IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Pharmacological Review On Prostaglandin

Name: Akash Rajiv Farkade [1]. Ms: Vaishnavi Jadhav[2]
Dr: Gajanan Sanap[3]
Department Of Pharmacy[1]
Assistant Professor, Pharmaceutical Chemistry Pharmacy[2]
Principal, Department Of Pharmacy[3]

Late Bhagirathi Yashwantrao Pathrikar College Of Pharmacy.Pathri Tq.Phulambri District.Aurangabad, Maharashtra 431111

Objectives of Prostaglandin:

Abstract

Three classes of compounds inhibit prostaglandin synthetase. The first group consists of the substrate analogues. The specificity of these analogues is unknown but many possess good inhibitory potency which makes them useful tools to demonstrate the involvement of the synthetase enzyme. However, although they are active in some organised tissue preparations, their use in vivo has not been widespread. The absorption, excretion and distribution of these fatty acids is not yet fully understood and this tends to detract from their usefulness in whole animal work. Apart from the substrate analogues a number of other fatty acids also inhibit the synthetase but probably in a non-specific manner and only in high concentrations.

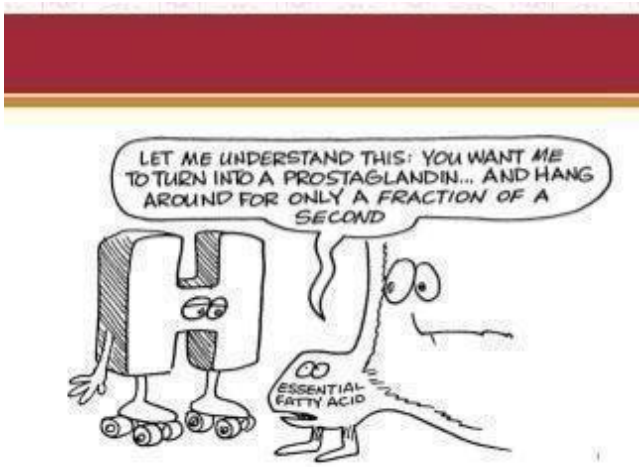
The second class of inhibitors consists of the aspirin-like drugs. Although these may not be as specific as the substrate analogues, they have several advantages; they are readily available, easily administered and in many species abolish prostaglandin synthesis almost completely in therapeutic doses. In addition, a considerable amount is known concerning their absorption, distribution and excretion. The final group of inhibitors which inhibit the synthetase includes such diverse agents as metal ions, anti-oxidants and nucleotides. The concentrations necessary to achieve inhibition are often high and no degree of specificity can be claimed. Thus, these agents are not likely to be of value for in vivo work, although in vitro studies with different cofactors and ions may contribute to our understanding of how the synthetase system is regulated.

Keywords

Prostaglandin,ergot,nucleotide

1.1Describe the pharmacology of prostaglandin and its clinical implications.

1.2List the major clinical implications and toxicity of ergot alkaloids on the majororgan system.



1.Literature Survey

1. Emanuela Ricciotti, Garret A FitzGerald (2011)

Prostaglandins are lipid autacoids derived from arachidonic acid. They both sustain homeostatic functions and mediate pathogenic mechanisms, including the inflammatory response. They are generated from arachidonate by the action of cyclooxygenase isoenzymes, and their biosynthesis is blocked by non steroidal anti inflammatory drugs, including those selective for inhibition of cyclooxygenase-

2.Despite the clinical efficacy of non steroidal anti inflammatory drugs, prostaglandins may function in both the promotion and resolution of inflammation. This review summarizes insights into the mechanisms of prostaglandin generation and the roles of individual mediators and their receptors in modulating the inflammatory response. Prostaglandin biology has potential clinical relevance for atherosclerosis, the response to vascular injury and aortic aneurysm.

2. Bengt Samuelsson (1978)

This chapter discusses prostaglandins and thromboxanes. The prostaglandins are C20 acids formed from polyunsaturated fatty acids by oxygenation and cyclization. The thromboxanes, which were originally found in platelets, have now been identified in a variety of tissues. Rapidprogress is being made in understanding their biological roles. Earlier studies on vascular and airway smooth muscle demonstrated that endoperoxides had unique effects that could not be attributed to conversion into the stable prostaglandins

3. Dingzhi Wang, Raymond N DuBois (2006)

Chemoprevention has been considered as a possible approach for cancer prevention. A significant effort has been made in the development of novel drugs for both cancer prevention and treatment over the past decade. Recent epidemiological studies and clinical trials indicate that long term use of aspirin and similar agents, also called non-steroidal anti-inflammatory drugs (NSAIDs), can decrease the incidence of certain malignancies, including colorectal, oesophageal, breast, lung, and bladder cancers. The best known targets of NSAIDs are cyclooxygenase (COX) enzymes, which convert arachidonic acid to prostaglandins (PGs) and thromboxane. COX-2 derived prostaglandin E 2 (PGE 2) can promote tumour growth by binding its receptors and activating signalling pathways which control cell proliferation, migration, apoptosis, and/or angiogenesis.

4. Stephen B Miller (2006)

Prostaglandins are a group of biologically active compounds that play major roles in human physiology in both health and disease. They function in many different ways and in all major organs. This article reviews the basic physiology of prostaglandins and their application to specific effects on these systems in normal and abnormal clinical states. The critical therapeutic implications of the use of nonsteroidal antiinflammatory drugs in altering organ homeostasis are also examined

5. Sarah G Harris, Josue Padilla, Laura Koumas, Denise Ray, Richard PPhipps (2002)

Prostaglandins are potent lipid molecules that affect key aspects of immunity. The original view of prostaglandins was that they were simply immunoinhibitory. This review focuses on recent findings concerning prostaglandin E2 (PGE2) and the PGD2 metabolite 15-deoxy- Δ12,14- PGJ2, and their divergent roles in immune regulation. We will highlight how these two seminal prostaglandins regulate immunity and inflammation, and play an emerging role in cancer progression. Understanding the diverse activities of these prostaglandins is crucial for the development of new therapies aimed at immune modulation.

