BIOCHEMICAL BASIS OF PAIN, Part I: PAIN & EICOSANOIDS – An Overview

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What is pain?

- Pain is a complex experience consisting of Physiological response to Noxious stimulus, which in some cases is followed by Emotional response,
- Pain can sometimes serve as a warning mechanism that helps to protect an organism, signaling withdrawal from harmful stimuli causing the pain,
- Pain can be a symptom of injury, inflammation, heat, or pressure
- Perception of pain may be enhanced by non-physical factors such as Anxiety,
- Some pain has no physical cause whatsoever,

Why do individuals respond differently to pain?

- Neuro-anatomic basis for pain reception develops in the fetus, but individual pain responses are acquired in early childhood and are affected by several factors:
  - Social, Cultural, Psychological, Cognitive, Genetic factors, etc.
- Combination of factors serve as the basis to explain the apparent difference in pain tolerance among different groups or individuals; Example:
  - Soldiers can withstand or ignore pain while engaged in battle,
  - Certain cultural practices require participants to endure pain that seems intolerable to others,

What is Nociception?

- Nociception is detection and perception of noxious stimuli, such as pain,
- Pain tends to alert the individual to potential damage (Nociception),
- Perception of pain is a multi-step process, originating at the site of insult with stimulation of specific nerve fibers (**Nociceptors),**
- Pain sensation is one part of Nociceptive response; Other responses include:
  - Rise in blood pressure,
  - Increase in heart rate,
  - Reflexive withdrawal from noxious stimulus;

What are Nociceptors?

- Nociceptors are Peripheral Sensory Systems that respond to noxious stimuli,
- Nociceptors are connected to CNS via thinly myelinated or unmyelinated nerve fibers with free nerve endings,
- Once activated Nociceptors may become sensitized, i.e., respond to low threshold stimuli and exhibit spontaneous firing,
- Some Nociceptors react to several painful stimulation,
- Others are more selective,
- Certain Nociceptors react to Pinprick, but ignore painful heat,
- Link between pain stimulation and pain perception is highly variable,
- Injury may occur without pain, and pain without injury,

NOCICEPTORS

Receptors	Fibre group	Receptor response to	Function	Characteristics
Small myelineated	Aδ	Noxious stimuli	Sharp, pricking pain	Myelinated fibers with (bare/free) unmyelinated endings
Unmyelinated	C	Noxious stimuli	Dull, burning pain	Unmyelinated fibers with bare/free nerve endings in Epidermis, Dermis and deeper tissues
Itch receptors	C	Pruritic stimuli	Itch	Unmyelinated fibers that end in or near the Epidermis and are highly sensitive to Histamine

What mediators are released by Nociceptors?

- After nerve fibers or Nociceptors are stimulated, the irritated or damage cells release chemical mediators of pain and inflammation, such as:
  - Bradykinin,
  - Serotonin,
  - Potassium ions,
  - Hydrogen ions,
  - Histamine,
  - Prostaglandins, etc

What are the different types of pain?

- Fast pain:
  - It has rapid onset and offset,
  - It is carried by group III fibers,
- Slow pain:
  - It is poorly localized,
  - It is carried by C fibers,
- Acute pain: breaking a bone or touching hot surface,
- Two phases are perceived in acute pain:
  - Immediate, Intense feeling of short duration, described as Sharp, Pricking sensation,
  - Followed by Dull, Throbbing sensation

- Chronic pain, often associated with Pathological conditions such as Cancer or Arthritis,
- Chronic pain is sometimes difficult to locate and control,
- **If a chronic pain cannot be alleviated, Psychological factors such as depression and anxiety can intensify the condition, complicating an already challenging treatment situation**

What are Eicosanoids?

