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PHARMACOGENOMICS OF PROSTAGLANDINS AND THEIR ROLES IN DIFFERENT BODY TISSUES AND ORGANS: A REVIEW

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ABSTRACT

Innumerable physiological and pathophysiological roles in different body tissues and organs of animals and humans are synchronized by special molecules called prostaglandins. These molecules are lipid mediators, produced from arachidonic acid by cyclooxygenase enzyme system in all nucleated cells. There are two forms of cyclooxygenase enzymes COX-1 and COX-2, activated under different stimuli and implement different activities. PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2, $PGF_{2\alpha}$, and Thromboxane A_2 are some important prostaglandins. Other than D, E and F there is also a J series of prostaglandins. All types of prostaglandins are synthesized by different enzymes and bind with specific receptors then in each type, a different series of reactions is started and different cellular activities and functions are performed. This review summarizes types, some general properties and effects of prostaglandins in different tissues and organs of human body. How defect in cyclooxygenase enzyme causes effects on prostaglandins synthesis and this effect will lead to what type of problems and different diseases that occur due to altered prostaglandins or any defect in cyclooxygenase pathway are also discussed.

KEYWORDS: Cyclooxygenase enzyme system, Thromboxane, Arachidonic acid.

INTRODUCTION

Prostaglandins are hydroxy fatty acids. They are bioactive lipid mediators and widely distributed in different animal and human body tissues and organs. These are produced by all nucleated cells. They are biologically active molecules perform different physiological functions and are active in minute amount. In 1930s these were discovered and they were named so because it was thought that these are products from prostate. Prostaglandins (PTGs) and leukotrienes (LTs) are produced when under a stimulus phospholipase A_2 is activated and in return induces release of Arachidonic acid from phospholipids of both cell and nuclear membranes and then this arachidonic acid is oxidized through cyclooxygenase (COX)-1 or 5-lipoxygenase (5LO) and as a result prostaglandins and leukotrienes are produced respectively. Prostaglandins (PTGs) and Leukotrienes (LTs) are both collectively called eicosanoids and perform different functions, mainly associated with homeostasis and inflammation.[1] Here in this review our focus is only on prostaglandins. In COX-1 pathway, enzymatic metabolism of arachidonic acid first yields PGG_2 from this prostanoids PGH_2 is formed, from this endoperoxide intermediate PGH_2 in presence of tissue specific synthetase, bioactive PGs- PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2 and Thromboxane A_2 are produced as shown in Fig 1.[2]

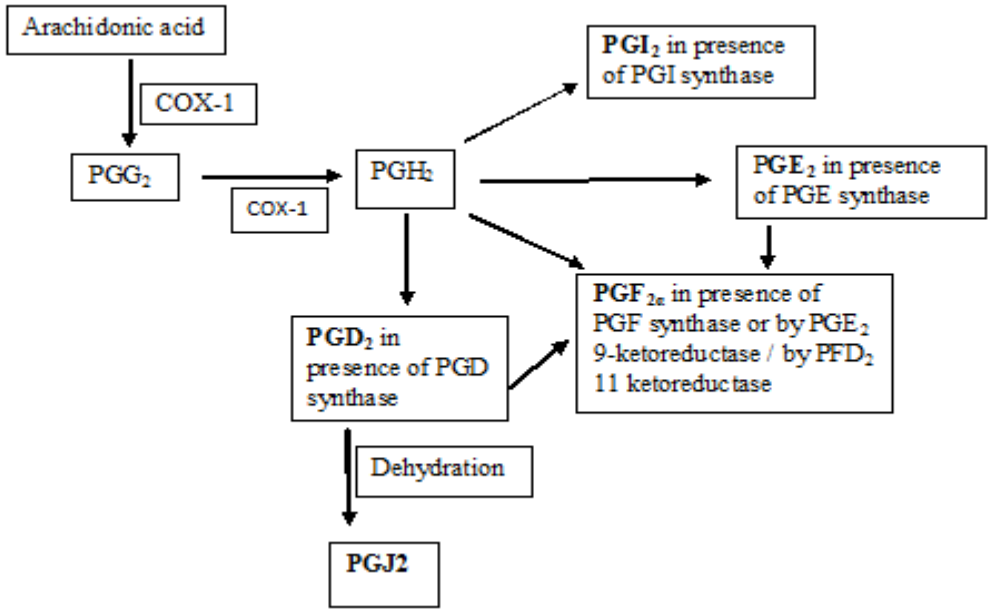

Fig No. 1: Schematic representation of prostaglandins biosynthetic pathway. Arachidonic acid is converted to PGG_2 in presence of COX-1 and this PGG_2 is converted in PGH_2 by the same enzyme and PGH_2 is then catalyzed for formation of different prostaglandins. $PGF_{2\alpha}$ is produced in three ways. Either in presence of PGF synthase by PGH_2 or by PGE_2 9-ketoreductase from PGE_2/ by PFD_2 11 ketoreductase from PGD_2. Dehydration of PGD_2 produces PGJ_2.

Different types of prostaglandins are produced by catalyzing activity of different enzymes. In synthesis of prostaglandins cyclooxygenase (COX) is rate limiting enzyme in first two steps in which from arachidonic acid PGG_2 and from this metabolite PGH_2 is formed. There are two forms of COX enzyme, COX-1 and COX-2 their molecular weights are 71 and 73 kDa respectively. Their expression and distribution in different body organs differs. For example COX-1 is expressed in high amount and on the other hand COX-2 is expressed in lower amount in kidney and their production in kidney is induced by inflammation and renal injury.[3]

Prostaglandins are different from other biological molecules as they have no nitrogen atom when they are studied chemically and they are C_{20} molecules having a five membered ring which is present between C_8 and C_{12}. F type of prostaglandins differ from E type of prostaglandins. In F type there is hydroxyl in place of ketone on C_9 position (E types of prostaglandins have ketone group on C_9 position). Due to this difference in structure their properties are different from each other.[4] Chemical structures of different prostaglandins are given below in figure No. 2.

