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 carbon atoms,
• Eicosanoids are Paracrine “Local hormones” (Why?)
  • Because of their specific effects on target cells very close to their site of synthesis,
  • They are rapidly degraded, thus are not transported to distal sites for action;
What are the Clinically Relevant Eicosanoids?

Clinically Relevant Eicosanoids are (Fig. 1):

- **Prostaglandins (PGs):**
  - Originally assumed to be produced in Prostate gland, but are produced in Seminal vesicles and many other tissues;

- **Thromboxanes (TXs):**
  - Originally assumed to be produced in Platelets (Thrombocytes);

- **Leukotrienes (LTs):**
  - Originally assumed to be produced in Leukocytes,

- **Prostacyclins (PGIs),**
- **Lipoxins (LXs),**
- PGs, TXs and PGIs are collectively known as Prostanoids
Fig. 1: Schematic diagrams of the structures of some Clinically relevant Eicosanoids

[Diagram showing structures of PGE₂, TXA₂, and LTA₄]
What are the precursors for biosynthesis of Eicosanoids?

• Principle Eicosanoids are from Arachidonic acid
  • (cis-5, 8, 11, 14 – Eicosatetraenoic acid; )
• Arachidonic acid is \( \omega 6 \) Polyunsaturated fatty acid; (\( \omega 6, 20:4 \));

• Minor Eicosanoids are from Dihomo-\( \gamma \)-Linoleic acid and Eicosapentaenoic acid (EPA, \( \omega 3, 20:5 \));
How important are the Essential Fatty Acids?

- Dietary Essential Fatty Acids are **Omega** Fatty Acids:
  - Linoleic Acid (\omega-6, 18:2),
  - \(\alpha\)-Linolenic Acid (\omega-3, 18:3)
  - Arachidonic Acid is semi-essential fatty acid
    - it can be produced from Linoleic acid;
- **Arachidonic Acid**: precursor for clinically relevant Eicosanoids;
- **Linoleic acid**: precursor for Dihomo-\(\gamma\)-Linoleic acid and Eicosapentaenoic acid;
- Dietary deficiency of **Linoleic acid** seriously threaten the ability of the body to synthesize Eicosanoids,
What do you understand by “Omega” Fatty Acids?

Fig. 2: OMEGA NOMENCLATURE OF FATTY ACIDS
What are the sources of Arachidonic acid?

- Major source of Arachidonic acid is cellular stores, predominantly located at C-2 position of membrane Phospholipids (Phosphatidyl-Inositol & Phosphatidyl-Choline),
- **Phospholipase A<sub>2</sub>** catalyzes hydrolysis of membrane Phospholipids to produce Arachidonic acid as one of its products (**Fig. 3**),
- Dietary source of Arachidonic acid is Linoleic acid;
Fig. 3: Sites of action of Phospholipases on Phospholipid
Cyclic pathway for biosynthesis of PGs and TXs

• All mammalian cells except the Red Blood Cells can synthesize Eicosanoids,

• Fig. 4: Summary of Cyclic Pathway for biosynthesis of clinically relevant Prostaglandins and Thromboxanes from Arachidonic acid,

• Bradykinin, Epinephrine or Thrombin can activate Phospholipase A₂ (PLA₂),

• PLA₂ hydrolyzes Phospholipids in cell membrane to produce Arachidonic acid, which is the Substrate for Cyclic Pathway,
• Cyclic Pathway is catalyzed by **Prostaglandin Endo-peroxide Synthase** — made up of 2 enzymes:
  • Cyclooxygenase,
  • Peroxidase
• Prostaglandin Endo-peroxide Synthase is called **Cyclooxygenase (COX)**;
• Nitric Oxide (NO) can initiate the biosynthesis of Prostaglandin
• Inhibitors of Nitric Oxide Synthase Inhibits synthesis of Prostaglandins;
Fig. 4: Cyclic Pathway for biosynthesis of Prostaglandins, Prostacyclins and Thromboxanes
Why is Cyclooxygenase (COX) called “Suicide Enzyme”? 