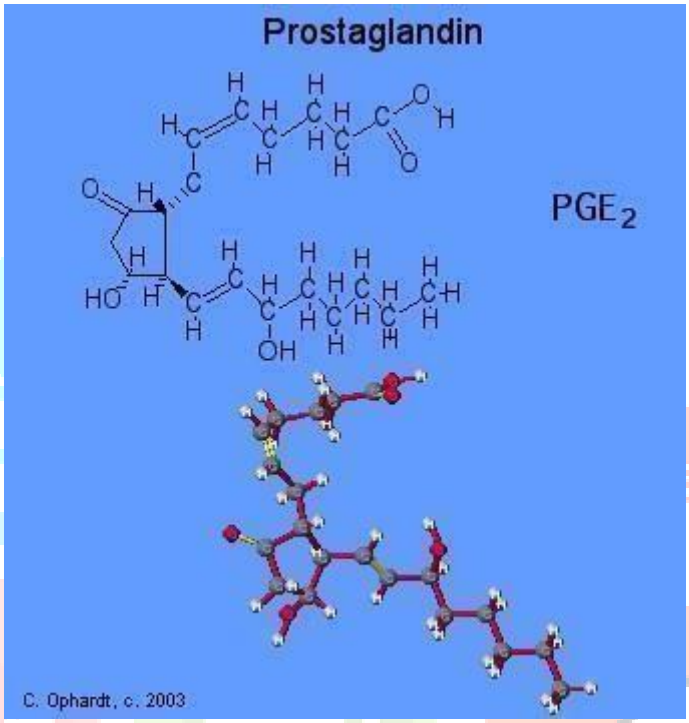
6. Laszlo Z Bito (1987)

An article in this issue of theArchivesby Crawford and Kaufman1provides substantial evidence that the intraocular pressure (IOP)-lowering effect of topically applied prostaglandin F2α(PGF2α) results from an increase in uveoscleral outflow. To fully appreciate the significance of the article, we must look briefly at the history of our understanding of the ocular effects not only of PGF2αbut of the whole family of arachidonic acid derivatives, the eicosanoids.

3. INTRODUCTION:

3.1 Prostaglandin structure:

Prostaglandins are unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring and are based upon the fatty acid, arachidonic acid. Thereare a variety of structures one, two, or three double bonds. On the five member ring there mayalso be double bonds, a ketone, or alcohol groups. A typical structure is on the left graphic.



Prostaglandins are unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring. They are biochemically synthesized from the fatty acid, arachidonic acid. See the graphic on the left. The unique shape of the arachidonic acid caused by a series of cis double bonds helps to put it into position to make the five member ring.

4. Classification:

Prostaglandins, thromboxanes, and leukotrienes are enzymatically derived from essential fattyacids and constitute a unique class of polyunsaturated, hydroxylated, 20-carbon fatty acids categorized as eicosanoids.

All prostaglandins are composed of a cyclopentanone nucleus with two side chains. Primary prostaglandins contain a 15-hydroxyl group with a 13,14-trans double bond (Fig. 1). Currently,three classes of prostaglandins are recognized, and these are categorized on the basis of the number of double bonds present within the prostaglandin molecule and on the fatty acid from which they are derived.

Type	Receptor	Receptortype	Function
PGI2	IP	Gs	• vasodilation • inhibit plateletaggregation • bronchodilation
PGD2	PTGDR (DP1 and (DP2) CRTH 2	GPCR	• produced by mast cells; recruits Th2 cells,eosinophils, and basophils • Inmammalianorgans, large amounts of PGD2 arefound only in the brain and in mast cells • Critical to development of allergic diseases such as asthma
PGE2	EP1	Gq	bronchoconstriction GItract smoothmusclecontraction

	EP2	Gs	bronchodilation GItract smoothmusclerelaxationvasodilation
	EP3	Gi	↓ gastricacid secretion ↑ gastricmucussecretion uterus contraction (when pregnant) GItractsmoothmusclecontraction lipolysisinhibition ↑autonomicneurotransmitters[19] ↑ platelet response to their agonists[20]and ↑atherothrombosis in vivo[21]
	Unspecified		[19] hyperalgesia pyrogenic
PGF2α	FP	Gq	uteruscontractionbronchoconstriction urinary bladder contractions[22]vasoconstriction in cerebralcirculation[23]

