Prostaglandins, Leukotrienes and Platelet activating factors

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Prostaglandins and Leukotrienes

- Prostaglandins (PGs) and Leukotrienes (LTs): Biologically active 20 carbon atom polyunsaturated essential fatty acids released from cell membrane fatty acids – lipid derived autacoids
- Eicosanoids: PG, Thromboxanes (TX) and LTs - derived from *"eicosa"penta enoic acid* - referring to 20 carbon atoms (*"enoic"* – double bonds)
- The eicosanoids are considered "local hormones"
  - Most universally distributed autacoids – practically all tissues can synthesize 1or 2 PG or LT
  - They have specific effects on target cells close to their site of formation
  - They are rapidly degraded, so they are not transported to distal sites within the body

Eicosanoids - Background

- 1930: Human semen – contracts uterus and other smooth muscles (SM) – fall in BP
  - Prostaglandin – derived from prostate (!)
- 1960: Mixture of closely related compounds (a family)
- 1970: Aspirin like drugs inhibit PG synthesis
  - Thromboxanes (TX) and Prostacyclin (PGI)

Chemistry

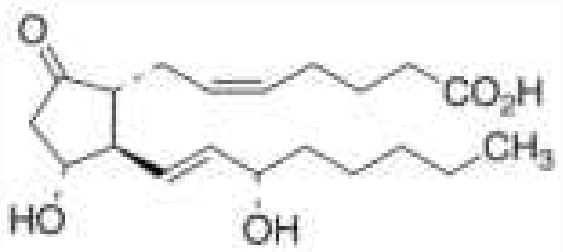
Prostanoic Acid

- Chemically, PGs are derivative of *Prostanoic acid* – does not occur naturally in body
- PGs are designated in series as – A, B, C ….I etc. depending on ring structure and substitution
  - Each series is named 1,2,3 indicating no. of double bonds
- LTs are also similarly – A, B, C ….F and 1,2, 3,4

Chemistry of eicosanoids – contd.

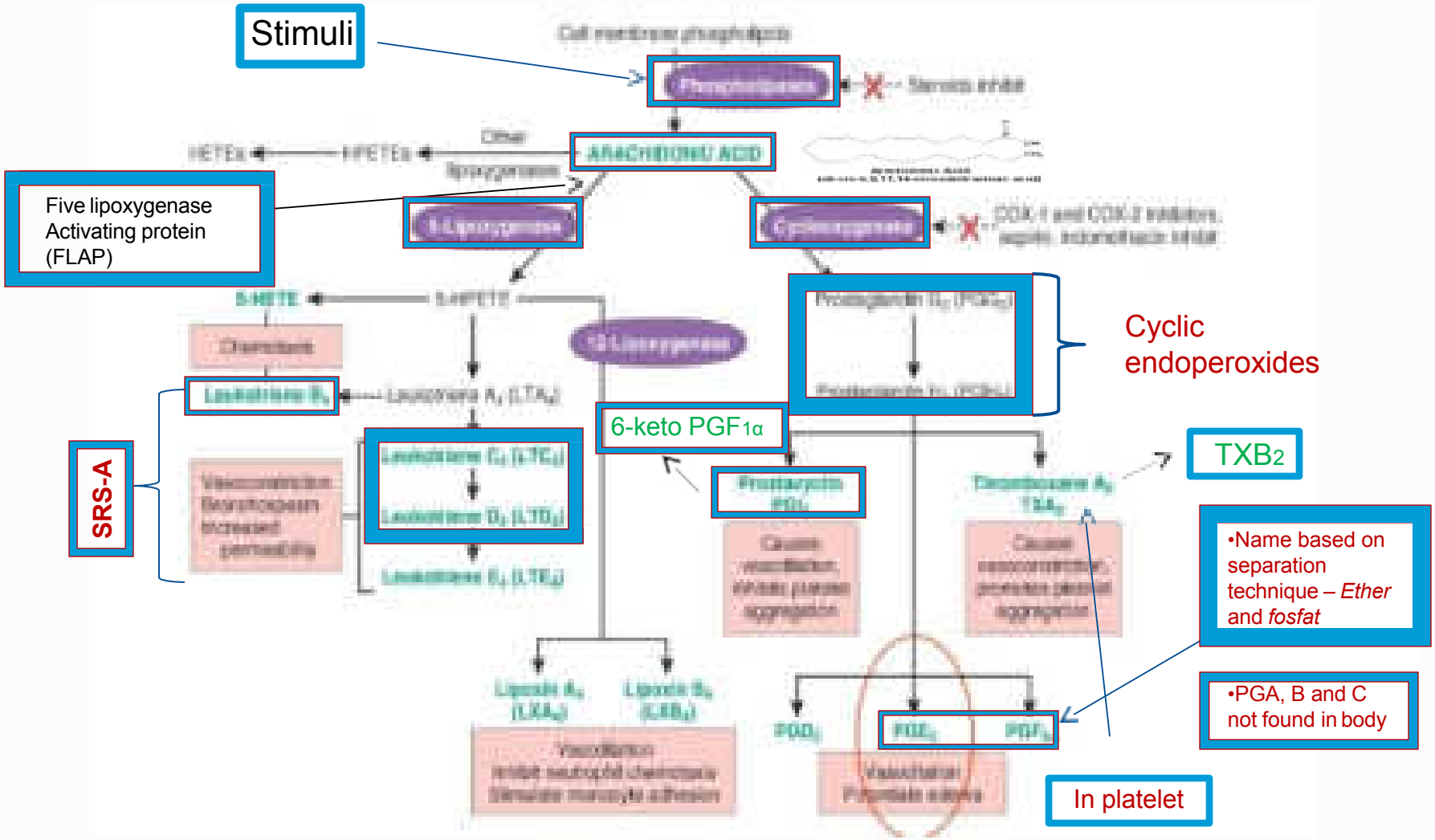
- In the body all are derived from *eicosa* (20 C atoms) – tri/tetra/penta *enoic acid*
- In human –derived from *5,8,11,14 eicosa tetra eonic acid* (arachidonic acid)
- During synthesis of PG, TX and LT – 2 double bonds get saturated due to cyclization – only 2 double bonds in side chain – so, 2 PGs are important ….. PGE_2, $PGF_{2\alpha}$, PGI_2, TXA_2……..
- No cyclization or reduction for LTs – LTB_4, LTC_4, LTD_4