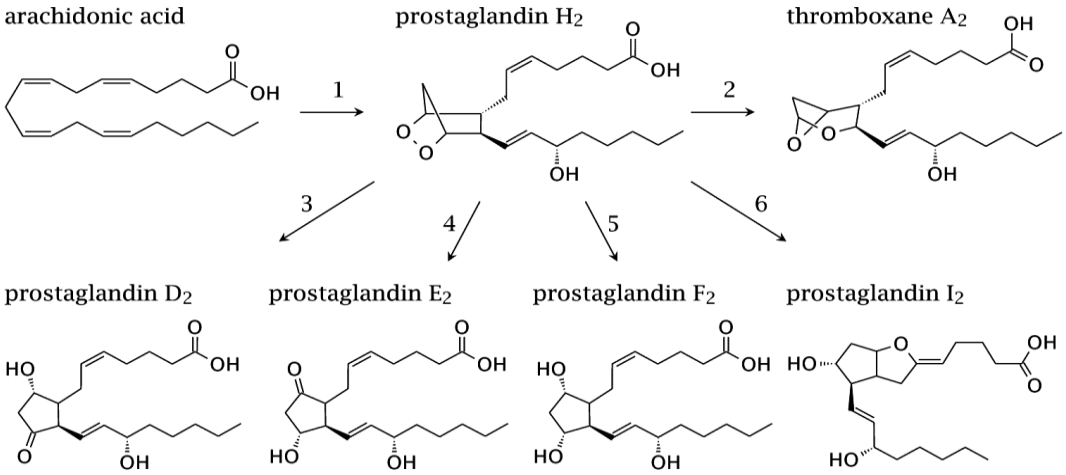

Fig No. 2: Chemical structure of different prostaglandins.

Aspirin and non-steroidal anti-inflammatory drugs (NAIDs) such as indomethacin are potent inhibitors of COX enzymes pathway responsible for PGs synthesis so in turn they inhibit production of prostaglandins from arachidonic acid. Vasodilation and vascular leakage, (mainly function of PGE_2) Mast cell maturation, allergic responses and eosinophil recruitment, (by PGD_2) contraction of vascular and respiratory smooth muscles,

(by PGF_2) inhibition of platelets aggregation, (PGI_2) regulation of inflammatory and immune responses, cell growth, intraocular pressure, calcium movement sensitivity of spinal neurons to pain, body temperature in response to fever and parturition are some functions by prostaglandins.[5] Distribution of prostaglandins in different body organs with respect to their functions is given below in table No. 1.

Table No. 1: Distribution of prostaglandins in different organs.

Prostaglandins	Functions
PGE_2	Brain, Kidney, Vascular smooth muscle cells, Platelets.
PGD_2	Mat cells, Brain and Airways.
PGF_2	Uterus, Eyes, Vascular smooth muscles cells and Airways.
T_XA_2	Platelets, Macrophages, Kidney, Muscle cells.
PGI_2	Endothelium, Brain, Kidney

Different members of prostaglandins family

Prostaglandin D_2 is mast cell derived prostanoids, it is produced in these cells in Nano gram quantities as a result of IgE mediated activation.[6] Other than mast cells it is also produced in eosinophils.[7] Hematopoietic PGD_2 (H- PGSD) and lipocalin PGD_2 (L- PGDS) synthetase are the two enzymes that produce PGD_2. First enzyme produces PGD_2 in mast cells and second one generates PGD_2 in hematopoietic cells. L- PGDS is found in oligodendrocyte and choroid plexus which are organs in male genital tract, humans and monkeys hearts and in leptomeninges. Gene expression of this enzyme in the central nervous system is controlled by different hormones like: Estrogen, Glucocorticoid and Thyroid. And expression in heart is controlled by Estrogen. H-PGDS is expressed in adipose tissues, lungs, placenta and fetal liver at very high levels and in low levels it is expressed in bone marrow, lymph nodes, appendix and heart. Other cells in which H-PGDS is expressed are, $CD8^+$ Tc2 cells, megakaryocytes, dendritic cells (DCs), $CD4^+$ Th2 lymphocytes and histiocytes. PGD_2 is further metabolized to form PGF2α and J series of prostanoids which include PGJ_2, Δ^{12}-PGJ_2, and 15d-PGJ_2.[6] Inflammation, role in asthma and in male pattern baldness, other allergic disorders, inhibition of hair growth and causing bald scalp in males are different roles of PGD_2.

Three distinct enzymes, cytosolic PGE synthase (cPGES), microsomal PGE synthase-1and 2 (mPGES-1), (mPGES-2) perform metabolism of PGE_2 from PGH_2.[6] Microsomal PGE synthase-1 is glutathione dependent, trimeric in structure, membrane associated and localized to the perinuclear area. If a cell contains both mPGES-1 and COX-2 then production of PGE_2 is increased. It means that when COX-2 is active mPGE-2 preferentially couples with COX-2 and generates PGE_2. It signals through four different receptors called ER receptors. Each receptor has different G-protein coupling and then it is activated. These all types of receptors are present in lungs and other tissues in which allergic reactions occur.[6] This PGs contribute to homeostasis in the Gastro-intestinal tract, kidney, immune system and vasculature in body.