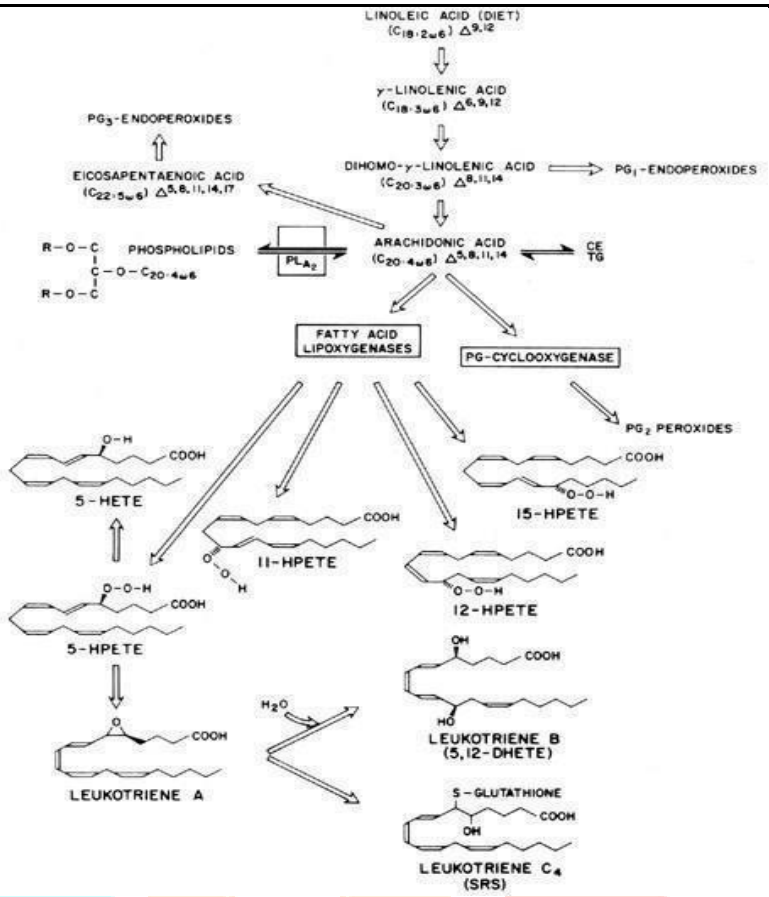


Fig.1.: Origins of prostaglandin precursors and formation of endoperoxides and leukotrienes.

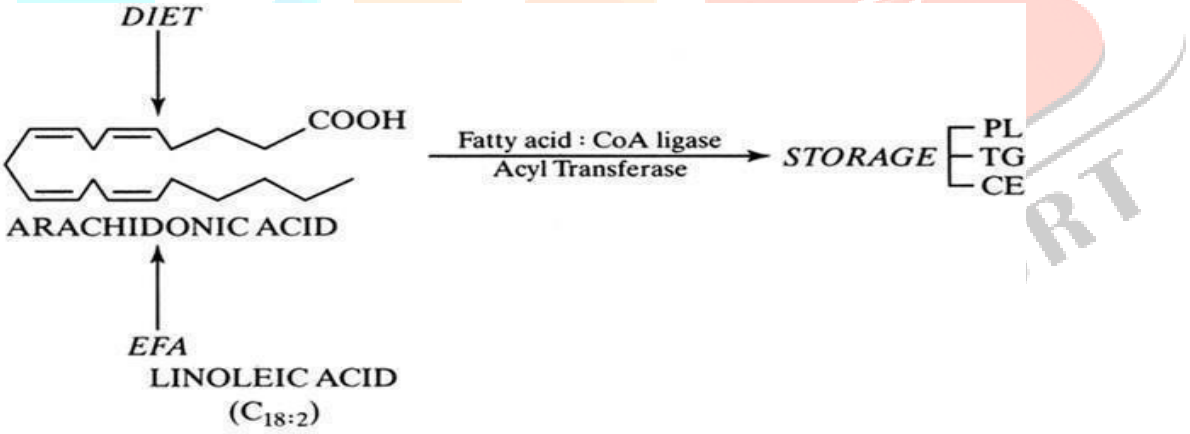


Fig.2.: Origins of arachidonic acid: Both diet and biosynthesis from essential fatty acids**.**

5. Synthesis of prostaglandins:

The prostaglandins are made up of unsaturated fatty acids that contain a cyclopentane (5carbon)ring and are derived from the 20-carbon, straight-chain, polyunsaturated fatty acid precursorarachidonic acid.

Prostaglandins are mediators that act uponplatelets,endothelium,uterineandmastcells.They are synthesized in the cell from thefatty acidarachidonicacid.[2]

Arachidonic acid is created from diacylglycerol via phospholipase-A2, then brought to either the cyclooxygenase pathwayor the lipoxygenase pathway.The cyclooxygenase pathway produces thromboxane,prostacyclinand prostaglandin D, E and F..

Following 15-OH-PGDH action, the 15-ketoprostaglandin is metabolized to the 13,14dihydro metabolite via reduction of the double bond at position 13 by 13,14-PG reductase (see Fig. 5). This catabolic step is followed by oxidation of both α and ω side chains, and a 4carbon fragmentis lost. The terminal carbon of the ω chain is oxidized to a carboxylic acid group. The resultant compound appears to be the major urinary product, and the cyclopentane nucleus, characteristicof PGE and PGF, remains intact.

Much interest was rekindled in prostaglandin research by Moncada and colleagues, with their discovery of prostacyclin (PGI_2, formerly called prostaglandin X), a highly unstable metabolite released into the peripheral circulation from the lungs and vascular endothelium ofarteries. PGI_2 has been referred to as an endogenous antithrombotic agent and is one of the very few prostaglandins that may be a circulating hormone.[18] The major importance of PGI_2 may be in the cardiovascular field, in which its ability to prevent the aggregation of platelets (and hence thrombus formation) by increasing platelet cyclic adenosine monophosphate (cAMP) biosynthesis directly opposes the actions of another novel group of compounds, the thromboxanes.

