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Review Article

# 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.[1,2,3] Arachidonic acid is derived from membrane phospholipids catalyzed by $PLA_2$.[4] 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.[5] There are different types of prostaglandins like $PGD_2$, $PGE_2$, $PGF_2$, $PGI_2$.[6,7]

## 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. (PGS, PGTS, PGHS).[7]

COX is involved in two pathways or two catalytic activities.

1. Cyclooxygenation
2.peroxidation.

Cyclooxygenase activity is responsible for bisoxygenation of arachidonic acid to $PGG_2$.i.e., COX cyclizes and adds 2 molecules of oxygen to AA for formation of cyclo hydroperoxide $PGG_2$. Peroxidase activity is involved in reduction of $PGG_2$ to $PGH_2$.[8] 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.[9] COXs catalyze the conversion of AA to PGs and thromboxanes, which trigger as autocrine and paracrine chemical messengers in many physiological and pathophysiological responses.[10] COX-1 and -2 share the same substrates, produce the same products, and catalyze the same reaction using identical catalytic mechanisms.[11,12]

## COX-1

The primarystructure 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).[7] The COX-1 gene is ,22 kilobases (kb) in length, contains 11 exons, maps to human chromosome 9q32-q33.3, and is transcribed as a 2.8 kb mRNA.[8,13]

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It is involved in several physiological functions like maintainance 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 andhighly 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]

## $PGE_2$

One of the most abundant PG produced in humans is $PGE_2$. It is formed by all cell types of the body like epithelia, fibroblasts, infiltrating inflammatory cells.[24] $PGE_2$ binds to different EP receptors like $EP_1$, $EP_2$, $EP_3$, $EP_4$ that regulate function of macrophages and dendritic cells[25,26]

Degradation of $PGE_2$:-

The rate of $PGE_2$ degradation is controlled by 15-PGDH.[27,28,29,30,31.]

**Receptors:**$PGE_2$ 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]

$EP_1$ and $EP_2$ usually act at higher concentrations and slow effective signaling. $EP_3$ and $EP_4$ show high affinity for $PGE_2$. $EP_2$ and $EP_4$ 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] $PGE_2$ 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 $PGE_2$ 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] $PGE_2$ is found to be key mediator in inflammatory process. IT includes redness, swellingand pain. Redness and edema result from increased blood flow into inflamed tissue through $PGE_2$- mediated augmentation of arterial dilation and increased microvascular permeability. Pain results from the action of $PGE_2$ on peripheral sensory neurons and on central sites within spinal cord and brain.[39]

**Immunosuppresssion:**

It is also involved in immunosuppression. In cancer patients, $PGE_2$ inhibit B and T-cell proliferation and then allowing defective cells to proliferate undetected by immune system.[5] $PGE_2$ 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

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and PGE synthase, results in formation of $PGE_2$. The $PGE_2$ formed diffuses out of endothelial cellsinto OVLT regulation of hypothalamus that is responsible for controlling fever.[2] Pyrogens, including cytokines released during bacterial infection also potentiate synthesis of $PGE_2$ in hypothalamus, that resets the thermostat to cause fever.[41]

**Metabolism:**$PGE_2$ are lipolytic, exert an insulin-like effect on carbohydrate metabolism and mobilize $ca^{2+}$ from bone: may mediate hypercalcemia due to bony metastasis.[41]

**GIT:**$PGE_2$acts directly on intestinal mucosa and increases water, electrolyte and mucus secretion.[42]
It acts on $EP_3$ receptor and decreases gastric acid secretion, histamine stimulated acid secretion. It also stimulates $EP_1$ receptor, causes contraction of smooth muscle.[2]

**Bronchial muscle:**They act on bronchial smooth muscle and cause vasodilation.[42]

**Kidney:**$PGE_2$ increase water, $Na^+$ and $K^+$ excretion and have diuretic effect. It also antagonize ADH action and this adds to diuretic effect.[42]
$PGE_2$ 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. $PGE_2$ synthesized in cortex is an important stimulator of renin.[2]

**Endocrine system:**
$PGE_2$ 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.[41]

**Alzeimer disease:**In patients with AD, $PGE_2$ concentration is elevated in CSF than age matched control subjects.[43]

**Blood vessels:**$PGE_2$causes vasodilation of blood vessels, there by resulting in decreased bp.

**Intestine:**$PGE_2$has the tendency of contracting longitudinal muscles and relax circular muscles thereby increasing peristalsis.[44]