$PGF_{2\alpha}$ is produced by an enzyme, PGF synthetase. This enzyme perform two roles. First is in the presence of NADPH to produce $PGF_{2\alpha}$ from PGH_2 in presence of PGH_2 9, 11-endoperoxide reductase. And second function is to convert $PGF_{2\alpha}$ from PGD_2 in presence of PGD_2 11-ketoreductase. Binding sites for PGH_2 and PGD_2 are different from each other.[8] There is solitary receptor for $PGF_{2\alpha}$ called FP receptor. Renal physiology, reproduction, and modulation of intraocular pressure are the main functions of prostaglandins $F_{2\alpha}$.

Prostaglandins I_2 is mainly expressed in lungs, heart, kidney, ovary and smooth muscles in high levels. And in moderate levels this is expressed in brain, pancreas, and prostate and in low levels in spleen, placenta and leukocytes. It is converted from PGH_2 by an enzyme PGI synthase (PGIs). IP is receptor by which PGI_2 signaling occurs. Binding of this PG to receptor activates adenylate cyclase through stimulatory G- protein and cAMP concentration increases. This increase inhibits platelets aggregation. And disperses platelets aggregates in circulation.[9]

Thromboxane A_2 is a platelets aggregating agent formed by platelets in arachidonic acid metabolism. Conversion of PGH_2 to form T_XA_2 is catalyzed by an enzyme Thromboxane synthase (TXAS) which is an endoplasmic reticulum membrane protein. This enzyme is expressed in high amount in blood cells, including megakaryocytes and monocytes and also in lung, liver and kidney. In kidney, placenta and thymus there is a lower but significant concentration of this prostaglandins is present. This thromboxane A_2 is produced by neutrophils, monocytes, macrophages, platelets and lung parenchyma.[10] From hydrolysis of T_XA_2 thromboxane B_2 is formed, further metabolism of this T_XB_2 forms 2,3-dinor-thromboxane B_2 and 11-dehydro-thromboxane B_2 that are principle urinary metabolites. TP is receptor for T_XA2. TPα and TPβ are two isoforms of this receptor. Both isoforms of this receptors are coupled with Gq protein and as a result of binding phospholipase C is activated, this activation results in increase in level of cellular calcium and protein kinase C is activated due to increase in level of cellular calcium.[11]

Prostaglandins in kidneys

Under normal situations, renal hemodynamics and renin release in kidney is controlled by prostaglandins together with control of salt and water balance. But under pathophysiological conditions in kidney, e. g; pain, inflammation and cancer prostaglandins production is also stimulated at high level. Prostaglandins play major role in kidney that is control of renal erythropoeitin production in kidney by: influencing renal blood flow and glomerular filtration, releasing the renin and by performing urinary concentrating mechanism. NaCI, phosphate and hydrogen ions are also handled by prostaglandins in kidneys. PGE_2 is major metabolite of kidney. All renal cells of kidney produce this renal metabolite due to presence of enzyme PGE_2 synthetase. PGE_2 modulates effect of vasopressin in water reabsorption in renal collecting ducts. It causes cAMP synthesis inhibition and increases level of cytosolic Ca^{+2}.[12]

If vasoconstrictor system is activated importance of renal prostaglandins for the control of blood flow and glomerular filtration can be considered.[13] PGE_2 and PGI_2 are vasodilators in the kidney. If PGE_2 and PGI_2 are administered in kidney they cause vasoconstriction but this is due to release of renin and formation of angiotensin II.[14] If formation of angiotensin II is blocked then both types of prostaglandins act as vasodilators. Vasodilators counteract effect of vasoconstrictor. On the other hand thromboxane is vasoconstrictor. Renal vasoconstrictors perform negative feedback in which if thromboxane concentration increases it causes production of vasodilators that are PGI_2 and PGE_2.[15] If prostaglandins are inhibited it will decrease blood flow in kidney. And if concentration of PGs is high it will increase blood flow.

Glomerular filtration rate is increased by prostaglandins because afferent and efferent arteriolar resistance is changed by influencing the renin-angiotensin system. As a result glomerular filtration is affected by changes in mesangial contraction. Increases in the synthesis of vasodilatory PGs results in mesangial cell contraction and as consequence size of glomerulus is decreased. So PGs control size and surface area of glomerulus and in turn glomerular filtration rate. Surface area and size of glomerulus if increased then surface area for absorption also increases. Renin, angiotensin II and different PGs play a role in controlling renal blood flow and glomerular filtration rate.[16] Fig No. 3 explains role of prostaglandins on glomerular filtration rate.

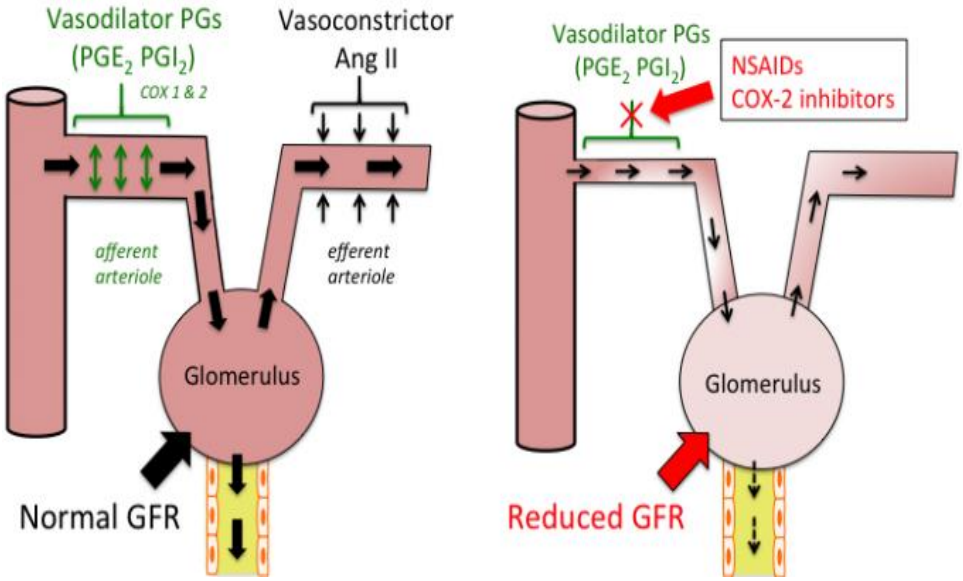

Fig No. 3: effect of prostaglandins on glomerular filtration rate. Prostaglandins increase this rate by vasodilation.