The thromboxanes are also formed by degradation of prostaglandin endoperoxides (see Fig. 4).[11]Thromboxanes are synthesized in platelets and act to lower platelet cAMP formation, which then leads to aggregation of the platelets and their deposition on the vascular endothelium.[19] TXA_2 is a very potent venoconstricting agent, despite its very short biological half-life (30 seconds). The discovery of TXA_2 and PGI_2, together with a knowledge of their interactions in the control of thrombus formation and vascular tone, has led to a greater

understanding of platelet function in cardiovascular physiology. For example, it has been suggested that patients who have had a heart attack may be protected against any further attacks by taking as little as one tablet of aspirin daily.[20] The basis for such therapy appears tobe that platelet cyclooxygenase (and subsequent TXA_2 biosynthesis) recovers from aspirin inhibition at a much slower rate than does the PGI_2 synthetase of the intimal regions of arterial tissue, thus imparting an antithrombotic property on aspirin. A major thrust of cardiovascular prostaglandin research appears to be the synthesis of PGI_2 analogues and TXA_2 antagonists, together with inhibitors of their

biosynthesis or metabolism.

6. Functions of Prostaglandin:

There are a variety of physiological effects including:

1. Activation of the inflammatory response, production of pain, and fever. When tissues are damaged, white blood cells flood to the site to try to minimize tissue destruction. Prostaglandins are produced as a result.
2. Blood clots form when a blood vessel is damaged. A type of prostaglandin called thromboxane stimulates constriction and clotting of platelets. Conversely, PGI2, is produced to have the opposite effect on the walls of blood vessels where clots should not be forming.
3. Certain prostaglandins are involved with the induction of labor and other reproductive processes. PGE2 causes uterine contractions and has been used to induce labor.
4. Prostaglandins are involved in several other organs such as the gastrointestinal tract (inhibit acid synthesis and increase secretion of protective mucus), increase blood flow in kidneys, and leukotriens promote constriction of bronchi associated with asthma.
5. 7.Action of prostaglandin:

1. **Smooth muscle:** most stimulate myometrium and are known to be important in the initiation and maintenance of labor. Prostaglandin E has bronchodilator action.
2. **GIT:** they increase intestinal motility. PG E inhibits gastric acid secretion and has cytoprotective action on the gastroduodenal mucosa. Both PG E and F produce contraction of the longitudinal muscle of the gut. They also stimulate intestinal fluid secretion, resulting in diarrhea.
3. **CVS:** PGE is peripheral vasodilator and powerful natriuretic. PGF constricts arterioles and veins.
4. **Platelets:** Thromobxane causes platelet aggregation and vasoconstriction. PG I (prostacycline) is found in the vascular endothelium and is a potent inhibitor of platelet aggregation and is a vasodilator.
5. **Miscellaneous:** PGE and PGI produce hyperalgesia associated with inflammation. . In addition, PG E is a potent pyrogenic substance.
6. **Kidney:** PGE_2 & PGI_2 increase water, sodium & potassium extraction and have adiuretic effect.
7. **Sympathetic nerves:** Depending upon PG, species &tissueboth inhibition as well as augmentation of sodium release from sympathetic nerve ending has been observed.
8. **Peripheral nerves:** PGs serves as algesic agent during inflammation.
9. **Eye:** Locally produced PGs appears to fascinate aqeoushumaordranage.
10. **Uterus:** Unlike the myometrium, which mainly produces PGI_2, the nonpregnant endometrium predominantly produces $PGF_{2\alpha}$ and PGE_2. The synthesis of prostaglandins is greater in the glandular epithelium than in the stroma of the endometrium, and during the secretory phase than during the proliferative phase of the cycle. Both $PGF_{2\alpha}$ and

PGE2, through their interaction with specific receptors, areknown to stimulate myometrial contractility, leading to an increase in intracellular Ca^{2+}. Such a mechanism of prostaglandin-induced uterinehypercontractility has beenimplicated in the pathogenesis of primary dysmenorrhea.

10. **Endocrine System:** PG facilates the release of anterior pituitary hormoneas well as that of insulin and adrenal steroids.

8. Fuctions of prostaglandin in reproductive system:

Ovulation and Prostaglandins:

After the discovery that indomethacin and aspirin (inhibitors of prostaglandin synthesis) could block ovulation,[33,37] it was suggested that prostaglandins were involved in the ovarian follicular rupture process. This contention was further strengthened by the finding that intraovarian injection of $PGF2\alpha$ antiserum also inhibited ovulation.[38] There is now a substantial amount of evidence indicating that follicular prostaglandin formation is enhanced during ovulation and that this elevation is dependent on gonadotropins.[39]

The midcycle surge of gonadotropins stimulates follicular eicosanoid biosynthesis by a cAMP-mediated process that is dependent on gene activation, but independent of steroidogenesis. LH appears to be the dominant physiologic pituitary gonadotropin responsible for the induction of ovulation, and it seems likely that the effects of LH on follicular rupture may be mediated by leukocytes that secrete proteolytic enzymes, oxygen radicals, and prostaglandins. Indomethacin, for instance, will block ovulation normally induced by large doses of human chorionic gonadotropin in vivo. Prostaglandins may mediatethe stimulatory effects of LH on

"ovulatory enzymes," such as protease or collagenase.[40] There is also the possibility that prostaglandins may elicit a contractile response in the follicle wall,[41] which is now known to contain contractile elements, such as myosin and actin. Plasminogen activator or some other protease appears to be intrinsically involved in follicle rupture,[42] and it is evident that secretionof this protein is associated with the LH-induced rise in follicular prostaglandin biosynthesis, although it has been pointed out that these two events may not be interdependent. A possible mechanism of prostaglandin action in follicular rupture is shownin Figure.

