blood flow and decreasing peripheral resistance,
State sites of action of inhibitors of Prostaglandin biosynthesis

• Some therapeutic drugs that affect biosynthesis of Prostaglandins:

  • **NSAIDs** (examples):
    • Aspirin,
    • Indomethacin,
    • Phenylbutazone,

• They block biosynthesis of Prostaglandin by irreversibly inhibiting **COX** (See Figs: 4 & 6),

• Aspirin, inhibition occurs by Acetylation of COX,
Fig. 6: Action of Aspirin: Acetylation of active site of Cox
• Steroidal Anti-inflammatory Drug:
  • Corticosteroid blocks Prostaglandin production by inhibiting action of PLA$_2$
  • It affects mobilization of Arachidonic acid, which is substrate for COX (Figs 4 & 6),
Factors that control biosynthesis of Prostaglandins are poorly understood, but, in general:

- Prostaglandin release is triggered following Hormonal or Neural excitation or after muscular activity,

Examples:

- Histamine stimulates increase in Prostaglandin concentration in Gastric Perfusates,
- Prostaglandins are released during labor and after cellular injury,
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