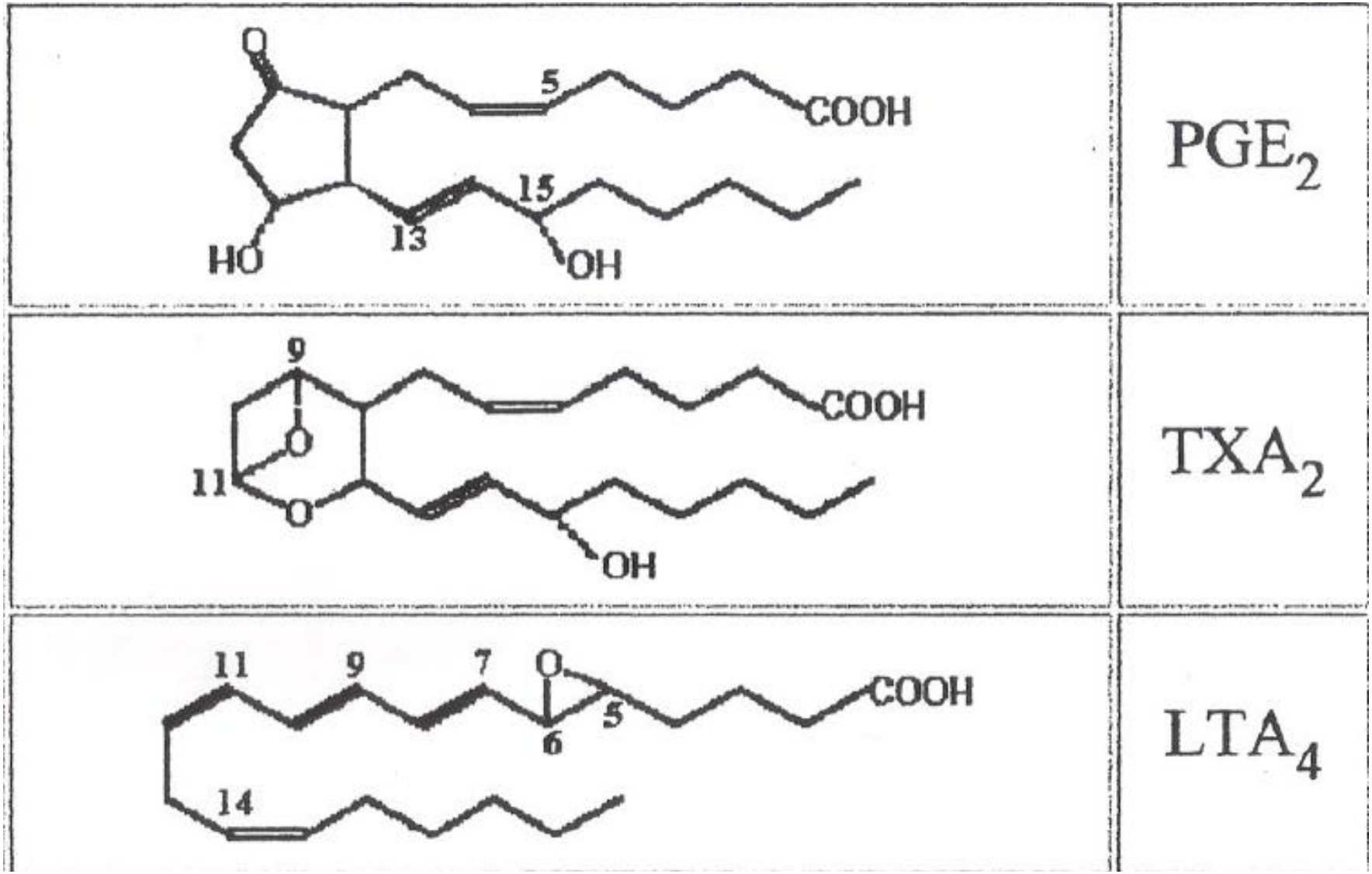
- Eicosanoids are a group of compounds derived from metabolism of **Eicosa-polyenoic** Fatty Acids,
  - Polyunsaturated fatty acids with 20 Carbons

What are the Clinically Relevant Eicosanoids?