Arachidonic Acid
(all-cis-5,8,11,14-eicosatetraenoic acid)



Prostaglandin - PGE_2

Biosynthesis of Eicosanoids - Pathway



The Cycloxygenages (Cox)

1. Cox-1 ('the good guy'):
   - Constitutively expressed
   - Synthesized in basal states – not changed even if cell is fully grown
   - Credited for 'house-keeping functions' – secretion of mucus in Gastric mucosa, haemostasis and renal function
1. Cox-2 ('the bad guy'): Normally, in tissues I insignificant amount
   - Inducible by inflammatory mediators (cytokines, interleukin-1, tumor necrosis factor (TNF) - Induction inhibited by corticosteroids
   - Blamed for inflammation / pain / fever Exception: Kidney, brain and
   - foetus
1. Cox-3 ('the dark horse'):
   - Very recently discovered in dog brain
   - Splice variant of Cox-1 (intron 1remains in mRNA) - genesis of fever
   - Inhibited by acetaminophen – which acts only weakly on Cox-1 and Cox-2

Synthesis inhibitors & Degradation

- NSAIDS – Mostly non-selective (both COX-1 and COX-2)
  - *Aspirin* – acetylates COX at serine site – irreversible inhibition
  - Other NSAIDs - competitive and reversible inhibition
  - Selective Cox 1inhibitors – *celecoxib, etoricoxib*
- *Zileuton* – Inhibits LOX – was used in asthma
- Glucocorticoides – inhibit release of arachidonic acid – produces protein *annexin* – inhibits Phospholipase A_2
  - Also inhibits induction of COX-2
- **Degradation:** Most tissues – rapidly – fastest in Lungs
  - Most PGs, TXA_2 and Prostacyclins (PGI_2) – half life of few seconds only
  - Carrier mediated uptake into cells followed by – side chains are oxidized and so on ….