PGI_2 and PGE_2 are effective in releasing renin and increasing plasma renin concentration. By renal cortical preparations renin release is increased. Renin release is also increased by arachidonic acid from which PGE_2 and PGI_2 are formed. Antidiuretic hormone (ADH) effect to dilute urine it is found that both PGE_1 and PGE_2 are antagonist to ADH hormone. Prostaglandins increase renal medullary blood flow so complete washout of solutes occur and an osmotic gradient that is required for complete reabsorption of water is also maintained. So urine becomes concentrated as water is reabsorbed. Secondly prostaglandins decrease sodium transport and urea accumulation in the medulla so medullary solute composition is changed that effects absorption rate.[17] As in many functions of kidney, prostaglandins play major role, so abnormal prostaglandins obviously will lead to renal disorders. Congestive heart failure, Systemic lupus erythematosus, chronic renal failure, liver cirrhosis, diabetes mellitus, volume depletion, diuretics, or old age these are the conditions in which prostaglandins must be synthesized in normal way otherwise it leads to serious health issues in kidneys.

Role of prostaglandins on regulation of platelets activity

Most important prostaglandins for regulation of platelets activity is T_XA_2. But others alike PGE_2, PGI_2, PGD_2 and TxA_2 are also important to some extent. These prostaglandins are produced by endothelial cells, platelets, leukocytes, vascular smooth muscles cells, macrophages and mast cells. T_XA_2 is although most unstable prostaglandins, having half-life that is less than a minute but still it is most predominant PGs that are produced in activated platelets. It acts by binding to TPα receptors and perform various functions including: changes in platelet shape, release of contents from platelets granules and production of irreversible platelets aggregation. Other than these Thromboxane A_2 acts as vasoconstrictor and play a role in inflammation and angiogenesis.[18] T_XA_2 acts as vasoconstrictor in both venous and arterial systems so, this can be used to avoid vasodilation medically.[19]

Angiogenesis and differentiation plus proliferation of endothelial cells is important role of thromboxane A_2. A mimic of T_XA_2 binds with TP_β receptors and causes VEGF-mediated endothelial cell migration and angiogenesis.[20] An agonist of thromboxane A_2 is U46, 619 induces IL-1 beta and which causes angiogenesis. Other agonist of thromboxane A_2 are PGG_2 and PGH_2. If there are disorders in thromboxane activity or deficiency in its release it causes bleeding disorders.[21] Cyclic AMP plays a role in platelets homeostasis because it is an important factor in platelets regulatory pathway. It is found that prostaglandins either stimulate or inhibit cAMP release and in return there is an effect on platelets activity.[22] If level of cAMP is increased it will cause inhibition of platelets aggregation e. g; by PGI_2 and if cAMP level decreases it will cause an increase in platelets aggregation by increasing calcium mobility across membranes.[23] Thromboxane A2 produced by platelets and its effect on vasodilation and vasoconstriction is explained by fig No. 4.

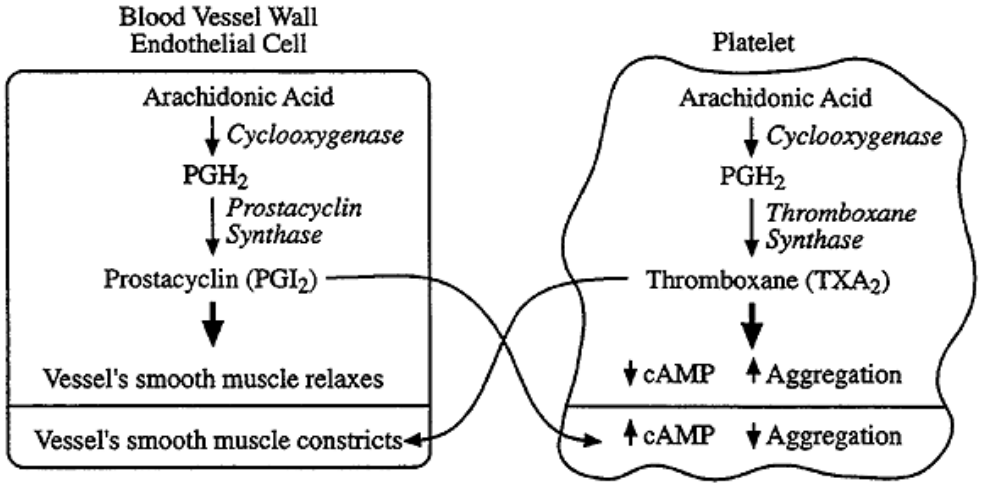

Fig No. 4: Thromboxane A2 produced by platelets controls constriction of smooth muscles in blood vessels and PGI2 produced by endothelial cells controls platelets aggregation.

