Prostaglandins and their Biological role

By

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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

Membrane Phospholipids

Phospholipase A
Activation by chemical and mechanical stimuli

Arachidonic acid

Cyclooxygenase

Lipooxygenase

Isomerases

Thromboxane synthetase

Prostacyclin synthetase

PGE$_2$
PGD$_2$
PGF$_2\alpha$
TXA$_2$
TXB$_2$

PGL$_2$

6 keto-PGF$_1\alpha$
Inhibition:
1. NSAID’S – COX-1 & COX-2 Inhibitors
2. Glucocorticosteroids

Degradation:
1. All tissues
2. Lungs-TXA2, Prostacyclin
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 phosphatidylinositol signal pathway

  Intracellular Ca ++ Release

- PPAR gamma – Transcription factor activity
Actions and Pathophysiological Roles

A) CARDIO VASCULAR SYSTEM:
   i) PGE\(_2\) and PGF\(_{\alpha2}\) 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 PGF2α uniformly contract human uterus, pregnant and non pregnant in vivo
iii) When tested in vitro PGF2α consistently produces contraction while PGE2 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) PGF2α, PGD2 are potent bronchoconstictors (more potent than histamine)
ii) PGE2 is a powerful bronchodilator
iii) PGI2 produces mild dilatation
iv) PGE2 & PGI2 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$_2$O, 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 PGE2 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( E2 & I2) 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 mammals 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 PGD2. In 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.
• IL-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 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-\( \text{PGL}_2 \)
- To reduce infarct size-\( \text{PGL}_2 \)
- Impotence-\( \text{PGE}_1 \)
- Menstruation during contraceptive
- Bronchial asthma-\( \text{PGE}_2 \)
Side effects

• Nausea, Vomiting, Watery diarrhoea, Uterine cramps, Un duly forceful uterine contractions, Vaginal bleeding, flushing, shivering, fever, malaise, fall in BP, tachycardia, Chest pain
• PGs 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

“It’s 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.”