Prostaglandins and its Types

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ABSTRACT
Prostaglandins are potent bioactive lipid messengers synthesized from arachidonic acid mediated by enzyme COX. Prostaglandins (PGs) play a key role in the initiation of the inflammatory response. Their biosynthesis is significantly increased in inflamed tissue, and they contribute to the development of the cardinal signs of acute inflammation. Although the proinflammatory properties of individual PGs during the acute inflammatory response are well established, their role in the resolution of inflammation is more controversial.

Keywords: Prostaglandins, Cyclooxygenase, Arachidonic acid

INTRODUCTION
Prostaglandins are potent bioactive lipid messengers synthesized from arachidonic acid mediated by enzyme COX. Arachidonic acid is derived from membrane phospholipids catalyzed by PLA₂. They play a very prominent role in reproductive biology like ovulation, endometrial physiology, proliferation of endometrial glands and menstruation and pathological conditions like dysmenorrhoea, carcinoma, endometriosis, menorrhagia. There are different types of prostaglandins like PGD₂, PGE₂, PGF₂, PGI₂.

COX
COX is an enzyme that is responsible for formation of different forms of prostaglandins. It is also referred as prostaglandin synthase, prostaglandin endoperoxidase or prostaglandin G/H synthase. COX is involved in two pathways or two catalytic activities.
1. Cyclooxygenation
2. Peroxidation.

Cyclooxygenase activity is responsible for biocyclooxygenation of arachidonic acid to PGG₂, i.e., COX cyclizes and adds 2 molecules of oxygen to AA for formation of cyclo hydroperoxide PGG₂. Peroxidase activity is involved in reduction of PGG₂ to PGH₂. The COXs exist in two isoforms, a constitutive form (COX-1) and an inducible form (COX-2), and a COX-1 splice variant termed as COX-3 has been reported. COXs catalyze the conversion of AA to PGs and thromboxanes, which trigger as autocrine and paracrine chemical messengers in many physiological and pathophysiological responses.

COX-1
The primary structure of COX-1 was first characterized in sheep and subsequently in a number of species (Merlie et al., 1988; DeWitt and Smith, 1988; Smith et al., 2000). The COX-1 gene is 22 kilobases (kb) in length, contains 11 exons, maps to human chromosome 9q32-33.3, and is transcribed as a 2.8 kb mRNA.

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It is involved in several physiological functions like maintenance of homeostasis (gastric and renal integrity) and normal production of PG.[14,15,16] It is involved in several carcinomas.[17,18,19,20]

**COX-2**

The COX-2 gene is about 8 kb long with 10 exons and it is transcribed as 4.6, 4.0 and 2.8 kb mRNAs variants.[8,13] It is involved in several inflammatory and pathological conditions.[5,7,21] COX-2 is found in brain, kidney and endothelial cells. COX-2 expression can be induced in response to growth factors, cytokines, proinflammatory stimuli, carcinogens, tumor promoting phorbol esters.[14,15,16]

**COX-3**

A third COX isoform, named COX-3, has recently been characterized in dogs.[22] The enzyme is sensitive to acetaminophen and highly expressed in the central nervous system, suggesting that inhibiting COX-3 may represent an important mechanism for controlling the synthesis of prostanoids mediating pain and fever.[23]

**PGE₂**

One of the most abundant PG produced in humans is PGE₂. It is formed by all cell types of the body like epithelia, fibroblasts, infiltrating inflammatory cells.[24] PGE₂ binds to different EP receptors like EP₁, EP₂, EP₃, EP₄ that regulate function of macrophages and dendritic cells.[25,26] Degradation of PGE₂:- The rate of PGE₂ degradation is controlled by 15-PGDH.[27,28,29,30,31]

**Receptors:** PGE₂ acts by autocrine-paracrine signaling on four different types of receptors on target cells. Interaction of PGE2 with the EP1 receptor mobilizes intracellular calcium and inositol trisphosphate (IP3) via Gαq.[5] EP₃ and EP₄ usually act at higher concentrations and slow effective signaling. EP₃ and EP₄ show high affinity for PGE₂. EP₂ and EP₄ are G-protein coupled receptors and are mediated by AC-triggered cAMP/PKA/CREB pathway.[32,33]