Gastrointestinal tract and prostaglandins

PGE_1, PGE_2 and $PGF_{2\alpha}$ are prostaglandins that mainly effect gastrointestinal tract and PGA_1 and $PGF_{1\alpha}$ effect GIT but to very lesser extent. Smooth muscles of gastrointestinal tract show sensitivity to prostaglandins. Effect of prostaglandins on smooth muscles depends upon several factors such as dose, species of prostaglandins and type of muscles on which it is acting. Longitudinal muscles of small and large intestine in both humans and animals are contracted by E type of prostaglandins and $PGF_{2\alpha}$. PGE_1 and PGE_2 causes relaxation of circular muscles and on the other hand $PGF_{2\alpha}$ causes contraction of circular muscles.[24]

Circular Gastric muscles undergo relaxation by PGE_2 and both circular and longitudinal muscles of stomach undergo contraction by $PGF_{2\alpha}$. As human gastric muscles are insensitive to A type of prostaglandins but some longitudinal muscles of animals contract after exposure to prostaglandins A.[25] There are different mechanisms that mediate contractions or relaxations by prostaglandins. PGs effect receptors in or on the muscles and cause relaxation. But contractions are due to effect on intrinsic nerves or at non-neural sites.[26] Effect on smooth muscles is oxygen dependent and changes in concentration of intracellular bound Ca^{+2}, cell permeability to calcium ions or changes in calcium due to change in cyclic AMP levels is responsible for effect on muscles.[27] It is found that if type A and E (not type F) of prostaglandins and their precursors are given orally or parenterally to innervated and denervated stomachs of both conscious and anaesthetized animals these PGs will reduce volume of stomach acid and pepsin. This inhibition in level of stomach acid and pepsin is non-selective and basal, as well as submaximal and maximal acid secretion are inhibited by this. Dose of prostaglandins determines degree of inhibition. Nausea and vomiting and reflux of bile into the stomach from the

duodenum are functions in which prostaglandins also play a secondary role.[28] In fasting animals prostaglandins are vasoactive agents and cause dilation of gastric blood vessels.[29] Gastric blood flow is reduced when acid production is inhibited in stomach by different A and E types of prostaglandins.[30]

Intestinal absorptive function is effected by PGs. For therapeutic abortion, if women are given high doses of oral or intravenous E and F type of prostaglandins it will cause diarrhea in women.[31] But if lower doses of PGE_1, $PGF_{2\alpha}$ and PGE_2 are given for labor induction in women at the time of birth it will not result in diarrhea.[32, 33] It is found that prostaglandins exert their effect on intestinal cells by changing water and electrolytes transport across cells of mucous membrane of gut. That causes contents of intestine to come out from cells and cause diarrhea. PGE_1, $PGF_{2\alpha}$ and PGE_2 inhibit absorption of sodium ions and stimulate release of chloride ion in *vitro* studies. PGE_2 reduces net absorption of water and electrolyte in gut cells. These imbalance in water and ions conc. is responsible for diarrhea.[34,35]

Prostaglandins and bones

No. and activity of osteoclasts is increased due to prostaglandins that results in bone resorption. PGE_2 acts as agonist in bone resorption and PGI_2 acts as stimulator in bone resorption. Development of tartrate-resistant acid phosphatase positive ($TRAP^+$) giant cells is a major role by prostaglandins these cells in marrow cell culture are with osteoclastic features. If prostaglandins synthesis is inhibited it will block the ability of stimulators to increase ($TRAP^+$) giant cells formation. Function of osteoclast is also suppressed.[36,37] PGs synthesis in bones is stimulated by stimulators of bone resorption, these stimulators increase COX-2 in bones although bone resorption is independent of PGs.[38] Some analogs of cAMP can mimic stimulation and inhibition of bone resorption.

Osteoblasts' replication and then their differentiation is stimulated by PGs and it results in bone formation.[39] EP_2 receptors are expressed in osteoblast precursor cells and these receptors mediate formation of bones.[40] When osteoblasts are fully differentiated due to PGs now these PGs will inhibit collagen synthesis. This inhibitory effect is due to F type of prostaglandins.[41,42] IL-1 is effected due to prostaglandins and then gene for collagen synthesis is inhibited.[43]

Prostaglandins in modulation of T-cells

cAMP is an inhibitor of various functions of T-cells such as cytokines production and antigen induced proliferation. PGE_2 and some other ligands bind with GPCR receptors and initiate cAMP protein kinase A signaling pathway in which AC is activated and cAMP is produced from ATP.[44,45] One remarkable property of prostaglandins (mainly E type of prostaglandins) is ability to activate adenylate cyclase in vitro systems.[46] This ability of prostaglandins makes them able to inhibit the secretory activity of diverse types of cells. Due to activation of adenylate cyclase elevation in levels of cyclic AMP occurs that suppress secretion from different types of cells. Prostaglandins play modulatory roles in type I and type IV allergic responses.

In type I hypersensitivity anaphylactic mediators' secretions are inhibited by E_1 and E_2 prostaglandins. This inhibition causes changes in cyclic AMP level. Prostaglandins are inhibitors of histamine from leukocytes then stimulates cyclic AMP.[47] Human alveolar macrophages and mast cells secrete adequate amount of E type of prostaglandins after antigenic stimulation. PGE_2 are produced by eosinophil and neutrophils but in lesser amount.[48] Prostaglandins are formed by eosinophils after antigenic stimulation and their amount is enough to suppress secretion of mediators from human basophils. Indomethacin is one of NSAIDs and enhances allergic mediator secretion because this is inhibitor of cyclooxygenase. Absence of PGE_2 will enhance secretion of histamine and other mediators from storage granules of mast cells. Anaphylaxis in lungs involves SRS-A secretion that bin turn produces PGs. That will perform its anti-allergic reaction. Aspirin-sensitive asthma (ASA) is a condition of ling disorder in which ingestion or inhalation of aspirin causes bronchospasm. This bronchospasm is also induced by NSAIDs because they inhibit synthesis of prostaglandins.[49] Prostaglandins inhibit mediator secretion while aspirin causes inhibition of prostaglandins so bronchospasm is caused.

