

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, so they are not transported to distal sites for action

What are the Clinically relevant Eicosanoids?

- **Prostaglandins (PGs),**
- **Thromboxanes (TXs)**
- **Leukotrienes (LTs)**
- PGs, TXs and PGIs are collectively known as Prostanoids
- Clinical relevant Eicosanoids are named after the cells in which they were first seen:
 - **Prostaglandins (PGs):**
 - First seen in Semen,
 - Assumed that they are produced in Prostate gland (actually it is from the seminal vesicles)
 - Many tissues produce Prostaglandins
 - **Thromboxanes (TXs):** First seen in Blood Platelets (Thrombocytes)
 - **Leukotrienes (LTs):** First seen in Leukocytes

How do Eicosanoids interact with receptors in target cells?

- Prostaglandins and other Eicosanoids carry out their action via Receptor-Mediated G-protein Linked to signaling pathways (Metabotropic Receptors)
 - 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⁺⁺ release
- Prostaglandin receptor related to a family of Nuclear receptors with Transcription Factor activity has been identified

Biosynthesis of Eicosanoids:

What are the precursors for biosynthesis of Eicosanoids?

- Principle Eicosanoids are derived from Arachidonic acid (cis-5, 8, 11, 14 – Eicosatetraenoic acid)
 - Arachidonic acid is an ω -6 Polyunsaturated fatty acids
- Minor Eicosanoids are derived from Dihomo- γ -Linoleic acid and Eicosapentaenoic acid (EPA)

What are the sources of Arachidonic acid?

- Major source of Arachidonic acid is the Phospholipids in cell membrane
- Arachidonic acid is predominantly located at the C-2 position of membrane Phospholipids, especially Phosphatidyl Inositol
- Phospholipase A₂ catalyzes hydrolysis of membrane Phospholipids to produce Arachidonic acid as one of its products (**Fig. 2**)
- Immediate dietary precursor of Arachidonic acid is Linoleic acid
- Linoleic acid is also the precursor for Dihomo- γ -Linoleic acid and Eicosapentaenoic acid
- **Deficiency of Linoleic acid in the diet seriously affects the ability of the body to synthesize the Eicosanoids**

{Linoleic acid and Linolenic acid are the Essential fatty acids}

Briefly outline the Cyclic Pathway for biosynthesis of some Eicosanoids?

- All mammalian cells except Erythrocytes synthesize Eicosanoids
- **Fig 3: Summary of Cyclic Pathway** for biosynthesis of Clinically relevant Prostaglandins (PGs) and Thromboxanes (TXs) from Arachidonic acid
- **Bradykinin, Epinephrine, Thrombin can activate Phospholipase A₂ (PLA₂)**, which then hydrolyzes membrane Phospholipids to produce Arachidonic acid, which is the substrate for Cyclic Pathway
- Cyclic Pathway is catalyzed by **Prostaglandin Endo-peroxide Synthase** – which is made up of two enzymes:
 - **Cyclooxygenase and**
 - **Peroxidase**
- Prostaglandin Endo-peroxide Synthase is called **Cyclooxygenase (COX)**
- Nitric Oxide (NO) can initiate the biosynthesis of Prostaglandin
- Inhibitors of Nitric Oxide Synthase Inhibits biosynthesis of Prostaglandins

Cyclooxygenase (a “Suicide Enzyme”):

- “Switching off” the biosynthesis of Prostaglandins is partly achieved by a remarkable property of Cyclooxygenase – that of self-catalyzed destruction (enzyme suicide)

- Self destruction May be due to presence in mammalian tissues of a specific enzyme called **15-Hydroxy-Prostaglandin Dehydrogenase (15 HPD)**
- Blocking the action of 15 HPD (with either Sulfa-salazine or Indomethacin) can prolong the half-life of Prostaglandins

Briefly outline the Linear Pathway for biosynthesis of some Eicosanoids

- **Fig. 4: Summary of Linear pathway for biosynthesis of Leukotrienes from Arachidonic acid** is shown in
- **5-Lipoxygenase** requires the presence of the membrane protein FLAP (5-Lipoxygenase-Activating Protein)
- FLAP binds Arachidonic acid, facilitating its interaction with the enzyme
- 5-Lipoxygenase, FLAP, and Phospholipase A₂ form a complex in association with the nuclear envelope during biosynthesis of Leukotrienes in Leukocytes

What are some of the effects/functions of Eicosanoids?

- Prostaglandins have a wide variety 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
- Thromboxanes affect Platelet aggregation and thus blood clotting

What are some of the specific effects of Prostaglandins?

Examples of some specific effects:

- The Prostaglandins (PGE₂ and PGE₁) induce the signs of inflammation that includes redness and heat (due to arteriolar vasodilatation), and swelling and edema resulting from increasing capillary permeability. This condition can be treated with Corticosteroids that inhibit biosynthesis of Prostaglandins.
- Bradykinin and Histamine can activate the biosynthesis of PGE₂ in the region of the hypothalamus where body temperature is regulated, thus resulting in increasing the body temperature causing fever.
- Interleukin-1 (IL-1 α), which is a cytokine, can also act on the hypothalamus causing an increase in the biosynthesis of Prostaglandins, thereby increasing body temperature.
 - (Note that Prostaglandins are “Pyrogenic” – meaning that they can raise body temperature).
 - Aspirin, which is an Anti-pyretic drug, can inhibit the Pyrogenic effect of Prostaglandins.
- The Prostaglandins (PGE, PGA) and Prostacyclin (PGI₂), are vasodilators, they lower systemic arterial pressure, thereby increasing local blood flow and decreasing peripheral resistance.

What are some of the site of Action of Inhibitors of Prostaglandin biosynthesis?

Clinically there are two types of therapeutically useful drugs that affect the biosynthesis of the Prostaglandins.

- The **first type** is the **non-steroidal anti-inflammatory drug (NSAIDs)** such as **Aspirin** (Acetylsalicylic acid), **Indomethacin**, and **Phenylbutazone**.
 - They inhibit formation of Prostaglandins involved in fever, pain and inflammation.
 - They inhibit blood clotting by blocking Thromboxane formation in blood platelets.
 - These drugs block the biosynthesis of Prostaglandin by irreversibly inhibiting the enzyme **Cyclooxygenase (COX)** (See Fig 5).
 - In the case of Acetylsalicylic acid, inhibition occurs by Acetylation of a Serine residue near the Cyclooxygenase active site. This prevents binding of Arachidonic acid to the enzyme. The inhibition of COX by Acetylsalicylic acid is irreversible.
 - The anti-clotting effect of Acetylsalicylic acid is due to the inhibition of Thromboxane formation in blood platelets. The effect is long-lived because Platelets lack a nucleus and thus cannot synthesize new enzyme.
- The **second type** is the **steroidal anti-inflammatory drug – Corticosteroids**.
 - These drugs appear to block the biosynthesis of Prostaglandin by inhibiting the action of the enzyme **Phospholipase A₂**, thus interfering with mobilization of Arachidonic acid, which is the substrate for COX (Fig 5).

The factors that control the biosynthesis of Prostaglandins are poorly understood, but, in general, prostaglandin release seems to be triggered following hormonal or neural excitation or after muscular activity.

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