## $PGI_2$

$PGI_2$ is synthesized in the presence of COX and PGIs from $PGH_2$. PGIS colocalizes with COX in endoplasmic reticulum, plasma membrane, nuclear membrane.[7] $PGI_2$ is released by healthy endothelial cells.[45] Vascular cells including endothelial cells, VSMCs and endothelial progenitor cells are major source of $PGI_2$.[46] It is antimitogenic and inhibits DNA synthesis in VSMC.[16] It is involved in edema, pain and inflammation. These levels found to be elevated in synovial fluid of human arthritic patients.[47]$PGI_2$ is an essential vasodilator and is involved in leukocyte adhesion and VSMC proliferation.[48]

**IP receptor:**
IP receptor is present in spinal cord and has been involved in spinal cord transmission.[49] This receptor is present in kidney, liver, platelets, heart and aorta.[16] 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.[50]

**Mode of action:**$PGI_2$ 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 $A_2$ ($TXA_2$) binding (leading to platelet activation and subsequent coagulation).

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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]

## $PGD_2$

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 $PGG_2$ to $PGH_2$. $PGH_2$ is unstable intermediate endoperoxidase that is immediately converted to $PGD_2$ by PGDS. $PGD_2$ 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]

**Receptors:**

It acts on 2 types of receptors. So, $PGD_2$ action is mediated by both $DP_1$ and $DP_2/CRTH_2$ receptors. D prostanoid receptor(DP) is a classic PGD2 receptor also known asPTGDR or DP; the second is chemoattractantreceptor-homologous molecule expressed on Th2(CRTH2), also known as DP2. These receptors are GPCR. $DP_1$ is coupled to $G_S$ protein that elevates the levels of cAMP. $DP_2$ is coupled to $G_i$ protein, that increase concentration of calcium and decrease in cAMP.[52]Both receptors binding to $PGD_2$ have high affinity.[47]

**Function:**

$PGD_2$ 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. $PGD_2$ and its metabolites play crucial role in leukocyte biology, acting via several different signaling mechanisms to play pro and anti-inflammatory role.$PGD_2$ can influence multiple stages in the life of themature 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 signalingcascade leading to PG release by the epitheliumhas been recognized as one of the importantcauses underlying many disease processes withsmooth muscle disorders, such as asthma, overactivebladder, dyspepsia, and dysmenorrhea. Otherdisease

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processes are irritable bowel syndromeor 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 $PLA_2$.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 $PGD_2$, $PGE_2$, $PGF_2$, $PGI_2$are present. Abnormal PG production or disrupted signalingcascade leading to PG release by the epitheliumhas been recognized as one of the importantcauses underlying many disease processes withsmooth muscle disorders, such as asthma, overactivebladder, dyspepsia, and dysmenorrhea. Otherdisease processes are irritable bowel syndromeor inflammatory bowel disease and infertility.

## ↓ REFERENCES

1.Olivier Morteau. Prostaglandins and Inflammation: the Cyclooxygenase Controversy. Archivum Immunologiae et Therapiae Experimentalis. 2000; 48: 473–480
2.Daniel l. Simmons, Regina M. Botting, and Timothy Hla. cyclooxygenase Isozymes: The Biology of Prostaglandin Synthesis and Inhibition. Pharmacol Rev 2004; 56:387–437
3.Pawel Kalinski. Regulation of Immune Responses by Prostaglandin E 2. The Journal of Immunology 2012; 188: 21–28.
4.Simmons DL, Botting RM, Hla T. Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. Pharmacol Rev 2004;56: 387–437.
5.Kurt J. Sales and Henry N. Jabbour. Cyclooxygenase enzymes and prostaglandins in pathology of the endometrium. Reproduction. 2003 November ; 126(5): 559–567.
6.Hecker M, Foegh ML, Ramwell PW. The eicosanoids: Prostaglandins, Thromboxanes, Leukotrienes and related compounds. In Basic and Clinical Pharmacology. Katzung, B.G. Eds; Appleton & Lange, Norwalk, CT 1995; pp 290-304.
7.Smith WL, DeWitt DL, Garavito RM. Cyclooxygenases: Structural, cellular, and molecular biology. Annu Rev Biochem. 2000; 69:145–182.
8.Joan Clària. Cyclooxygenase-2 Biology. Current Pharmaceutical Design 2003; 9:2177-2190
9.T. D. Warner and J. A. Mitchell, “Cyclooxygenase-3 (COX- 3): filling in the gaps toward a COX continuum?” Proceedings of the National Academy of Sciences of the United States of America 2002; 99(21):13371–13373.
10.R. G. Kurumbail, J. R. Kiefer, and L. J. Marnett. “Cyclooxygenase enzymes: catalysis and inhibition,” Current Opinion in Structural Biology. 2001; 11(6): 752–760
11.K. Gupta, B. S. Selinsky, C. J. Kaub, A. K. Katz, and P. J. Loll, “The 2.0 a resolution crystal structure of prostaglandin H2 synthase-1: structural insights into an unusual peroxidase,” Journal ofMolecular Biology. 2004; 335(2): 503–518
12.R. M. Garavito and A. M. Mulichak. “The structure of mammalian cyclooxygenases,” Annual Review of Biophysics and Biomolecular Structure. 2003;32:183–206
13.Tanabe T and Tohnai N. Cyclooxygenase isozymes and their gene structures and expression. Prostagl Other Lipid Mediat 2002;68-69:95–114.