In type IV hypersensitivity thymus dependent lymphocytes become activated. These lymphocytes when activated they secrete a large amount of glycoproteins called lymphokines. Low concentrations of E_1 and E_2 type of prostaglandins inhibit lymphocyte activation and lymphokines release. PGE2 production can be stimulated by preformed lymphokines in blood without activation of lymphocytes. After antigenic stimulation lymohokines are released from lymphocytes and they activate macrophages to generate PGE2 as inhibitors of lymphocytes. This negative feedback controls type IV hypersensitivity.[50]

Positive and negative effects of prostaglandins in Alzheimer's disease (AD)

A disease in which tau and Aβ accumulation in central nervous system results in microglia and astrocytes activation as a result a pro-inflammatory pathway occurs in which cytokines, reactive oxygen and nitrogen species and PGs are released these are neurotoxic substances and cause degeneration of neurons.[51] PGD_2 is most frequent prostaglandins of brain and controls nociception, temperature and sleep.[52] Its receptors have an opposite effect on cyclic AMP production. PGD_2 is neuroprotective when cyclic AMP level is low and in dispersed and organotypic neurons, neurotoxicity is generated by DP_2 receptors. In AD patients in microglia and astrocytes H-PGDS and DP1 are overexpressed.[53]

15d-PGJ_2 is an agonist of PRAR-γ this substance acts on activated microglia and cause inhibition of generation of pro-inflammatory interleukins 12, 23 and 1β. Aβ immunotherapy is limited by these cytokines. This J type of prostaglandins inhibit molecules that cause neuro-inflammatory disease.[54]

Prostaglandins and Cyclooxygenase in Psychiatric Disorders

COX is an important enzyme in nervous system as it converts Arachidonic acid into prostaglandins. Synaptic plasticity and refining of mature neuronal connections are the important functions of COX-2 pathway in CNS. Psychiatric disorders occur if COX-2 level is altered.[55] Imbalance of immune system can be regulated by COX inhibitors which influence immune system and have neuro-protectant effect. Thus they have potency against schizophrenia.[56] From arachidonic acid, eicosanoids are formed by two pathways cyclooxygenase and lipoxygenases, numerous homeostatic and pathophysiological processes are regulated by these lipid mediators.[57] Neurodegenerative and neuropsychiatric conditions are also included in these pathophysiological processes. For example: schizophrenia, Alzheimer's disease (AD), autism spectrum disorders (ASD) and refractory major depression.[58] Induction of COX enzyme and resulting PGS synthesis is mainly responsible for neurodegeneration.[59] Wnt signaling mainly is related to E type of prostaglandins among all types. This signaling mediates migration of cells, cell polarity, neural patterning and organogenesis during embryonic development.[60]

Cyclooxygenase and Prostaglandins in somatic cell populations of testis

PGs also have important reproductive roles in animals. When mice were studied it was seen that if female mice is deficient in COX-1 it will be infertile and if COX-2 is deficient it will lead to defect in parturition, but if male mice is deficient of COX-1 and 2 these effect were not observed.[61] But this not actually happens. PGs have a major role in male reproductive system too. It was observed that paracetamol and some nonsteroidal anti-inflammatory drugs (NSAIDs) for example aspirin effect testis of human fetus and cause endocrine disturbance. Because they interfere with fetus testicular decent. PGD_2 causes male germ cells differentiation. For sertoli cells differentiation PGD_2 synthetase is necessary because it participates in SOX_9 nuclear translocation.[62]

CONCLUSION

Prostaglandins are the centers of great interest as these are mediators of numerous pathological actions. Various functions in kidneys, bones, T-cells and platelets are regulated by these molecules. From review it is evident that they mediate a no of processes in different body tissues and organs. Analysis of role of prostaglandins will help us out to get insight to mechanism of number of diseases and their treatment or prevention can be understood in better way.

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REFERENCES

1. Capra V, Back M, Angiolillo DJ, Cattaneo M, Sakariassen KS. Impact of vascular thromboxane prostanoid receptor activation on hemostasis, thrombosis, oxidative stress, and inflammation. J Thromb Haemost, 2015; 12: 126-137.
2. Breyer RM, Bagdassarian CK, Myers SA, Breyer MD. Prostanoid receptors: subtypes and signaling. Annu Rev Pharmacol Toxicol, 2001; 41: 661-690.
3. Breyer MD, Harris RC. Cyclooxygenase 2 and the kidney. Curr Opin Nephrol Hypertens, 2001; 10: 89-98.
4. Bergstrom S, Carlson LA, Weeks JR. The prostaglandins: a family of biologically active lipids. Pharmacol Rev, 1968; 20: 1-48.
5. Claar D, Hartert TV, Peebles RSJ. The role of prostaglandins in allergic lung inflammation and asthma. Expert Rev Respir Med, 2015; 9: 55-72.
6. Smith WL, Urade Y, Jakobsson PJ. Enzymes of the cyclooxygenase pathways of prostanoid biosynthesis. Chem Rev, 2011; 111(10): 5821-5865.
7. Luna-Gomes T, Magalhaes KG, Mesquita-Santos FP. Eosinophils as a novel cell source of prostaglandin D2: autocrine role in allergic inflammation. J Immunol, 2011; 187(12): 6518-6526.
8. Komoto J, Yamada T, Watanabe K. 2006. Prostaglandin F2-alpha formation from prostaglandin H2 by prostaglandin F synthase (PGFS): crystal structure of PGFS containing bimatoprost. Biochemistry, 2006; 45(7): 1987-1996.
9. Breyer RM, Kennedy CR, Zhang Y. Structure-function analysis of eicosanoid receptors. Physiologic and therapeutic implications. Ann N Y Acad Sci, 2000; 905: 221-231.
10. Miyata A, Yokoyama C, Ihara H. 1994. Characterization of the human gene (TBXAS1) encoding thromboxane synthase. Eur J Biochem, 1994; 224(2): 273-279.
11. Huang JS, Ramamurthy SK, Lin X. Cell signaling through thromboxane A2 receptors. Cell Signal, 2004; 16(5): 521-533.
12. Sonnenburg WK, Smith WL. Regulation of cyclic AMP metabolism in rabbit cortical collecting tubule cells by prostaglandins. J Biol Chem, 1998; 263: 6155-6160.
13. Oliver JA, Sciacca RB, Pinto J, Cannon PI. Participation of the prostaglandins in the control of renal blood flow during acute reduction of cardiac output in the dog. J Clin Invest, 1981; 67: 229.
14. Schor N, Ichikawa I, Brenner BM. 1981. Mechanisms of action of various hormones and