- **COX**: is the major enzyme in the Cyclic Pathway;  
- COX can **“Switch off”** biosynthesis of Prostaglandins by self-catalyzed destruction (**Enzyme Suicide**),  
- Self destruction may be due to presence in mammalian tissues of a specific enzyme: **15-Hydroxy-Prostaglandin Dehydrogenase (15 HPD)**,  
- Blocking the action of **15 HPD** (with Sulfa-Salazine or Indomethacin) prolong the half-life of Prostaglandins,
Linear pathway for biosynthesis of Leukotrienes

- Fig 5: Linear Pathway for biosynthesis of Leukotrienes;
- Bradykinin activates Phospholipase A₂ (PLA₂),
- PLA₂ hydrolyzes Phospholipids in membrane to produce Arachidonic acid, the 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;
- 5-Lipoxygenase, FLAP, and Phospholipase A₂ form a complex in association with the nuclear envelope during biosynthesis of Leukotrienes in Leukocytes;
Fig. 5: Linear pathway for biosynthesis of some Leukotrienes
How do Eicosanoids interact with receptors in target cells?

- Prostaglandins and other Eicosanoids acts via **Receptor-Mediated G-proteins** Linked to signaling pathways (Metabotropic Receptors or 2\textsuperscript{nd} Messenger system)
- Depending on the cell type, activated **G-protein** may:
  - Stimulate formation of Cyclic-AMP,
  - Inhibit formation of Cyclic-AMP,
  - Activate a Phosphatidyl-Inositol Signal pathway leading to Intracellular Ca\textsuperscript{++} release,
- Some Prostaglandin receptors are related to a family of Nuclear receptors with Transcription Factor activity;
State some general functions of Eicosanoids

• Prostaglandins have wide range of functions:

• **Prostaglandins:**
  • Cause pain, Inflammation and Fever,
  • Cause contraction of smooth muscle,
  • Involved in Reproductive functions, including Induction of Labor,
  • Involved in Blood Pressure Control,
  • Suppress acid secretion in the stomach, etc

• **Thromboxananes** affect Platelet aggregation and blood clotting,
State some specific functions of Prostaglandins

- Prostaglandins (PGE₂ and PGE₁) can induce:
  - Signs of inflammation, redness and Heat (due to Arteriolar Vasodilatation),
  - Swelling and Edema resulting from increasing capillary permeability,
    - These condition can be treated with Corticosteroids that Inhibit biosynthesis of Prostaglandins,
  - Bradykinin and Histamine can activate biosynthesis of PGE₂ in region of Hypothalamus where body temperature is regulated, thus resulting in increase body temperature causing fever (Pyrogenic effect of Prostaglandins)
• Interleukin-1 (IL-1α) can act on the Hypothalamus causing increase in biosynthesis of Prostaglandins, thereby increasing body temperature,
  • Prostaglandins are “Pyrogenic” because they can raise body temperature,
• Aspirin (Anti-pyretic), inhibits Pyrogenic effect of PGs;
• Prostaglandins (PGE, PGA) and Prostacyclin (PGI₂), are Vasodilators,
  • They lower systemic arterial pressure, thereby increasing local blood flow and decreasing peripheral resistance,
What are the sites of action of inhibitors of Prostaglandin biosynthesis?

- Two types of Therapeutically useful drugs affect biosynthesis of Prostaglandins,
- **First**: Non-steroidal Anti-Inflammatory drug (NSAIDs):
  - Aspirin (Acetylsalicylic acid)
  - Indomethacin
  - Phenylbutazone
- These drugs block biosynthesis of Prostaglandin by irreversibly inhibiting **Cyclooxygenase (COX)** (Fig: 4)
- Aspirin, inhibition occurs by Acetylation of COX,
• **Second**: Steroidal Anti-inflammatory Drug Corticosteroid

• Corticosteroid block biosynthesis of Prostaglandin by inhibiting the action of Phospholipase $A_2$,

  • It tends to interfere with mobilization of Arachidonic acid, which is the substrate for COX (**Fig. 4**),
• Factors that control biosynthesis of Prostaglandins are poorly understood, but, in general, Prostaglandin release seems to be 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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