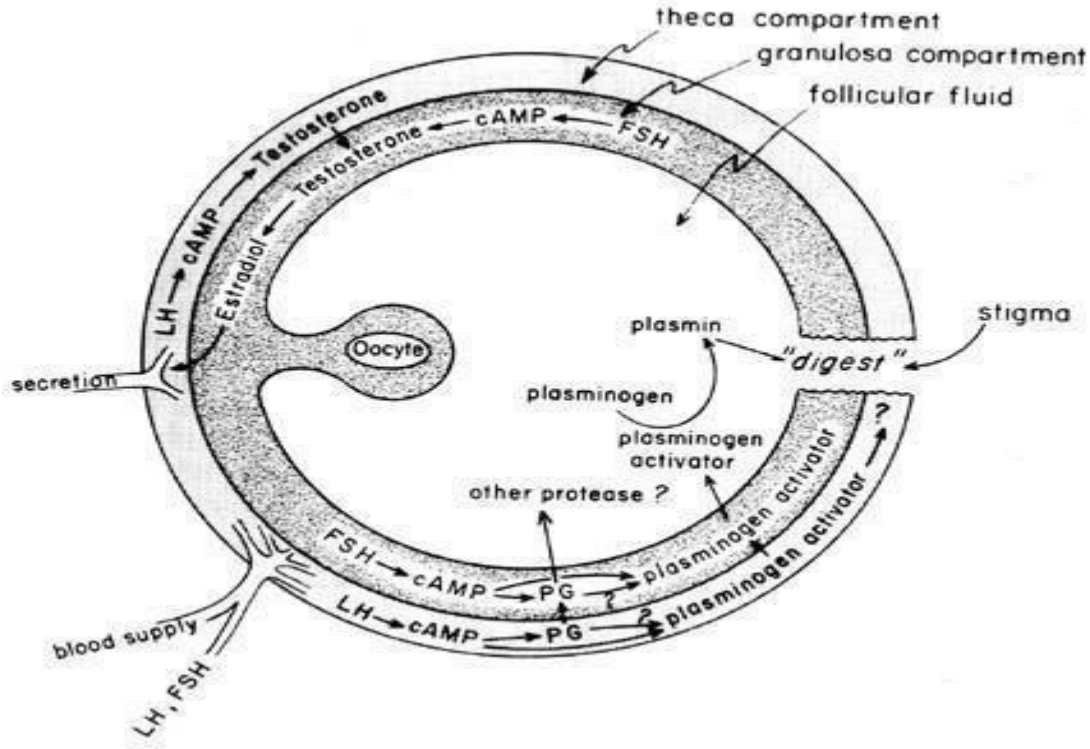


Fig.3.: Possible mechanism of prostaglandin action in follicular rupture.(Behrman HR: Prostaglandins in hypothalamo-pituitary and ovarian function.

Prostaglandins and the Ductus Arteriosus:

The maintenance of patency (relaxation of vasodilation) of the ductus arteriosus is pivotal in controlling the oxygenation of tissues in the fetus. After birth, the ductus arteriosus normally becomes constricted or loses its patency. The mechanism by which this closure occurs is unclear, although blood oxygen tension is believed to be an important factor (Fig. 7). The primary function of the ductus arteriosus in the fetus is to maintain some degree of left-toright arterial blood shunting, thereby controlling the amount of venous return to the lungs. Closure of the ductus at term is an important physiologic process that, if incomplete, leads to respiratory distress and cyanosis/hypoxia—syndromes that are responsible for the high morbidity and mortality in many premature infants suffering from patent ductus arteriosus. Forthis reason, there is a good deal of interest in the mechanism(s) of controlling ductus arteriosusfunction. Thisinterest is particularly acute in the field of prostaglandin research, in which there is now a considerable amount of evidence suggesting the involvement of prostaglandins in controlling ductus arteriosus patency at term.

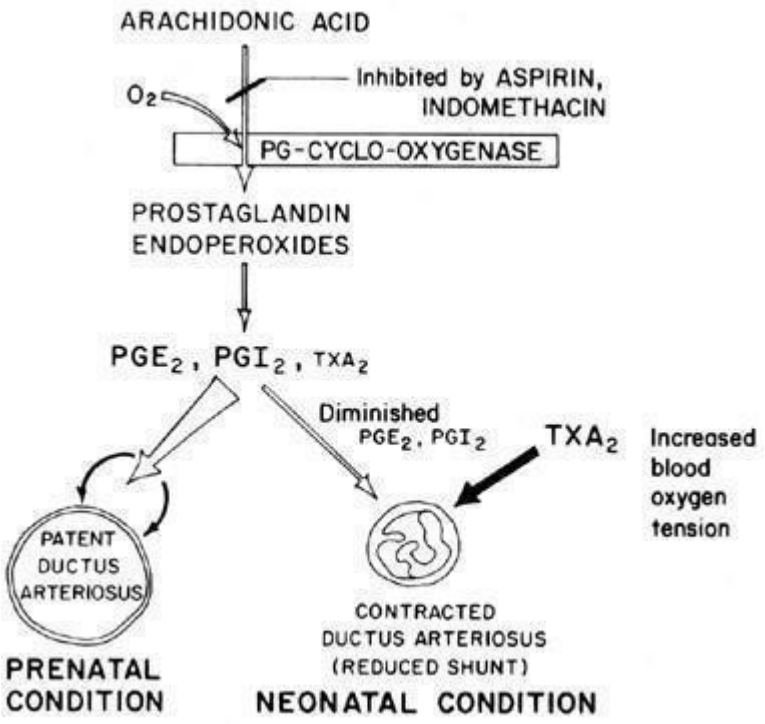


Fig.4.: Scheme for prostaglandin modulation of patency of ductus arteriosus in fetus and neonate as a function of oxygen tension.