vasoactive substances on glomerular ultrafiltration in the rat. Kidney Mt, 1981; 20: 442.
15. Scharsclimidt LA, Lianos E, Dunn M. Arachidonate metabolites and the control of glomerular function. Fed Proc, 1983; 42: 3058-3063.
16. Ganguli M, Tobian L, Azar S, Odonnell M. Evidence that prostaglandin synthesis inhibitors increase the concentration of sodium and chloride in rat renal medulla. Circ Res, 1977; 40: 1135-1139.
17. Haylor J, Lote CJ. The influence of prostaglandin E2 and indomethacin on the renal cortico-medullary solute gradient in the rat. J Pharmaco, 1983; 35: 299-305.
18. Nakahata N. Thromboxane A2: physiology/pathophysiology, cellular signal transduction and pharmacology. Pharmacol Ther, 2008; 118(1): 18-35.
19. Yamada T. Thromboxane A2 regulates vascular tone via its inhibitory effect on the expression of inducible nitric oxide synthase. Circulation, 2003; 108(19): 2381-2386.
20. Ashton AW, Ware JA. 2004. Thromboxane A2 receptor signaling inhibits vascular endothelial growth factor-induced endothelial cell differentiation and migration. Circ Res, 2004; 95(4): 372-9.
21. Fuse I, Higuchi W, Aizawa Y. Pathogenesis of a bleeding disorder characterized by platelet unresponsiveness to thromboxane A2. Semin Thromb Hemost, 2000; 26(1): 43-45.
22. Ashby B. Novel mechanism of heterologous desensitization of adenylate cyclase: prostaglandins bind with different affinities to both stimulatory and inhibitory receptors on platelets. Mol Pharmacol, 1990; 38(1): 46-53.
23. Haslam RJ, Dickinson NT, Jang EK. Cyclic nucleotides and phosphodiesterases in platelets. Thromb Haemost, 1990; 82(2): 412-423.
24. Bergstrom S, Elliason R, von-Euler US, Sjovall J. Some biological effects of two crystalline prostaglandin factors. Acta physiol scand, 1959; 45: 133-144.
25. Horton EW, Jones RL. Prostaglandins A and 19-hydroxy Al: their actions on smooth muscle and their inactivation on passage through the pulmonary and hepatic portal vascular beds. Brit J Pharmacol, 1969; 37: 705-722.
26. Bennett A, Eley KG, Scholes GB. Effects of prostaglandins E, and E2 on human, guinea-pig and rat isolated small intestine. Brit J Pharmacol, 1968; 34: 630-638.
27. Akanuma M. Relationship between stimulating action of prostaglandin E and calcium on the gastrointestinal smooth muscle from the guinea pig. Sapporo med J, 1970; 38: 53-59.
28. Nezamis JE, Robert A, Stowe DF. Inhibition by prostaglandin El of gastric secretion in the dog. J Physiol, 1971; 218: 369-383.
29. Nakano J, Prancan AV. Effect of prostaglandins El and A5 on the gastric circulation in dogs. Proc Soc exp Biol 1972; 139: 1151-1154.
30. Main IHM, Whittle BJR. The effect of E and A prostaglandins on gastric mucosal blood flow and acid secretion in rats. Br J Pharmacol, 1974; 49: 428-436.
31. Karim SMM. Effects of oral administration of prostaglandins E and F201 on the human uterus. J Obstet Gynaec Brit Cwlth, 1971; 78: 289-293.
32. Embrey MP. Induction of labour with prostaglandins El and E. Brit med J, 1970; 2: 256-258.
33. Karim SMM, Sharma SD. Therapeutic abortion and induction of labour by the intravaginal administration of prostaglandins E, F and A. J Obstet Gynaec Brit Cwlth, 1971; 78: 294-300.
34. Greenough WBIII, Pierce NF, Al-Awqati Q, Carpenter CCJ. Stimulation of gut electrolyte secretion by prostaglandins, theophylline and cholera exotoxin. J clin Invest, 1969; 48: 32-33.
35. AI-Awqati Q, Field M, Pierce NF, Greenough WBIII. 1970. Effect of prostaglandin E1 on electrolyte transport in rabbit ileal mucosa. J clin Invest, 1970; 49: 2a.
36. Hurley MM, Lee SK, Raisz LG, Bernecker P, Lorenzo J. Basic fibroblast growth factor induces osteoclast formation in murine bone marrow cultures. Bone, 1998; 22: 309-316.
37. Lader CS, Flanagan AM. Prostaglandin E2, interleukin-1 and tumor necrosis factor-increase human osteoclast formation and bone resorption in vitro. Endocrinol, 1998; 139: 3157-3164.
38. Min YK, Rao Y, Okada Y, Raisz LG, Pilbeam CC. Regulation of prostaglandin G/H synthase-2 expression by interleukin-1 in human osteoblast-like cells. J Bone Miner Res, 1998; 13: 1066-1075.
39. Woodiel FN, Fall PM, Raisz LG. Anabolic effects of prostaglandins in cultured fetal rat calvariae: Structure-activity relations and signal transduction pathway. J Bone Miner Res, 1996; 11: 1249-1255.
40. Nemoto K, Pilbeam CC, Bilak SR, Raisz LG. Molecular cloning and expression of a rat prostaglandin E2 receptor of the EP2 subtype. Prostaglandins, 1997; 54: 713-725.
41. Fall PM, Breault DT, Raisz LG. Inhibition of collagen synthesis by prostaglandins in the immortalized rat osteoblastic clonal cell line, Py1a: Structure activity relations and signal transduction mechanisms. J Bone Miner Res, 1994; 9: 1935-1943.
42. Nemoto K, Bernecker PM, Pilbeam CC, Raisz LG. Expression and regulation of prostaglandin F receptor mRNA in rodent osteoblastic cells. Prostaglandins, 1995; 59: 349-58.
43. Harrison JR, Kleinert LM, Kelly PL, Krebsbach PH, Woody C, Clark S, Rowe DW, Lichtler AC, Kream BE. Interleukin-1 represses COL1A1 promoter activity in calvarial bones of transgenic COLCAT mice in vitro and in vivo. J Bone Miner Res, 1998; 13: 1076-1083.