PGs & TXAs: Pathophysiological - CVS

- Both PGE_2 and $PGF_{2\alpha}$: Mostly vasodilators - but $PGF_{2\alpha}$ constricts Pulmonary vein and artery
  - PGI_2 – uniform vasodilator and potent hypotensive >PGE_2
  - PGG_2 and PGH_2 – biphasic response (actually vasoconstrictor)
  - TXA – vasoconstrictor
- **Heart:** Stimulates: PGE_2 and $PGF_{2\alpha}$ – direct weak and reflex action
- **Role:** No role in systemic Vascular regulation – but PGI_2 (COX-2 generated) – local vascular tone (dilator)
  - PGE_2 keeps *ductus arteriosus* patent (Aspirin & Indomethacin)
  - Exudation: PGs generated by COX-2 with LTs and other autacoids - inflammation

Pathophysiological Roles - Uterus

- PGE_2 and $PGF_{2\alpha}$ – uniformly contracts uterus – pregnant and non-pregnant …higher as the pregnancy progresses
  - Consistent contraction – $PGF_{2\alpha}$ but PGE_2 – relaxes not-pregnant and contracts pregnant uterus
  - At term – softens uterus

- **Role:**
  - Initiation and progression of labour by $PGF_{2\alpha}$ (Aspirin delays)
  - Semen in high PGs – movement of female genital tract, transport of sperm and facilitation of fertilization
  - Dysmenorrhoea – Uncoordinated uterine contraction – ischemia – pain (Aspirin effective)

Roles – Bronchial Muscles

- $PGF_{2\alpha}$, PGD_2, TXA_2 and LTs – Potent bronchoconstrictor
- PGE_2 > PGI_2 – dilators + inhibit release of Histamine – but no clinical use (irritation)
- **Role:** Asthma – imbalance between the above
  - Aspirin: induces asthma – diverts arachidonic acid to produce more LTs (LTC_4 and LTD_4)
  - In allergic asthma – Leukotriene

Pathophysiological Roles – GIT

- **Intestine:** PGs (PGE_2) – increased propulsive activity – colic andwatery diarrhoea
  - PGE_2– increases water, electrolyte and mucus secretion ….PGI_2 opposes
  - **Role:** Toxin induced increased fluid movements in secretary diarrhoea (aspirin reduces fluid volume)
    - Colonic polyps and Cancer – reduced colonic cancer and reduced polyp formation
- **Stomach:** PGE_2>PGI_2reduces all gastric acid secretions (also pepsin) –Gastrin also reduced - even histamine, gastrin and other induced ones
  - Mucus, HCO_3 secretion increased with increased blood flow - Antiulcerogenic
  - **Role:** PGI_2 – regulation of gastric mucosal blood flow – natural ulcer protective ….NSAID induced ulcers – due to loss of protective function
    - Gastric mucosal PGs are produced by COX -1 – selective COX-2 inhibitors are NOT ULCEROGENIC

Pathophysiological Roles – contd.

- **Kidneys:** PGE_2 & PGI_2 – Diuretic effect
  - Renal vasodilatation and inhibit tubular reabsorption (Furosemide like – inhibits Cl- reabsorption
  - TXA_2 – renal vasoconstriction
  - **Role:** PGE_2 & PGI_2 (produced by COX-2) in kidney – intrarenal blood flow regulation and tubular reabsorption (less) ….NSAIDs - retain salt and water
    - Renin release – PGE_2 and PGI_2
- **CNS:** Poor penetration; injected directly – PGE_2 – sedation, rigidity and behavioural changes; PGI_2 – fever
  - **Role:** PGE_2-Hypothalamus: pyrogen induced fever and malaise (COX-2 involved – selective COX-2 inhibitors – antipyrretic
- Neuromodulator – pain perception, sleep and other functions

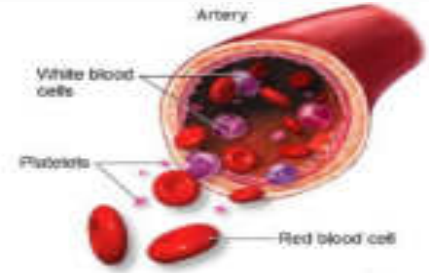
Pathophysiological Roles – contd.

- **ANS:** Inhibition as well as augmentation of NA release – depends on PG, species and tissue
  - **Role:** modulate sympathetic neurotransmission
- **Peripheral nerves:** Sensitize afferent nerve endings to pain inducing chemical and mechanical stimuli – irritate mucous membrane
  - **Role:** algesic during inflammation (aspirin cause analgesia)
- **Eye:** $PGF_{2\alpha}$– induces ocular inflammation and lowers IOP – enhances uveoscleral and tubular outflow (*latanoprost)*
  - **Role:** Local PGs facilitate aqueous humor drainage (less COX-2 in glaucoma)

Pathophysiological Roles – contd.