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PHARMACY INFOPEDIA
ISSN: 2347-7881

14.W. Ma and J. C. Eisenach. “Morphological and pharmacological evidence for the role of peripheral prostaglandins in the pathogenesis of neuropathic pain,” European Journal of Neuroscience. 2002; 15(6): 1037–1047
15. W. Ma and R. Quirion. “Does COX2-dependent PGE2 play a role in neuropathic pain?” Neuroscience Letters 2002; 437(3): 165–169.
16.Smyth EM, FitzGerald GA. Human prostacyclin receptor. Vitam Horm. 2002; 65:149–165.
17.Sales, K.J. et al. Cyclooxygenase-1 is up-regulated in cervical carcinomas: autocrine/paracrine regulation of cyclooxygenase-2, PGE receptors and angiogenic factors by cyclooxygenase-1. Cancer Res. 2002; 62: 424–432
18.Kirschenbaum, A. et al. Expression of cyclooxygenase-1 and cyclooxygenase-2 in the human prostate. Urology 2000; 56: 671–676.
19.Chulada, P.C. et al. Genetic disruption of Ptgs-1, as well as Ptgs-2, reduces intestinal tumorigenesis in Min mice. Cancer Res. 2000; 60: 4705–4708
20.Kitamura, T. et al. Inhibitory effects of mofezolac, a cyclooxygenase- 1 selective inhibitor, on intestinal carcinogenesis. Carcinogenesis 2002; 23: 1463–1466
21.Flower RJ. The development of COX2 inhibitors. Nat Rev Drug Discov 2003;2:179–191.
22.Chandrasekharan NV, Dai H, Roos KL, Evanson NK, Tomsik J, Elton TS and Simmons DL. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. Proc Natl Acad Sci USA 2002; 99:13926–13931.
23.Schwab JM, Schluesener HJ, Meyermann R and Serhan CN .COX-3 the enzyme and the concept: steps towards highly specialized pathways and precision therapeutics? Prostaglandins Leukot Essent Fatty Acids 2003a; 69:339–343.
24.Park, J. Y., M. H. Pillinger, S. B. Abramson. Prostaglandin E2 synthesis and secretion: the role of PGE2 synthases. Clin. Immunol 2006; 119: 229–240.
25.Kabashima K, Sakata D, Nagamachi M, Miyachi Y, Inaba K, Narumiya S. Prostaglandin E2-EP4 signaling initiates skin immune responses by promoting migration and maturation of Langerhans cells. Nat Med 2003; 9:744–749.
26.Legler DF, Krause P, Scandella E, Singer E, Groettrup M. Prostaglandin E2 is generally requiredfor human dendritic cell migration and exerts its effect via EP2 and EP4 receptors. J Immunol 2006; 176:966–973.
27.Backlund, M. G., J. R. Mann, V. R. Holla, F. G. Buchanan, H. H. Tai, E. S. Musiek, G. L. Milne, S. Katkuri, and R. N. DuBois. 15-Hydroxyprostaglandin dehydrogenase is down-regulated in colorectal cancer. J. Biol. Chem 2005; 280: 3217–3223.
28.Hirsch, F. R., and S. M. Lippman. Advances in the biology of lung cancer chemoprevention. J. Clin. Oncol 2005; 23: 3186–3197.
29.Tseng-Rogenski, S., J. Gee, K. W. Ignatoski, L. P. Kunju, A. Bucheit, H. J. Kintner, D. Morris, C. Tallman, J. Evron, C. G. Wood, et al. Loss of 15-hydroxyprostaglandin dehydrogenase expression contributes to bladder cancer progression. Am. J. Pathol 2010; 176: 1462–1468.
30.Eruslanov, E., S. Kaliberov, I. Daurkin, L. Kaliberova, D. Buchsbaum, J. Vieweg, and S. Kusmartsev. Altered expression of 15-hydroxyprostaglandin dehydrogenase in tumor-infiltrated CD11b myeloid cells: a mechanism for immune evasion in cancer. J. Immunol 2009; 182: 7548–7557.
31.Yan, M., S. J. Myung, S. P. Fink, E. Lawrence, J. Lutterbaugh, P. Yang, X. Zhou, D. Liu, R. M. Rerko, J. Willis, et al. 2009. 15-Hydroxyprostaglandin dehydrogenase inactivation as a mechanism of resistance to celecoxib chemoprevention of colon tumors. Proc. Natl. Acad. Sci. USA 106: 9409–9413.
32.Fujino, H., S. Salvi, and J. W. Regan. Differential regulation of phosphorylation of the cAMP response

