Eicosanoids & Platelet Activating Factor

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Autacoids

- These are the substances produced by wide variety of cells that act locally at the site of production. (local hormones)

- **Amine**
  - Histamine
  - Serotonin

- **Lipid**
  - Prostaglandins
  - Leukotrienes
  - Platelet activating factor

- **Peptide**
  - Bradykinin
  - Angiotensin
  - Kallidin
Mediators of Inflammation and Immune reaction

1. Vasoactive amines (Histamine and Serotonin)
2. Eicosanoids
3. Platelet Activating Factor
4. Bradykinins
5. Nitric Oxide
6. Neuropeptides
7. Cytokinines
EICOSANOIDs

- PGs, TXs and LTs are all derived from eicosa (referring to 20 C atoms) tri/tetra/ penta enoic acids. Therefore, they can be collectively called eicosanoids.

- Major source: 5,8,11,14 eicosa tetraenoic acid (arachidonic acid).

- Other eicosanoids of increasing interest are: lipoxins and resolvins.

- The term prostanoid encompasses both prostaglandins and thromboxanes.
In most instances, the initial and rate-limiting step in eicosanoid synthesis is the liberation of intracellular arachidonate, usually in a one-step process catalyzed by the enzyme phospholipase A$_2$ (PLA$_2$).

PLA$_2$ generates not only arachidonic acid but also lysoglyceryl -phosphorylcholine (lyso-PAF), the precursor of platelet activating factor (PAF).
EICOSANOIDs Contd....

Corticosteroids inhibit the enzyme PLA$_2$ by inducing the production of lipocortins (annexins).

The free arachidonic acid is metabolised separately (or sometimes jointly) by several pathways, including the following:

- **Cyclo-oxygenase (COX)**: Two main isoforms exist, COX-1 and COX-2

- **Lipoxygenases**: Several subtypes, which often work sequentially, synthesise leukotrienes.
Summary diagram of the inflammatory mediators derived from phospholipids, with an outline of their actions and the sites of action of anti-inflammatory drugs.
## CYCLOOXYGENASES

<table>
<thead>
<tr>
<th></th>
<th>COX-1</th>
<th>COX-2</th>
<th>COX-3</th>
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<tbody>
<tr>
<td></td>
<td>• Constitutive (always present in cells)</td>
<td>• Inducible (synthesis stimulated by endotoxins and other inflammatory mediators)</td>
<td>• Recently isolated from cerebral cortex</td>
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<tr>
<td></td>
<td>• Serves house-keeping function e.g. gastroprotective</td>
<td>• Participates in inflammation</td>
<td>• Involved in pain perception and fever</td>
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<tr>
<td></td>
<td></td>
<td>• Constitutive in brain, endothelium and kidney</td>
<td>• Not involved in inflammation</td>
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<td></td>
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<td>• Procarcinogenic</td>
<td>• Paracetamol targets COX-3</td>
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Differential Actions of Cyclooxygenases

- COX1: Constitutive
- COX2: Inducible

Unwanted side-effects
- PGI2
- PGE2
- TXA2

Housekeeping Function

Consecutive

Inducible
Inflammatory

Therapeutic anti-inflammatory effects

Inflammation

PGE2
PGF2a
Proteases
**Pathophysiologial Roles**

**CNS**

- PGE$_1$ and PGE$_2$ are pyrogenic and cause fever.
- NSAIDs act as antipyretic agents by inhibiting these PGs.

**Peripheral Nerve Endings**

- PGE$_2$ and PGI$_2$ sensitize pain receptors to various mediators.
- NSAIDs act as analgesics by decreasing the synthesis of PGs.
**Pathophysiological Roles**

**CVS**
- **PGE$_2$, PGI$_2$** are vasodilators whereas **TXA$_2$** are vasoconstrictor agents.
- **PGI$_2$** is used in **pulmonary hypertension**
- **PGE$_2$** increases capillary permeability.
- **PGE$_2$ and PGI$_2$** keeps ductus arteriosus patent.

**PLATELETS**
- **PGI$_2$** inhibits platelet aggregation whereas **TXA$_2$** is a potent aggregator of platelets.
- **PGI$_2$** can be used as an anti-aggregator drug in dialysis and cardiopulmonary bypass, storage of platelets for transfusion.
Pathophysiological Roles

PLATELETS Contd...

- Thromboxane A$_2$ stimulates blood platelet aggregation, essential to the role of platelets in blood clotting.

UTERUS

- PGE$_2$ and PGF$_{2\alpha}$ are powerful uterine stimulants (contraction) and cervical ripening
- PGs are responsible for pain during menstruation and NSAIDs like mefenamic acid are useful for relieving this pain.
Pathophysiologial Roles

**BRONCHUS**

- PGE$_2$ and PGI$_2$ are bronchodilators and PGF$_{2\alpha}$ & TXA$_2$ are bronchoconstrictor agents.

- Aerosolized PGE$_2$ has been used effectively to abort acute attacks of asthma.

- COX inhibitors like aspirin causes more production of LTs.

- Aspirin can result in participation of asthma attacks because LTs are the main bronchoconstricting mediators in human asthma.
Pathophysiological Roles

**GIT**
- PGE₂ and PGI₂ decreases acid secretion and increases mucus production and mucosal blood flow.
- All these factors decrease the chances of peptic ulcer.
- PGE₂, PGF₂α: Spasmogenic, ↑ fluid & electrolyte secretion.

**KIDNEY**
- PGE₂ and PGI₂ causes renal vasodilation, natriuresis and increased water clearance due to inhibition of the action of ADH. These agents also facilitate renin release.