- Clinically Relevant Eicosanoids are (**Fig. 1**):
- **Prostaglandins (PGs)**:
  - Originally assumed to be produced in Prostate gland,
- **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 structures of Clinically relevant Eicosanoids



http://web.indstate.edu/thcme/mwking/lipid-synthesis.h

What are the precursors for biosynthesis of Eicosanoids?

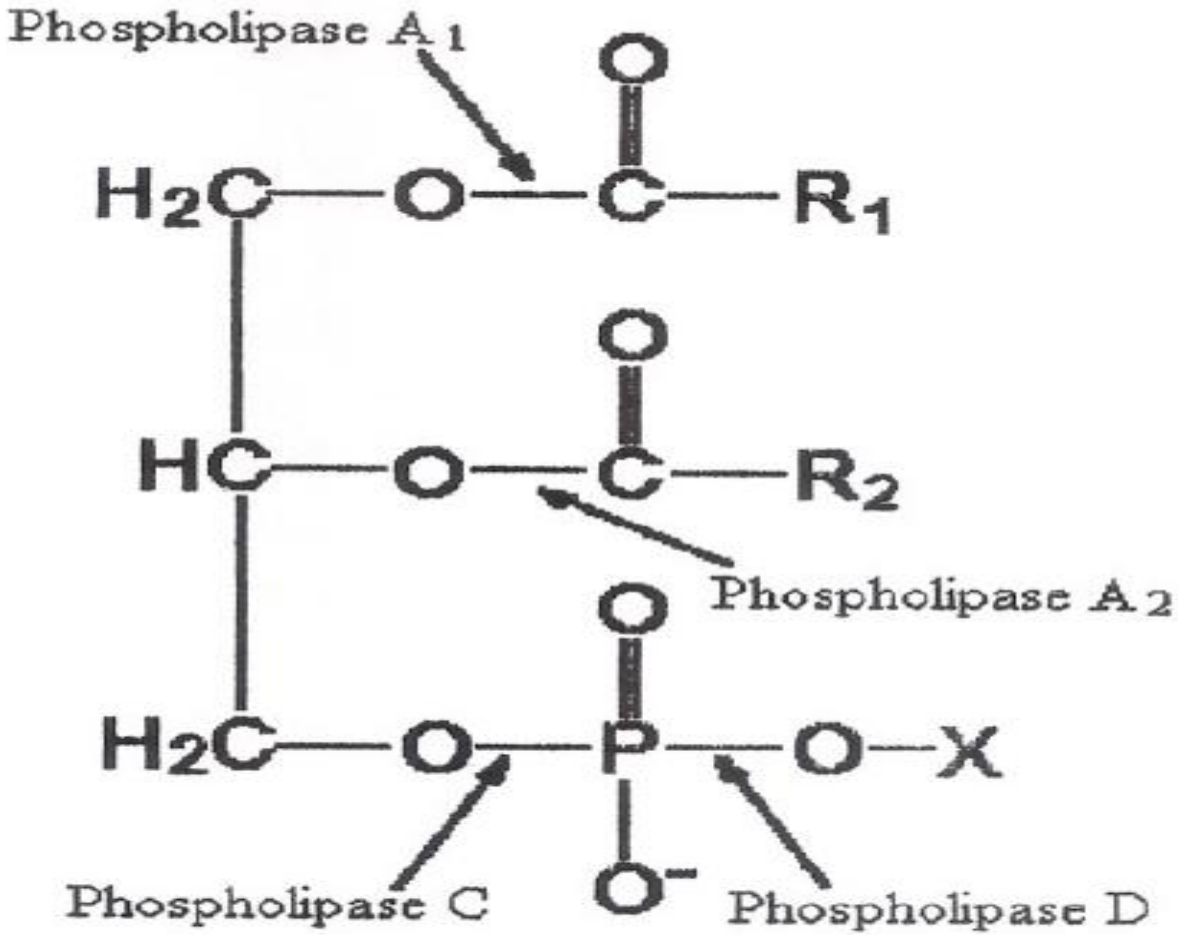
- **Principle Eicosanoids** are from **Arachidonic Acid**