This evidence is based on the following series of observations:

The ductus arteriosus in the fetus with cardiopulmonary deterioration and hyaline membrane disease can be closed by administration of prostaglandin synthetase inhibitors.[78] Indomethacin can induce contraction of the hypoxic vessel, as demonstrated by its effects in animals near term.[79]

Administration of PGE2 (and PGE1) induces relaxation (loss of patency) of isolated fetal lamb ductus arteriosus preparations (circular strips) in a low oxygen environment (PO2 less than 14 mmHg).[80]

It seems likely that prostaglandins of the E series, together with prostaglandin antagonists and prostaglandin-synthetase blockers (aspirin), may prove to be desirable nonsurgical treatments for preterm infants with potentially fatal patent ductus arteriosus. Recent evidence suggests a balance between ductus patency and constriction that is maintained by synthesis of dilating prostaglandins (PGI2 and PGE2) and constricting prostaglandin (TXA2). In the lamb fetus, boththe ductus arteriosus and the lung synthesize PGI2 and PGE2; then, as term approaches, the lung shifts toward TXA2 synthesis.[81] Further information on prostaglandin involvement in the control of ductus arteriosus function is available.

9. Disorders related to PG :

PGE2 has varying effects on the immune system. In some instances viruses can interact with PGE2 and possibly benefit from the effects of PGE2 . A few of the potential effects of PGE2 on various viral infections are enlisted.

Viral Infections related to prostaglandin:

A. Double-Stranded DNA Viruses

B. Herpes Simplex Virus:

C. Cytomegalovirus:

D. Epstein Barr Virus:

E. Double-Stranded RNA Viruses

F. Rotavirus:

G. (+) Single-Stranded RNA Viruses

H. Coxsackie Virus:

10. Prostaglandin E2 as a Potential Therapeutic Target:

The current review highlights the potential of the biosynthetic pathway of PGE_2 (Figure 1) as a therapeutic target in viral infections. This is possible as PGE_2 has been shown to play a role in various viral infection, by either having a stimulatory/inhibitory effect on the viral life cycle or host's immune system.

One of the first potential therapies is limiting the amount of AA (or FA that can be converted to AA) that is taken in up in the diet of an individual (Calder, 2005, 2010). This can be done by limiting the amount of n-6 polyunsaturated fatty acids (PUFAs) (vegetable oils, animal sources) and rather ingesting n-3 PUFAs (fish oils, marine sources) which are preferentially converted into either docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA). They act by replacing AA as an eicosanoid substrate and inhibiting AA metabolism (directly) or altering the effects of inflammatory genes through effects on transcriptional activation (indirectly) (Calder, 2005).Although EPA also gives rise to eicosanoids, these have anti inflammatory effects in contrast to AA-derived

11. Some effects of prostaglandins in the body:

The prostaglandins are a group of lipids made at sites of tissue damage or infection that are involved in dealing with injury and illness. They control processes such as inflammation, blood flow, the formation of blood clots and the induction of labour.

The pharmacology of prostaglandins for induction of labor:

Prostaglandin medications are frequently used in the process of induction of labor. Understanding the history and research that supports prostaglandin use for induction of labor is crucial for safe practice. Dinoprostone has been the standard of care for cervical ripening in term pregnancies. Misoprostol administration via various routes has been shown to be efficacious. Oral misoprostol in particular is effective and associated with reassuring maternal and fetal outcomes. In addition, cost has become a variable in decision making regarding best practice. More research is necessary to determine the safest medication, route, dose, and interval of administration. This article reviews cervical physiology and endogenous prostaglandin activity in relation to labor, and the pharmacologic profiles of synthetic prostaglandins currentlyused for induction of labor.

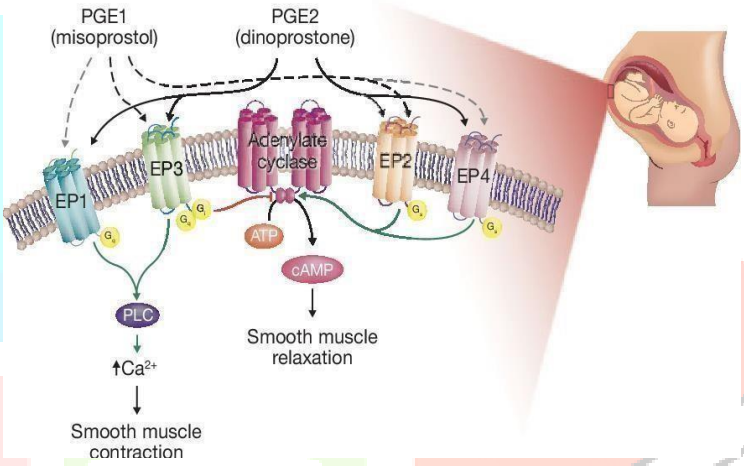


Fig.5.: Labor induction using Prostaglandin

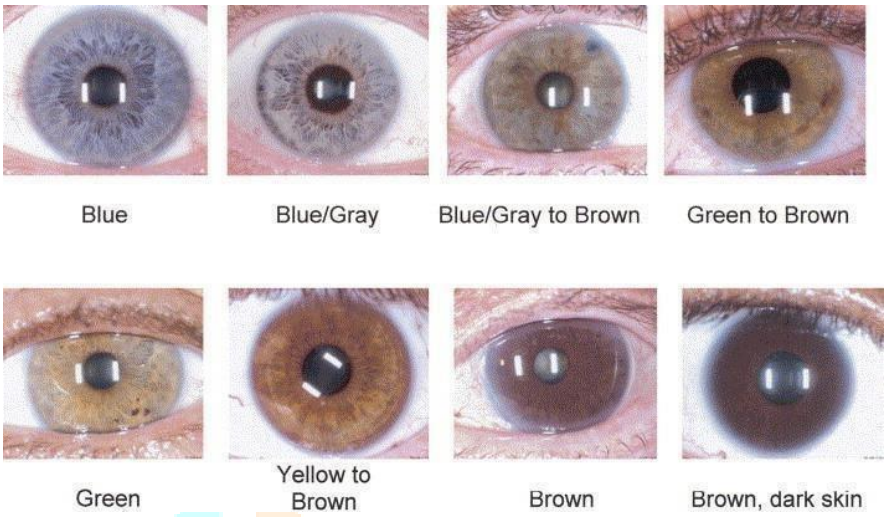
12. Prostaglandin and its analogs:

PGE1	Misoprostol
	Alprostadil
PGI2	Epoprostenol
PGF 2α	Latnoprost
PGD2	Levocetrizine
PGE2	Carboprost
	Dinoprostone

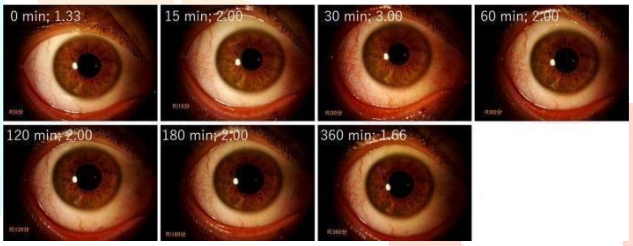
13. Side effects of prostaglandin analog :

11.1 The different prostaglandin analog used in clinical practice.

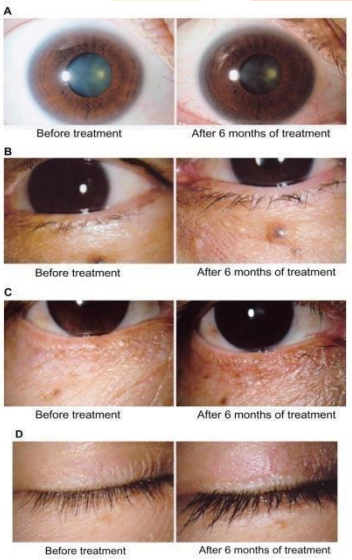
11.2 Eyelash changes.



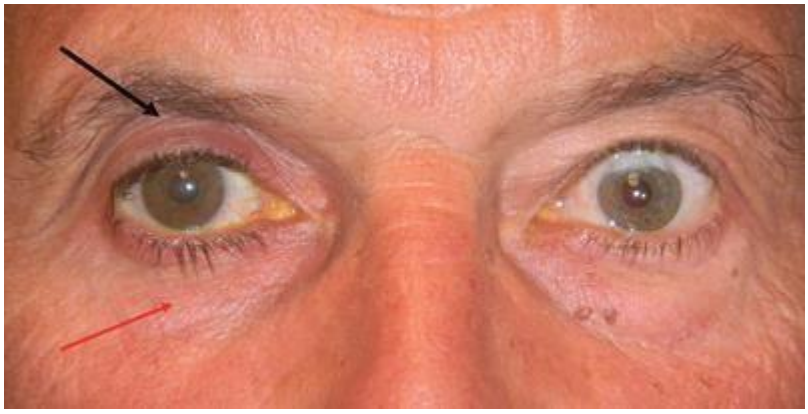
11.3 Cojunctival hyperaemia.



11.4 Increase of iris pigmentation.



13.4 Increase of eyelid skin pigmentation.



13.5 Occular surface problems, blephartis, ocular pain and visual disturbance.

14..Drugs affect on prostaglandin:

1. Aspirin and a large number of nonsteroidal anti-inflammatory drugs act primarily through the inhibition of prostaglandin synthesis by inhibiting the enzyme cyclooxygenase.
2. The effect of anti-inflammatory drugs on prostaglandin production by rheumatoid synovial tissue has been investigated. Synovial explants were maintained in tissue culture for periods up to six days and PGE2 concentrations in culture were determinedby radioimmunoassay.
3. The more potent nonsteroidal inhibitors of PGE2 production and their IC50 (micrometer) values were indomethacin 0.005, flufenamic acid 0.2, flurbiprofen 0.6, ibuprofen 2.0 , naproxen 6.0, phenylbutazone 10.0, and aspirin 20.0.

4. Drugs with weak or insignificant effects were hydroxychloroquin, acetaminophen, azathioprine, chloroquin, penicillamine, gold Na thiomalate, and Na salicylate. Glucocorticoids were potent inhibitors; dexamethasone 0.003, prednisolone 0.01, hydrocortisone 0.03; while mineralocorticoids deoxycorticosterone and aldosterone were inactive at 1.0 micrometer.