**Physiological role:** It plays a pivotal mediator in several biological functions like regulation of immune responses, bp, gastrointestinal integrity, fertility. [26] PGE₂ signalling suppresses colitis symptoms and mucosal damage by protecting the integrity of epithelial intestinal wall, presumably through the enhancement of epithelial survival and regeneration.[34]

**Pathological role:** An alterations in PGE₂ synthesis or degradation leads to pathological conditions like inflammation, chronic infections,[26] colorectal and different types of cancer,[35] stem cell differentiation,[36] arthritis,[37] inflammatory bowel disease (IBD).[38]

The 15-PGDH activity is suppressed in some forms of cancer.[31] PGE₂ is found to be key mediator in inflammatory process. It includes redness, swelling and pain. Redness and edema result from increased blood flow into inflamed tissue through PGE₂-mediated augmentation of arterial dilation and increased microvascular permeability. Pain results from the action of PGE₂ on peripheral sensory neurons and on central sites within spinal cord and brain.[39]

**Immunosuppression:** It is also involved in immunosuppression. In cancer patients, PGE₂ inhibit B and T-cell proliferation and then allowing defective cells to proliferate undetected by immune system.[5] PGE₂ also inhibits IL-2 and IFN production from T-lymphocytes and IL-1 and TNF release from macrophages.[40]

**Fever:** When infected organisms enter the body, bacterial LPS or circulating IL-1 stimulate COX
and PGE synthase, results in formation of PGE₂. The PGE₂ formed diffuses out of endothelial cells into OVLT regulation of hypothalamus that is responsible for controlling fever. Pyrogens, including cytokines released during bacterial infection also potentiate synthesis of PGE₂ in hypothalamus, that resets the thermostat to cause fever.

**Metabolism:** PGE₂ are lipolytic, exert an insulin-like effect on carbohydrate metabolism and mobilize Ca²⁺ from bone: may mediate hypercalcemia due to bony metastasis.

**GIT:** PGE₂ acts directly on intestinal mucosa and increases water, electrolyte and mucus secretion. It acts on EP₃ receptor and decreases gastric acid secretion, histamine stimulated acid secretion. It also stimulates EP₁ receptor, causes contraction of smooth muscle.

**Bronchial muscle:** They act on bronchial smooth muscle and cause vasodilation.

**Kidney:** PGE₂ increase water, Na⁺ and K⁺ excretion and have diuretic effect. It also antagonize ADH action and this adds to diuretic effect. PGE₂ have vasodilator actions in the kidney, and intrarenal infusions of these PGs increase renal blood flow. PGs are also natriuretic, inhibiting tubular sodium reabsorption, and in the thick ascending limb of the loop of Henle, they reduce chloride transport. PGE₂ synthesized in cortex is an important stimulator of renin.

**Endocrine system:**

PGE₂ facilitates release of anterior pituitary hormones – growth hormone, prolactin, ACTH, FSH, LH as well as that of insulin and adrenal steroids. It has TSH like effect on thyroid.

**Alzheimer disease:** In patients with AD, PGE₂ concentration is elevated in CSF than age matched control subjects.

**Blood vessels:** PGE₂ causes vasodilation of blood vessels, there by resulting in decreased bp.

**Intestine:** PGE₂ has the tendency of contracting longitudinal muscles and relax circular muscles thereby increasing peristalsis.

**PGI₂**

PGI₂ is synthesized in the presence of COX and PGIs from PGH₂. PGIs colocalizes with COX in endoplasmic reticulum, plasma membrane, nuclear membrane. PGI₂ is released by healthy endothelial cells. Vascular cells including endothelial cells, VSMCs and endothelial progenitor cells are major source of PGI₂. It is antimitogenic and inhibits DNA synthesis in VSMC. It is involved in edema, pain and inflammation. These levels found to be elevated in synovial fluid of human arthritic patients. PGI₂ is an essential vasodilator and is involved in leukocyte adhesion and VSMC proliferation.

**IP receptor:**

IP receptor is present in spinal cord and has been involved in spinal cord transmission. This receptor is present in kidney, liver, platelets, heart and aorta. So, IP antagonists helps in reducing pain in several models like acetic acid–induced abdominal constriction, mechanical hyperalgesia produced by carrageenan, and pain associated with models of osteoarthritis and inflammatory arthritis.