(cis-5,8,11,14 – Eicosatetraenoic acid);

  - Arachidonic Acid is an ω-6 Fatty Acid, (ω - 6; 20:4)
- Major source of Arachidonic acid is cellular stores, predominantly located at C-2 position of membrane Phospholipids (Phosphatidyl-Choline),
- Phospholipase A_2 catalyzes hydrolysis of membrane Phospholipids to produce Arachidonic acid as one of its products (**Fig. 2**),
- Dietary sources of Arachidonic acid are Linoleic acid and Linolenic acid,

- **Minor Eicosanoids** are derived from:
  - Dihomo-γ-Linoleic acid and
  - Eicosapentaenoic Acid (EPA)
- Linolenic acid is the precursor for the biosynthesis of Dihomo-γ-Linoleic acid and Eicosapentaenoic acid
- Linoleic acid and Linolenic acid are Essential fatty acids,
- Dietary deficiency of Linoleic acid seriously threaten the ability of the body to synthesize Eicosanoids,

Fig. 2: Sites of action of Phospholipases on Phospholipid



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

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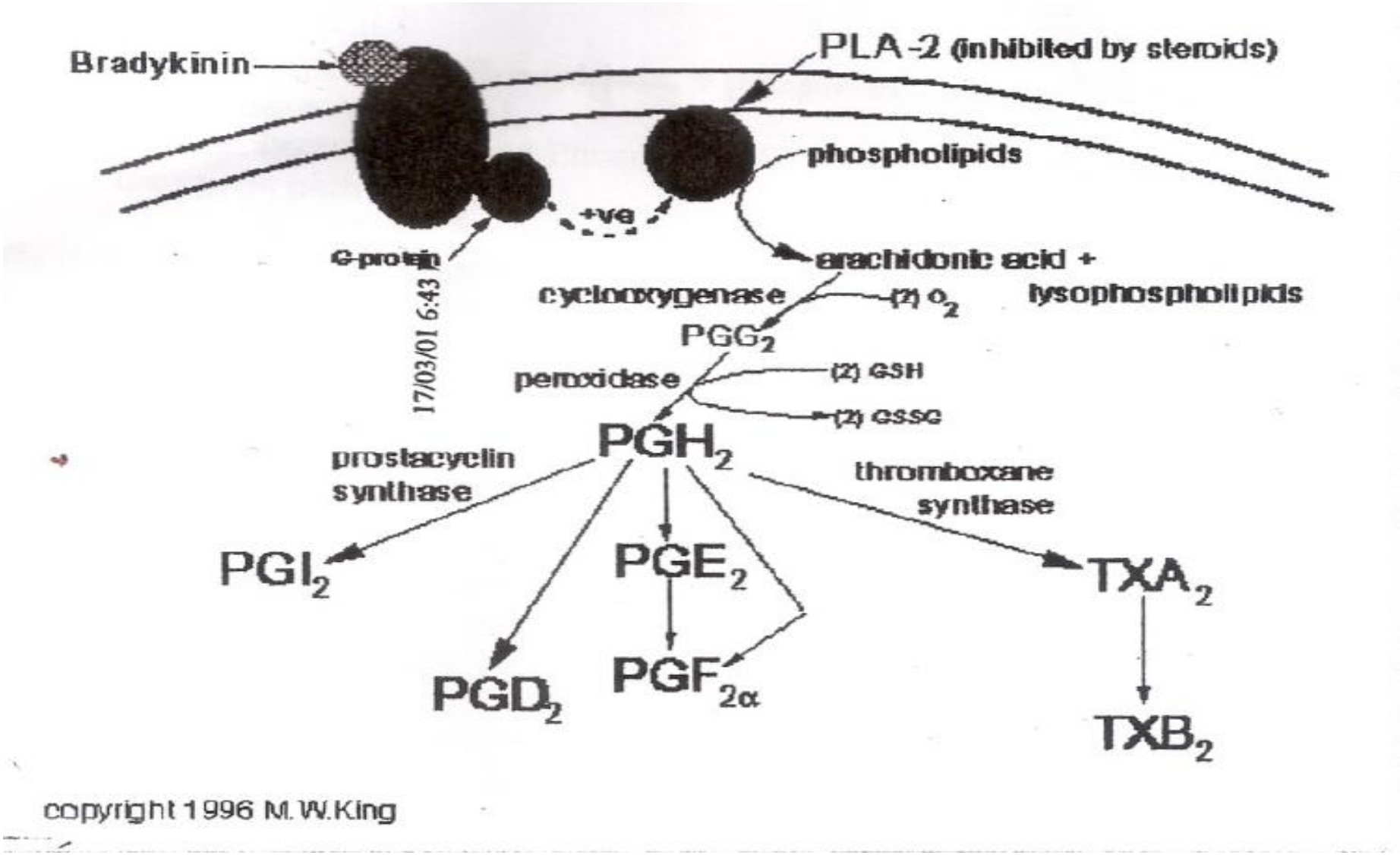
Cyclic pathway for biosynthesis of Eicosanoids