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PHARMACY INFOPEDIA
ISSN: 2347-7881

element-binding protein after activation of EP2 and EP4 prostanoid receptors by prostaglandin E2. Mol. Pharmacol 2005; 68: 251–259.
33.Sugimoto Y, Narumiya S. Prostaglandin E receptors. J. Biol. Chem 2007;282:11613–11617.
34.Jiang GL, Nieves A, Im WB, Old DW, Dinh DT, Wheeler L. The prevention of colitis by E Prostanoid receptor 4 agonist through enhancement of epithelium survival and regeneration. J Pharmacol Exp Ther 2007;320:22–28.
35.Rigas B, Goldman IS, Levine L. Altered eicosanoid levels in human colon cancer. J Lab Clin Med 1993;122:518–523.
36.North TE, Goessling W, Walkley CR, Lengerke C, Kopani KR, Lord AM, Weber GJ, Bowman TV, Jang IH, Grosser T, Fitzgerald GA, Daley GQ, Orkin SH, Zon LI. Prostaglandin E2 regulates vertebrate haematopoietic stem cell homeostasis. Nature 2007;447:1007–1011.
37.Kojima F, Kato S, Kawai S. Prostaglandin E synthase in the pathophysiology of arthritis. Fundam Clin Pharmacol 2005;19:255–261.
38.Sheibanie AF, Yen JH, Khayrullina T, Emig F, Zhang M, Tuma R, Ganea D. The proinflammatory effect of prostaglandin E2 in experimental inflammatory bowel disease is mediated through the IL-23-->IL-17 axis. J Immunol 2007;178:8138–8147.
39.Funk CD. Prostaglandins and leukotrienes: advances in eicosanoid biology. Science 2001; 294:1871–1875.
40. en.wikipedia.org/wiki/Prostaglandin
41. Tripathi KD., 2008. Essentials of Medical Pharmacology, sixth ed. New Delhi. pp -179
42. Tripathi KD., 2008. Essentials of Medical Pharmacology, sixth ed. New Delhi. pp 178.
43.T. J. Montine, K. R. Sidell, B. C. Crews et al. “Elevated CSF prostaglandin E2 levels in patients with probable AD.” Neurology 1999; 53(7): 1495–1498
44. Tripathi KD., 2008. Essentials of Medical Pharmacology, sixth ed. New Delhi. pp 177.
45. en.wikipedia.org/wiki/Prostaglandin_I2
46.Kawabe J, Ushikubi F, Hasebe N. Prostacyclin in Vascular Diseases. Circ J 2010; 74:836–843.
47.Emanuela Ricciotti and Garret A. FitzGeraldProstaglandins and Inflammation. Arterioscler Thromb Vasc Biol 2011;31:986-1000
48.Noda M, Kariura Y, Pannasch U, Nishikawa K, Wang L, Seike T, Ifuku M, Kosai Y, Wang B, Nolte C, Aoki S, Kettenmann H, Wada K. Neuroprotective role of bradykinin because of the attenuation of pro-inflammatory cytokine release from activated microglia. J Neurochem 2007; 101:397–410.
49.Doi Y, Minami T, Nishizawa M, Mabuchi T, Mori H, Ito S. Central nociceptive role of prostacyclin (IP) receptor induced by peripheral inflammation. NeuroReport 2002; 13:93–96.
50.Bley KR, Bhattacharya A, Daniels DV, Gever J, Jahangir A, O’Yang C, Smith S, Srinivasan D, Ford AP, Jett MF. RO1138452 and RO3244794: characterization of structurally distinct, potent and selective IP (prostacyclin) receptor antagonists. Br J Pharmacol 2006; 147:335–345.
51. Tsuyoshi Oguma, Koichiro Asano and Akitoshi Ishizaka Role of Prostaglandin D2 and Its Receptors in the Pathophysiology of AsthmaAllergology International. 2008;57:307-312
52. Urade Y, Hayaishi O. Prostaglandin D synthase: structure and function. Vitam Horm. 2000;58:89-120.
53. Hilary Sandig, James E. Pease, and Ian Sabroe. Contrary prostaglandins: the opposing roles of PGD2 and its metabolites in leukocyte function J. Leukoc. Biol. 2007, 81: 372–382.
54. Ye Chun Ruan,1,2 Wenliang Zhou,1 and Hsiao Chang Chan2Regulation of Smooth MuscleContraction by the Epithelium: Role of Prostaglandins, physiology, 2011,26;156-70