**EYE**
- PGF₂α decreases intraocular pressure by increasing the uveoscleral outflow.
Clinical Uses

CVS:

- *Epoprostenol (PGI2) and treprostinil (longer acting PGI2 analogue)* can be used for the treatment of pulmonary hypertension.

- To keep ductus arteriosus patent before surgery: *alprostadil (PGE1) and epoprostenol (PGI2)*

- Patent Ductus Arteriosus (PDA) at birth, NSAIDs like aspirin and indomethacin are given to close it.
Platelets:

- *Low dose aspirin* can be used as an *antiplatelet* drug for the prophylaxis of MI and stroke.
- *Epoprostenol* (PGI2) can be used as an *anti-aggregatory drug in dialysis and cardiopulmonary bypass*. It can also be used for storage of platelets for transfusion.
UTERUS:

- Dinoprostone (PGE$_2$) intravaginally and carboprost (15-methyl PGF$_2$α) intraamniotic injection can be used for inducing mid trimester abortion.
- Misoprostol (PGE$_1$) along with methotrexate or mifepristone is used for induction of abortion in first few weeks of pregnancy.
- Dinoprostone or misoprostol intravaginally are employed for cervical ripening during labour.
- Carboprost (15-methyl PGF$_2$α) can be used to control post partum hemorrhage (contraction of uterus leads to compression of blood vessels resulting in decreased bleeding).
Bronchus:

- Aerosolized PGE2 has been used effectively to abort acute attacks of asthma.

- COX inhibitors like aspirin cause more production of LTs (because due to enzyme inhibition arachidonic acid now produces only LTs).

- Aspirin can result in precipitation of asthma attacks.
GIT

- NSAIDs on long term use can precipitate PUD due to inhibition of PG synthesis.

- **Misoprostol is the most specific drug for the treatment of peptic ulcer due to chronic NSAID use.** [The drug of choice is proton pump inhibitors]

- PG seems to play some role in colonic cancer. **Regular use of aspirin or celecoxib decreases the risk of colonic polyps and cancers.**
Loop diuretics act partly by increasing the stimulation of COX; therefore **NSAIDs attenuate the diuretic action** of these drugs.

**Bartter syndrome** is characterized by **excess PGs** leading to **hyperreninemia**, **excess aldosterone** and the resultant **hypokalemia and alkalosis**.

**Indomethacin** is used for **treatment** of this syndrome.
Male reproductive system

- PGE2 and PGI2 increases sperm motility and enhances penile erection.
- *Alprostadil* can be used to *treat erectile dysfunction*. 
EYE

- PGF2α decreases intraocular pressure by increasing the uveoscleral outflow.
- Latanoprost (PGF2α) is being used as eye drops for glaucoma.
- Bimatoprost, travaprost and unoprostone are new prostaglandin analogues for this indication.
1. $PGL_2$ analogue - Epoprostenol and Treprostinil

2. $PGE_1$ analogue - alprostadil, Misoprostol

3. $PGE_2$ analogue - Dinoprostone

4. PGF2α analogue - Carboprost

Latanoprost, *Bimatoprost, travaprost and unoprostone*
Leukotrienes are synthesised from arachidonic acid by lipoxygenase-catalysed pathways.

These soluble cytosolic enzymes are mainly found in lung, platelets, mast cells and white blood cells. The main enzyme in this group is 5-lipoxygenase.

The 5-lipoxygenase forms 5-hydroperoxytetraenoic acid (5-HPETE), leading to the production of the unstable leukotriene (LT)A₄.

This may be converted enzymatically to LTB₄ and utilising a separate pathway to the cysteiny1 leukotrienes LTC₄, LTD₄, LTE₄.
Leukotrienes cont....

- **LTB4**, acting on specific receptors, causes adherence, chemotaxis and activation of polymorphs and monocytes, and stimulates proliferation and cytokine production from macrophages and lymphocytes.

- LTB4 is an important mediator in all types of inflammation; the cysteiny1 leukotrienes are of particular importance in asthma.

- The **cysteiny1 leukotrienes** cause: – contraction of bronchial muscle – vasodilatation in most vessels, but coronary vasoconstriction.
Leukotrienes have roles in inflammation.

They are produced in areas of inflammation in blood vessel walls as part of the pathology of atherosclerosis.

Leukotrienes are also implicated in asthmatic constriction of the bronchioles.
Action of LTs can be inhibited by:

- **Corticosteroids** (decrease the production of LTs by inhibiting phospholipase A2)
- Lipoxygenase inhibitors (**zileuton**)
- LT receptor antagonists (**zafirlukast, montelukast, iralukast**)
Platelet-activating factor is a biologically active lipid that can produce effects at exceedingly low concentrations ($G_{q/G_{11}}$; stimulates cAMP production).

PAF is believed to be an important mediator in both acute and chronic allergic and inflammatory phenomena.

PAF is produced by platelets in response to thrombin, and by activated inflammatory cells.

Rupatidine is a combined $H_1$ and PAF antagonist that is used for treating allergic symptoms.

Lexipafant (PAF antagonist) is in clinical trial in the treatment of acute pancreatitis.
LIPOXINS

- Lipoxins are formed by the concerted action of the 5- and the 12- or 15-lipoxygenase enzymes during inflammation.

- Lipoxins act on polymorphonuclear leukocytes, through a distinct G protein-coupled receptor system to oppose the action of pro-inflammatory stimuli, supplying what might be called ‘stop signals’ to inflammation.

- Aspirin (a COX inhibitor) stimulates the synthesis of lipoxins.
THANK YOU