44. Kammer GM. The adenylate cyclase-cAMP-protein kinase A pathway and regulation of the immune response. Immunol Today, 1988; 9: 222-229.
45. Hanoune J, Defer N. Regulation and role of adenylyl cyclase isoforms. Annu Rev Pharmacol Toxicol, 2001; 41: 145-174.
46. Bergstrom S. 1967. Prostaglandins: members of a new hormonal system. These physiologically very potent compounds of ubiquitous occurrence are formed from essential fatty acids. *Science*, 1967; 157: 382-391.
47. Tauber AI, Kaliner M, Stechschulte DJ, Austen KF. Immunologic release of histamine and slow reacting substance of Anaphylaxis from human lung. V. Effects of prostaglandins on release of histamine. J Immunol, 1973; 111(1): 27-32.
48. Morley J. Prostaglandins and lymphokines in arthritis. Prostaglandins, 1974; 8(4): 315-326.
49. Hubscher T. Role of the eosinophil in the allergic reactions. II. Release of prostaglandins from human eosinophilic leukocytes. J Immunol, 1975; 114(4): 1389-1393.
50. Bray MA, Gordon D, Morley J. Proceedings: Role of prostaglandins in reactions of cellular immunity. Br J Pharmacol, 1974; 52(3): 453-453.
51. Griffin WS. Inflammation and neurodegenerative diseases. Am J Clin Nutr, 2006; 83: 470-474.
52. Mizoguchi A, Eguchi N, Kimura K. Dominant localization of prostaglandin D receptors on arachnoid trabecular cells in mouse basal forebrain and their involvement in the regulation of non-rapid eye movement sleep. Proc Natl Acad Sci, 2001; 98: 11674-11679.
53. Hertting G, Seregi A. Formation and function of eicosanoids in the central nervous system. Ann N Y Acad Sci, 1989; 559: 84-99.
54. Xu J, Barger SW, Drew PD. The PPAR-gamma agonist 15-deoxy- $\Delta^{12, 14}$-prostaglandin J_2 attenuates microglial production of IL-12 family cytokines: Potential relevance to Alzheimer's disease. PPAR Res, 2008; 349185.
55. Tamiji J, Crawford DA. The neurobiology of lipid metabolism in autism spectrum disorders. Neurosignals, 2010; 18: 98-112.
56. Riedel M, Strassnig M, Schwarz MJ, Muller N. COX-2 inhibitorsas adjunctive therapy in schizophrenia: rationale for use and evidence to date. CNS Drugs, 2005; 19(10): 805-819.
57. Yin H, Zhou Y, Zhu M, Hou S, Li Z, Zhong H, Lu J, Meng T, Wang J, Xia L, Xu Y, Wu Y. Role of mitochondria in programmed cell death mediated by arachidonic acid-derived eicosanoids. Mitochondrion, 2013; 13(3): 209-224.
58. Huber C, Marschallinger J, Tempfer H, Furtner T, Couillard-Despres S, Bauer HC, Rivera FJ, Aigner L. Inhibition of leukotriene receptors boosts neural progenitor proliferation. Cell Physiol Biochem, 2011; 28(5): 793-804.
59. Mizuno M, Sotoyama H, Narita E, Kawamura H, Namba H, Zheng Y, Eda T, Nawa HA. Cyclooxygenase-2 inhibitor ameliorates behavioral impairments induced by striatal administration of epidermal growth factor. J Neurosci, 2007; 27(38): 10116-10127.
60. Wong CT, Ahmad E, Li H, Crawford DA. 2014. Prostaglandin E_2 alters Wnt-dependent migration and proliferation in neuroectodermal stem cells: implications for autism spectrum disorders. Cell Commun Signal, 2014; 12: 19.
61. Langenbach R, Loftin CD, Lee C, Tiano H. Cyclooxygenase-deficient mice. A summary of their characteristics and susceptibilities to inflammation and carcinogenesis. Ann N Y Acad Sci, 1999; 889: 52-61.
62. Rossitto M, Ujjan S, Poulat F, Boizet-Bonhoure B. Multiples roles of the prostaglandin D_2 signaling pathway in reproduction. Reproduction, 2015; 149: 49-58.