BIOCHEMICAL BASIS OF PAIN, Part I: PAIN & EICOSANOIDSS – 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,
<table>
<thead>
<tr>
<th>Receptors</th>
<th>Fibre group</th>
<th>Receptor response to</th>
<th>Function</th>
<th>Characteristics</th>
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</thead>
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<tr>
<td>Small myelinated</td>
<td>Aδ</td>
<td>Noxious stimuli</td>
<td>Sharp, pricking pain</td>
<td>Myelinated fibers with (bare/free) unmyelinated endings</td>
</tr>
<tr>
<td>Unmyelinated</td>
<td>C</td>
<td>Noxious stimuli</td>
<td>Dull, burning pain</td>
<td>Unmyelinated fibers with bare/free nerve endings in Epidermis, Dermis and deeper tissues</td>
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<tr>
<td>Itch receptors</td>
<td>C</td>
<td>Pruritic stimuli</td>
<td>Itch</td>
<td>Unmyelinated fibers that end in or near the Epidermis and are highly sensitive to Histamine</td>
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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://wcb.indstate.edu/thcme/mwking/lipid-synthesis.html
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 A₂ 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 $D$.  

http://web.indstate.edu/thcme/mwking/lipid-synthesis.html
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 A₂ (PLA₂)** is activated by numerous stimuli (e.g. **Bradykinin, Epinephrine, Thrombin, etc.**),

• PLA₂ 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

Bradykinin → PLA-2 (inhibited by steroids) → phospholipids

G-protein → cyclooxygenase → arachidonic acid + lysophospholipids

PGH₂ → peroxidase → prostacyclin synthase → PGI₂

PGH₂ → prostacyclin synthase → PGE₂

PGH₂ → thromboxane synthase → TXA₂

PGH₂ → PGD₂

PGH₂ → PGF₂α

TXB₂

http://web.indstate.edu/thcme/mwking/lipid-synthesis.html
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
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 ($\text{PGE}_2$ and $\text{PGE}_1$) 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 (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?

- 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
• **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 Hormonial 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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