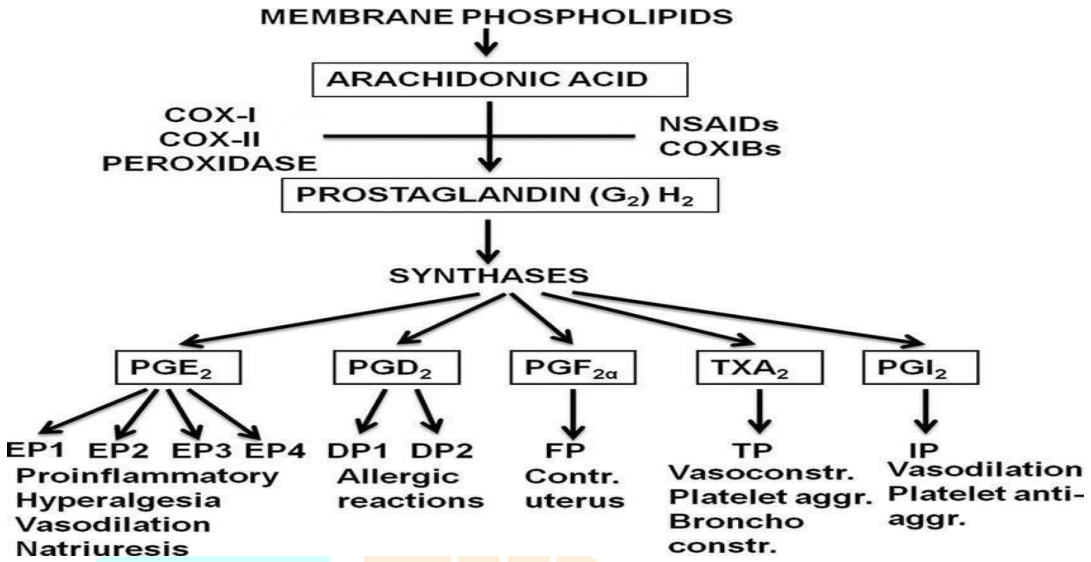


Fig.6.: Formation and biological effects of prostaglandins and thromboxane A 2. NSAIDs, nonsteroidal anti-inflammatory drugs.

SUMMARY

The many actions of the prostaglandins in reproductive physiology are truly remarkable, as is our rapidly expanding knowledge of these effects. Our knowledge remains far from complete, however, and much more research is needed to fully elucidate the role(s) of prostaglandins in many physiologic processes, particularly in areas such as luteolysis, where the hope is that thesebiologically active lipids may provide a method for regulating menstruation and fertility. Otherimportant fields of clinical significance that deserve further attention are parturition and ductusarteriosus function.

Further developments in prostaglandin research are likely to include the clinical application of more selective inhibitors, antagonists, and long-acting superpotent agonist analogues of prostaglandins.

15. CONCLUSION

The result of present systemic review indicate that, incompariion with placebo, oxytosin,oxytosin agonist, or ergometrin, the use of prostaglandin does not increase the rate of expulsion of retained placenta.Therefore, prostaglandins do not seem to be an effective alternative for the treatment of retained placenta.

Prostaglandins are regulatory compounds that play important roles in many physiologic processes in the human body. An understanding of the basic science of prostaglandins is valuable in anticipating the organ-specific biologic effects of these unique compounds in healthand disease.

REFFERENCES:

1. Elattar TMA: Prostaglandins: Physiology, biochemistry, pharmacology and clinical applications. J Oral Pathol 7: 239, 1978
2. Hall AK, Behrman HR: Prostaglandins: Biosynthesis, metabolism and mechanism of cellular action (review). In Lee JB (ed): Prostaglandins (Comprehensive Endocrinology). New York, Elsevier/North-Holland, 1980
3. Ramwell PW, Leovey EMK, Sintetos AL: Regulation of the arachidonic acid cascade. BiolReprod 16: 70, 1977
4. Nelson NA: Nomenclature and structure of prostaglandins. J Med Chem 17: 911, 1973
5. Lands WEM: The biosynthesis and metabolism of prostaglandins. Ann Rev Physiol 41: 633, 1979
6. Kunze H, Vogt W: Significance of phospholipase A2 for prostaglandin function. Ann NY Acad Sci 180: 122, 1971
7. Bell RL, Kennerly DA, Stanford N et al: Diglyceride lipase: A pathway for arachidonate release from human platelets. Proc Natl Acad Sci USA 76: 3238, 1979
8. Hirata F, Notsu Y, Matsuda K et al: Modulation of neuroreceptor functions by lipomodulin, a phospholipase inhibitory protein. Adv Exp Med Biol 175: 187, 1984
9. Whitehouse BJ: Lipocortins, mediators of the anti-inflammatory actions of corticosteroids? J Endocrinol 123: 363, 1989
10. Davidson FF, Dennis EA: Biological relevance of lipocortins and related proteins as inhibitors of phospholipase A2. BiochemPharmacol 38: 3645, 1989
11. Nugteren DH, Hazelhof E: Isolation and properties of intermediates in prostaglandin biosynthesis. BiophysBiochem Acta 326: 448, 1973
12. Wu KK: Inducible cyclooxygenase and nitric acid synthase. Adv Pharmacol 33: 179, 1995
13. Smith WL: Prostanoid biosynthesis and mechanism of action. Am J Physiol 263:F181, 1992
14. Dinchuk JE, Car BD, Foct RJ et al: Renal abnormalities and altered inflammatory response in mice lacking cyclooxygenase: II. Nature 378: 406, 1995

15. Hansen HS: 15-Hydroxy-prostaglandin dehydrogenase: A review. Prostaglandins 12:647, 1976

16. Allard CB, Dason S, Lusis J, Kapoor A. Prostate cancer screening: Attitudes and practices of family physicians in Ontario. Can Urol Assoc J [Internet]. Jun, 2012.

17. Hoffman RM, Fletcher RH, O'Leary MP, Rind DM. UpToDate [Internet]. Waltham(MA): UpToDate; 1992 -. Oct 17, 2013.

18. Qaseem A, Barry MJ, Denberg TD, Owens DK, Shekelle P. Clinical Guidelines Committee ofthe American College of Physicians. Screening for prostate cancer: a guidance statement fromthe Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med. 2013 May

19. Basch E, Oliver TK, Vickers A, Thompson I, Kantoff P, Parnes H, et al. Screening for prostate cancer with prostate-specific antigen testing: American Society of Clinical Oncology Provisional Clinical Opinion

20. Wolf AM, Wender RC, Etzioni RB, Thompson IM, D'Amico AV, Volk RJ, et al. American Cancer Society guideline for the early detection of prostate cancer.