**Mode of action:** PGI₂ acts through paracrine signaling. Its action commences by acting on GPCR on near platelets and endothelial cells. Platelets: As this receptor gets activated, GPCR signals AC to synthesize cAMP. cAMP cAMP goes on to inhibit any undue platelet activation (in order to promote circulation) and also counteracts any increase in cytosolic calcium levels that would result from thromboxane A₂ (TXA₂) binding (leading to platelet activation and subsequent coagulation).
Endothelial cells: This receptor is also involved in elevating cAMP levels in cytosol. This cAMP then goes on to activate protein kinase A (PKA). PKA then continues the cascade by phosphorylating and inhibiting myosin light-chain kinase, which leads to smooth muscle relaxation and vasodilation.[51]

**Function:** It is a potent inhibitor of platelet aggregation. It prevents formation of platelet plug involved in primary hemostasis (a part of blood clot formation).[48]

**PGD2**

It is main lipid mediator synthesized from arachidonic acid via the catalytic activities of cyclooxygenases (COX) and PGD2 synthases (PGDS) in mast cells, macrophages, and other cellular sources.

**Synthesis and metabolism:**

The peroxidase activity of COX-1,2 enzymes transforms PGG₂ to PGH₂. PGH₂ is unstable intermediate endoperoxidase that is immediately converted to PGD₂ by PGDS. PGD₂ is metabolized non-enzymatically to 15-deoxy-12,14-PGJ₂ (15dPGJ₂) or 12-PGJ₂ depending on the presence of serum albumin.

There are two types of PGDS. Hematopoietic PGDS (H-PGDS) is present in mast cells, macrophages, and dendritic cells, Hematopoietic PGD synthase is widely distributed in the peripheral tissues and localized in the antigen-presenting cells, mast cells, and megakaryocytes.

H-PGDS-producing inflammatory cells that are chemotactically compelled to permeate the vasculature.

Lipocalin-type PGD synthase is localized in the central nervous system and male genital organs of various mammals and the human heart and is secreted into cerebrospinal fluid, seminal plasma, and plasma, respectively. While lipocalin-type PGDS (L-PGDS) is mostly expressed in the central nervous system. L-PGDS expression is induced by laminar sheer stress invascular endothelial cells and is actively expressed in synthetic smooth muscle cells of atherosclerotic intima and coronary plaques of arteries with severe stenosis.[47,51,52]

**Function:**

PGD₂ is major eicosanoid that is synthesized in CNS and peripheral tissues.

CNS: It plays an important role in regulation of sleep. In peripheral tissues, it is produced mainly by mast cells and leukocytes, resulting in activating many signaling pathways leaving to different effects. It is also resulting in atherosclerosis.[47] It results in modulating physiology of airways by causing bronchoconstriction, vasodilation, increased capillary permeability and mucous production. PGD₂ and its metabolites play crucial role in leukocyte biology, acting via several different signaling mechanisms to play pro and anti-inflammatory role. PGD₂ can influence multiple stages in the life of the mature eosinophil, from causing its release from the bone marrow to inducing its recruitment and activation and, ultimately, regulating its apoptosis.[53]

**Pathophysiology:** Abnormal PG production or disrupted signaling cascade leading to PG release by the epithelium has been recognized as one of the important causes underlying many disease processes with smooth muscle disorders, such as asthma, overactive bladder, dyspepsia, and dysmenorrhea. Other disease
processes are irritable bowel syndrome inflammatory bowel disease and infertility.

**Treatment:** Treatment strategies are aimed to provide exogenous source of prostaglandins or to suppress endogenous PG production.[54]

**CONCLUSION**

Prostaglandins are potent bioactive lipid messengers synthesized from arachidonic acid mediated by enzyme COX. Arachidonic acid is derived from membrane phospholipids catalyzed by PLA₂. They play a very prominent role in reproductive biology like ovulation, endometrial physiology, proliferation of endometrial glands and menstruation and pathological conditions like dysmenorrhoea, carcinoma, endometriosis, menorrhagia. Several types of prostaglandins like PGD₂, PGE₂, PGF₂, PGI₂ are present. Abnormal PG production or disrupted signaling cascade leading to PG release by the epithelium has been recognized as one of the important causes underlying many disease processes with smooth muscle disorders, such as asthma, overactive bladder, dyspepsia, and dysmenorrhoea. Other disease processes are irritable bowel syndrome inflammatory bowel disease and infertility.

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