- 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,
- Cyclic pathway is initiated via Prostaglandin Endoperoxide Synthase that is made up of two enzymes:
  - **Cyclooxygenase**
  - **Peroxidase**
- **Phospholipase A_2 (PLA_2)** is activated by numerous stimuli (e.g. **Bradykinin, Epinephrine, Thrombin, etc**.),
- PLA_2 hydrolyzes membrane Phospholipids to produce Arachidonic acid, which is the substrate for the Cyclic pathway,

Fig. 3: Cyclic Pathway for biosynthesis of Prostaglandins, Prostacyclins and Thromboxanes



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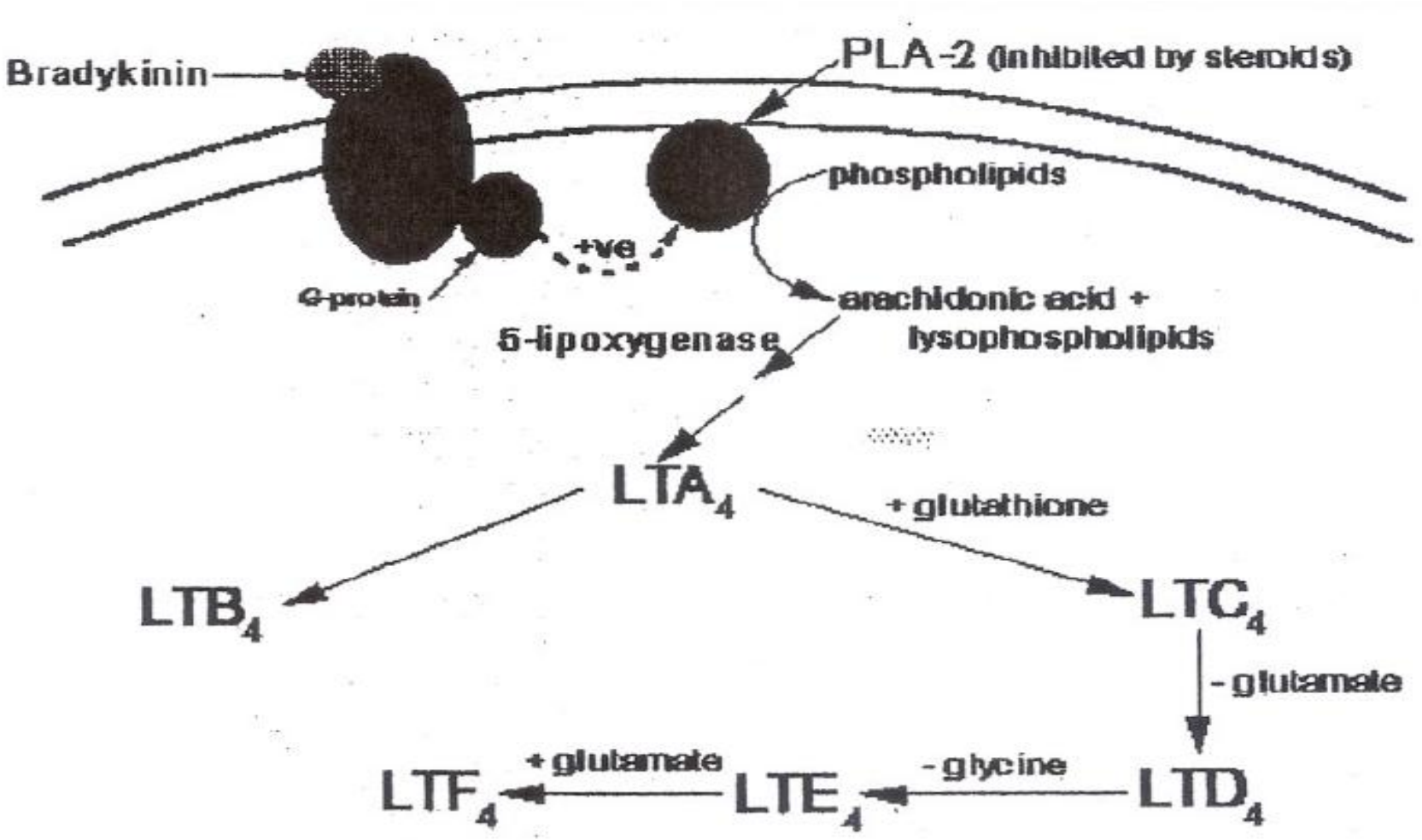
Linear pathway for biosynthesis of Leukotrienes

- **Fig 4:** Summary of Linear Pathway for biosynthesis of clinically relevant Leukotrienes from Arachidonic acid
- **Linear pathway** is initiated by **Lipoxygenases,**
- **5-Lipoxygenase** gives rise to **Leukotrienes (LTs)**

Fig. 4: Linear pathway for biosynthesis of some Leukotrienes



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State some general functions of Eicosanoids

- Eicosanoids are Autocrine, they function locally at their site of synthesis;
- Eicosanoids have a wide range of effects, such as:
  - Inflammatory responses (predominantly those of the joints, skin and eyes),
  - Intensity and duration of pain and fever,
  - Reproductive function (induction of labor),
  - Inhibition of Gastric acid secretion,
  - Regulation of Blood pressure through Vasodilatation or Constriction,
  - Inhibition or activation of Platelet Aggregation and Thrombosis,