- **Endocrine:** Facilitate release of Anterior Pituitary hormones – GH, Prolactin, ACTH, FSH, LH --- also Insulin and steroids
  - **Role:** terminate early pregnancy in women (luteolysis)
- **Metabolism:** Antilipolytic – Insuline like effect- mobilize Ca++from Bone

Pathophysiological Roles - Platelets



- $TXA_2 > PGG_2 > PGH_2$ – pro-aggregator…..PGI_2 and PGD_2 – anti-aggregator …. PGE_2 – inconsistent effect
- **Role:** TXA_2 and PGI_2 – mutual antagonists – prevent aggregation in circulation, but induces aggregation during injury
  - TXA_2 – produced by COX-1 – amplify aggregation
  - Aspirin (low dose): haemostasis interference by inhibiting platelet aggregation (COX-1 inhibition at portal circulation) – PGI_2 not interfered (endothelium)

Leukotrienes

Straight chain lipoxygenase products

Limited number of tissues

LTB_4– Neutrophils

LTC_4 and LTD_4 - Macrophages

Leukotrienes –Roles

- **CVS and Blood:** Injection of LTC_4 and LTD_4 – brief rise in BP followed by prolonged fall (not due to vasodilatation)
  - Due to coronary constriction – due to decreased cardiac output - reduction in circulating volume - increased capillary permeability
  - More potent than histamine - in Local oedema
  - LTB_4 – chemotactic for neutrophils and monocytes (also HETE) – also migration of neutrophils through capillaries and clumping
  - LTC_4 and LTD_4 – chemotactic for eosinophils
- **Role:** Important mediators of inflammation (with PGs)
  - LTC_4 and LTD_4 – exudation of plasma
  - LTB_4 – attracts the inflammatory cells
  - 5-HPETE and 5-HETE – facilitate release of histamine from mast cells

Pathophysiological Roles - LTs

- **Smooth Muscles:** LTC_4 and LTD_4 contracts smooth muscles – potent bronchoconstrictor and spastic contraction of GIT
  - Also increase in mucus secretion
- **Roles:** Mediator of human allergic asthma
  - Released with PGs and other autacoids during AG:AB reaction
  - More potent than others and metabolized slowly in lungs
  - Responsible for abdominal colics in anaphylaxis
- Afferent Nerves:
  - LTB_4 - sensitizes afferent nerves to pain mediators – Pain (like PGs) – pain and tenderness of inflammation

Prostanoid Receptors

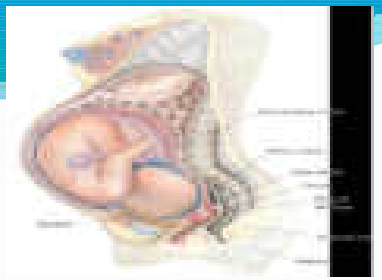
- PGs, TX and Prostacyclin act by their specific receptors
- Five families – corresponding to natural PGs
- All are GPCRs
- Functionally – excitatory or contractile and inhibitory or relaxants

- **Contractile group:** EP_1, FP and TP
  - Gq – PLC and IP_3/DAG
  - Ca++ release intracellularly
  - Functions: SM contraction and Platelet aggregation
- **Relaxant group:** DP_1, EP_2, EP_4 and IP
  - Gs – adenylyl cyclase c-AMP
  - Functions: SM relaxation and inhibition of Platelet aggregation

Leukotriene Receptors

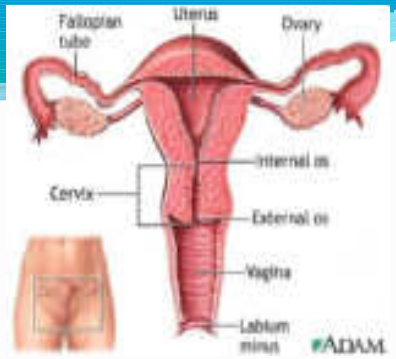
- Separate receptors for LTB_4; and LTC_4 and LTD_4
- LTB_4 – BLT_1 and BLT_2
- Cysteinyl: LTC_4 and LTD_4 – *cys*LT_1 and *cys*LT_2
- All are GPCRs – IP3/DAG
  - BLT – chemotactic – in spleen and leucocytes
  - *cys*LT_1 – bronchial and intestinal muscles (Zafirlukast and Montelukast)
  - *cys*LT_2 – leukocytes and spleen

