Prostaglandins and their Biological role

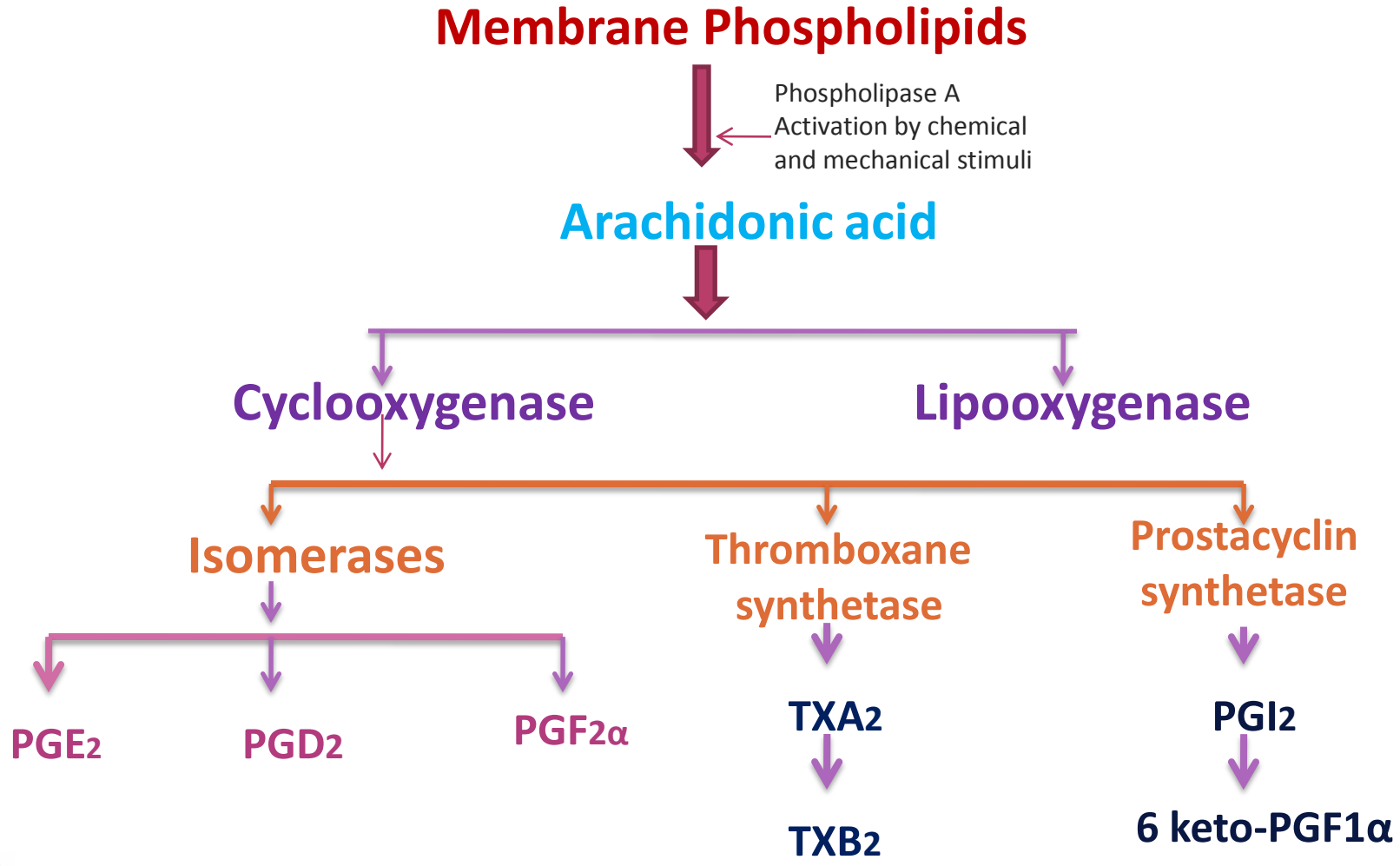
By

Dr Nataraj H R
Lecturer
Post graduate Department Dravyaguna

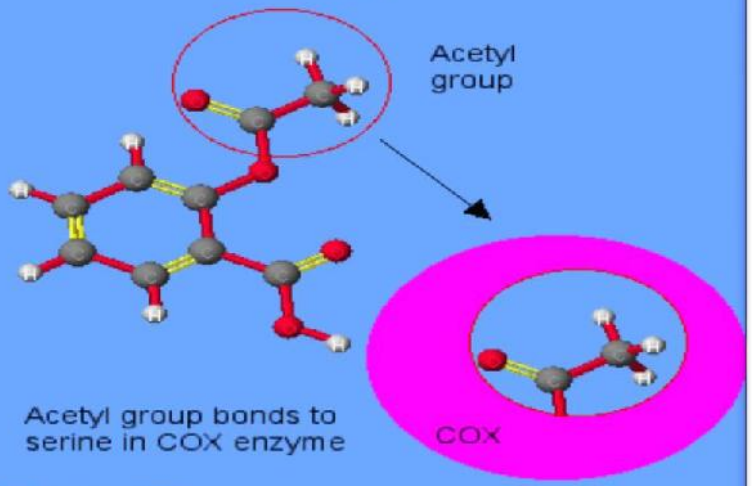
Introduction

- Prostaglandins are the most distributed autocoids in the body
- Prostaglandins are biological active derivatives of 20 carbon atom polysaturated essential fatty acids that are released from cell membrane phospholipids
- Chemically PG's may be derivatives of prostanoic acid
- The main precursor of the naturally occurring prostaglandins and thrombohexanes is the twenty carbon unsaturated essential fatty acid 5,8,11,14-eicosatetraenoic acid (arachidonic acid)

Chemistry, Biosynthesis and Degradation

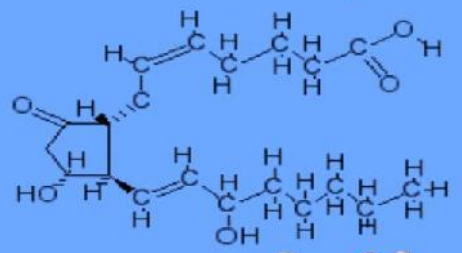


Aspirin



C. Ophardt, c. 2003

Prostaglandin



PGE_2

C. Ophardt, c. 2003

Arachidonic Acid

$CH_3(CH_2)_4(CH{=}CHCH_2)_4CH_2CH_2C(=O)OH$

$CH_3CH_2CH_2CH_2CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH_2CH_2C(=O)OH$

C. Ophardt, c. 2003

Inhibition:

1.NSAID'S – COX-1 &COX-2 Inhibitors

2.Glucocorticosteroids

Degradation:

1.All tissues

2.Lungs-TXA2,Prostocyclin

3.Renal(Urine)-PGI2

Mechanism of action of Prostaglandins

- Actions of variety and complexity
- As Modulators of tissue function

Affects other cells by interacting with plasma membrane
G-protein coupled receptors

Stimulation or inhibit formation of cAMP or may activate a phosphatidylionositol signal pathway

Intracellular Ca ++ Release

- PPAR gamma –Transcription factor activity