State some specific functions of Eicosanoids

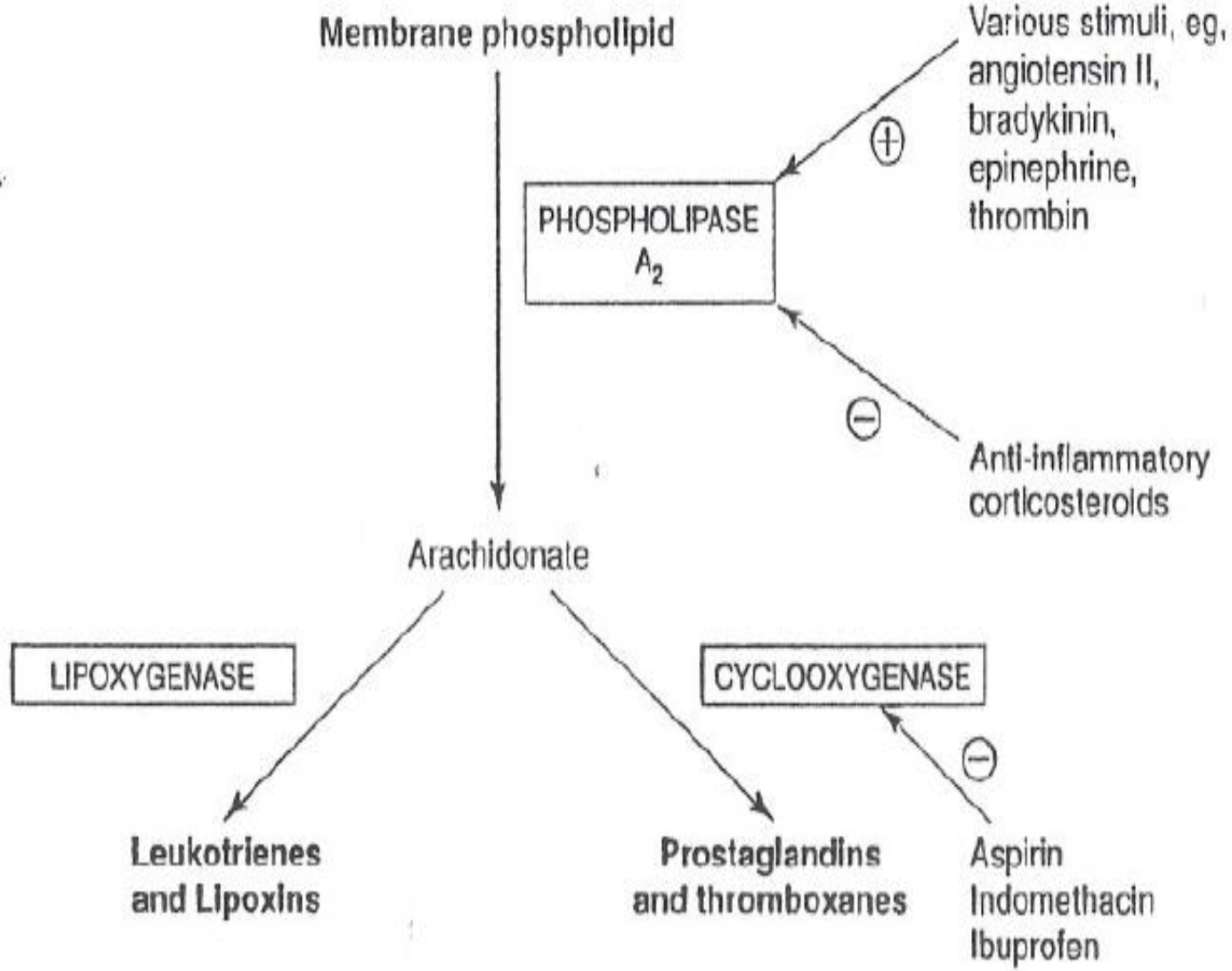
- Prostaglandins (PGE_2 and PGE_1) induce signs of inflammation, such as:
  - Redness and Heat (due to Arteriolar Vasodilatation),
  - Swelling and Edema resulting from increasing capillary permeability
    - Condition can be treated with Corticosteroids that Inhibit biosynthesis of Prostaglandins,
- Bradykinin and Histamine can activate biosynthesis of PGE_2 in the region of the Hypothalamus where body temperature is regulated, thus resulting in increasing body temperature causing fever,

- 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, an Anti-pyretic drug, inhibits the Pyrogenic effect of Prostaglandins,
- Prostaglandins (PGE, PGA) and Prostacyclin (PGI_2), 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?

- Clinically 2 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: 5**)
- Aspirin, inhibition occurs by Acetylation of COX,

Fig. 5: Sites of action of some inhibitors of prostaglandin biosynthesis



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- **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 5**),

- 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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