Therapeutic Uses – PGs and analogoues



- Limited availability, short lasting action, cost and frequent side effects
- Abortion: First trimester abortion - Suction evacuation plus PGE_2 intravaginal pessary (before 3 hours)
  - Now upto 7 weeks - 600 mg Mifepristone (antiprogestin) + misoprostol 400 µg …provoked uterine contraction
  - Intravaginal application or sublingual administration – lesser side effects
  - Rule out ectopic pregnancy
  - ADRs: Uterine cramps, vaginal bleeding, nausea, vomiting and diarrhoea also incomplete evacuation
  - Methotrexate + Misoprostol
- Midterm abortion: missed abortion, molar abortion --- erratic action and incomplete abortion ….. Oxytocin resistant to responsive
  - Extraamniotic injection of single dose PGE_2 – IV oxytocin or $PGF_{2\alpha}$ with hypertonic saline – high success rate

Uses of PGs & analogoues – contd.

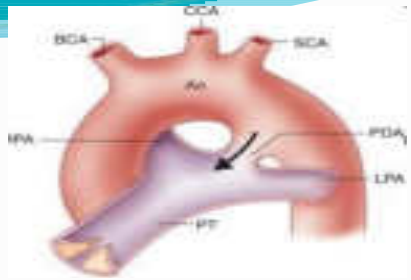


- **Induction of Labour:** less reliable and inter-individual variation - Oxytocin is preferred drug
  - In renal failure and toxaemic patients - PGE_2 or $PGF_{2\alpha}$ used – intravaginal route is preferred
- **Cervical priming:** Low dose of PGE_2 - cervical ripening in unfavourtable cervix – intravaginally used (12 hours before induction)
- **PPH:** 15-methyl – $PGF_{2\alpha}$ (Carboprost) IM in PPH unresponsiveness to ergometrine and oxytocin – uterine atony)

Other uses of PGs and analogoues

- Peptic Ulcer: Cytoprotective – healing of ulcer …patients with NSAIDS and smokers – Misoprostol (Synthetic PGE_1 derivative) 100 mcg/200mcg tab.– comparable to Ranitidine and Cimetidine
  - Ulcer pain is not relieved
  - ADRs – poor patient compliance – diarrhoea, abdominal cramps, uterine bleeding, abortion
  - Primary use: NSAIDS induced GI injury with blood loss (PPIs preferred)
- Glaucoma: $PGF_{2\alpha}$ analogues – latanoprost, travoprost etc. – first choice drug in open angle glaucoma
  - **MOA:** Ocular inflammation – increased uveoscleral outflow (due to increased permeability of tissues in ciliary muscles
  - decreased COX-2 in glaucoma at ciliary body (PGs Role)
  - **ADRs:** ocular irritation, pain, iris pigmentation, thickening and darkening of eyelashes and macular oedema

Other uses of PGs and analogoues



- To maintain Patency of Ductus arteriosus: PGE_1 alpha – Alprostadil – in congenital heart diseases – till surgery
- To avoid platelet damage: PGI_2 – Epoprostenol – in haemodialysis and Cardio-pulmonary bypass surgery – also in harvesting platelets
- Peripheral vascular disease: IV injection of PGI_2 – for healing of ischaemic ulcers
- Impotence – Alprostadil – injected into the penis

PREPARATIONS, DOSES & PLACEMENTS of PGs

- **PGE_2: Dinoprostone** – for Induction/augmentation of labour, midterm abortion .. (Prostine-E)
  - Vaginal Gel: 1mg inserted into posterior fronix followed by 1-2 mg after 6 hour if required
  - Vaginal Tab: 3mg inserted into posterior fornix, followed by another 3mg if labour does not start within 6 hour
  - Oral Tablet: Primiprost 0.5 mg tab, one tab. Hourly till induction, maximum 1.5mg per hr. ---- rarely used
  - Cervical Gel: Cerviprime 0.5 mg inserted into cervical canal for preinduction cervical softening and dilatation in patients with poor Bishop's score.
  - Gemeprost: 1mg vaginal pessary for softening of cervix in first trimester – 1mg 3hr before attempting dilatation, for 2nd trimester abortion/molar gestation – 1mg every 3hours, max. 5 doses
  - Extraamniotic solution and Intravenous solution – Rarely used

PREPARATIONS & DOSES of PGs – contd.

- **$PGF_{2\alpha}$: Dinoprost**
  - Prostin F_2 Alpha intraamniotic injection 5 mg/ml in 4 ml. amp. for midterm abortion/induction of labour – rarely used
  - 15– methyl $PGF_{2\alpha}$ (carboprost) ….Prostodin 0.25 mg in 1 ml ampoule IM every 30 - 120 minutes for PPH