Actions and Pathophysiological Roles

A) CARDIO VASCULAR SYSTEM:

i)PGE_2 and $PGF\alpha_2$ cause vasodilatation in most, but not all vascular beds

ii)PGI_2 is uniformly vasodilatory and is more potent hypotensive than PGE_2

iii)PGE_2 and $F_2\alpha$ stimulate heart by weak direct but more prominent reflex action due to fall in BP. The cardiac output increases

B) PLATELETS:

i) The Endoperoxides PGG_2 and PGH_2 are Proaggregatory

ii) PGI_2 is potent inhibitor of Platelet aggregation

iii) PGD_2 has antiaggregatory action less potent than PGI_2

iv) PGE_2 has inconsistent effects

C) UTERUS:

i) PG'S increase tone as well as amplitude of uterine contractions

ii) PGE2 and $PGF_{2\alpha}$ uniformly contract human uterus, pregnant and non pregnant in vivo

iii) When tested in vitro $PGF_{2\alpha}$ consistently produces contraction while PGE_2 relaxes nonpregnant but contracts pregnant human uterine strips

iv) PGs at low doses soften the cervix and make it more compliant

D) BRONCHIAL MUSCLE:

i) $PGF_{2\alpha}$, PGD_2 are potent bronchoconstictors(more potent than histamine)

ii) PGE_2 is a powerful bronchodilator

iii)PGI_2 produces mild dilatation

iv) PGE_2 & PGI_2 also inhibit histamine release

E) GASTROINTESTINAL TRACT:

i) In isolated preparations the longitudinal muscle of gut in contracted by PGE_2 and $PGF_{2\alpha}$

ii) Propulsive action in enhanced by PGE_2

iii) PGE_2 increases H_2O, electrolyte and mucous secretion

iv) PGI_2 does not produces diarrhea and infact opposes PGE_2 and toxin induced fluid movement

F) KIDNEY:

i) PGE_2 and PGI_2 increases water, Na^+ and K^+ excretion and have a diuretic effects

ii) PGE_2 has been shown to have a fruosemide like inhibitory effect on Cl^- reabsorption as well also cause vasodilatation and inhibit tubular reabsorption

iii) PGE_2 antagonizes ADH action and this adds to the diuretic effect

iv) PGI_2,PGE_2 and PGD_2 evoke release of Rennin

CENTRAL NERVOUS SYSTEM:

- Central effects are not prominent
- Inj Intracerebroventricularly PGE_2 produces sedation, rigidity,behavioural changes and marked rise in body temperature

AUTONOMIC NERVOUS SYSTEM:

- Depending on the PGs,species and tissue both inhibition as well as augmentation of NA release from adrenergic nerve endings has been observed

PERIPHERAL NERVES:

- PGs(E_2 &I_2) sensitize afferent nerve endings to pain inducing chemical and mechanical stimuli
- They irritate mucous membrane and produce long standing dull pain on intradermal injection

ENDOCRINE SYSTEM:

- PGE2 facilitates the release of anterior pituitary hormones growth hormone, prolactin,ACTH,FSH and LH as well as that of insulin and adrenal steroids. It has a TSH like effect on thyroid
- PGF2α causes luteolysis and terminates early pregnancy in many mammalas but not significant in humans

METABOLISM:

- PGEs are antilipolytic
- exert an insulin like effect on carbohydrate metabolism
- Mobilize Ca2+ from bone mediate hypercalcaemia due to bony metastasis

The Role of PGs in Inflammation

- The inflammatory response is always accompanied by release of PGs Predominantly PGE2 and PGI2
- In acute inflammation PGs released by local tissues and blood vessels, Mast cells release PGD2In chronic inflammation cells of monocyte macrophage series also release PGE2
- PGE2,PGI2 and PGD2 are powerful vasodilators
- PGs of E series are also implicated in the production of fever
- 1L-1 ix is mediated by PGE2
- Significant anti inflammatory modulator in inflammatory cells deceasing their activity
- PGE2 inhibit lysosomal enzyme
- Also inhibit macrophage activation ,lymphocyte activation and generation, secretion of some cytokinines

Uses of Prostaglandins

A.Abortion
B.Induction/ Augmentation of labour
C.Cervical priming
D.Post partum Haemorrhage
E.Peptic ulcer
F.To maintain patency of ductus arteriosus
G.To avoid platelet damage

?? Still under investigation

- Peripheral vascular disease-PGI_2
- To reduce infarct size-PGI_2
- Impotence-PGE_1
- Menstruation during contraceptive
- Bronchial asthma-PGE_2

Side effects

- Nausea, Vomiting, Watery diarrohoea,Uterine cramps,Un duely forceful uterine contractions, Vaginal bleeding, flushing, shivering, fever, malaise , fall in BP,tachycardia,Chest pain
- PG s should be used cautiously in the presence of raised levels of intraocular pressure, Hypertension, diabetes, angina or epilepsy
- Contraindicated in presence of cardiac, renal pulmonary or hepatic disease
- Alcoholics and smokers should not use PGs

Prostaglandin Analogues

1. Alprostadil(PGE_1)
2. Carboprost(15-methyl PGF_2 Alpha)
3. Dinoprostone(PGE_2)
4. Dinoprost (PGF_2 Alpha Tromethamine)
5. Doxaprost (PGE Analogue)
6. Misoprostol(PGE_2)

Inhibitors of PG's

Tolmetin
Propionic acid derivatives
Piroxicam
Nabumentone
Etodolac
Phenylbutazone
Aspirin and other Salicylates

Acetaminophen
Mephanemic acid
Ketoroloc
Indomethacin

Conclusion

"Its clearly evident from the above facts that PGs play a very important role in the body by many mechanisms, hence it is suggested that medical practitioners prescribe any drug that prevents the PG's synthesis with utmost care."


THANK YOU