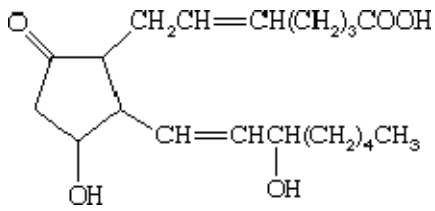
Prostaglandin and its Biosynthesis

Prostaglandin, any of a group of physiologically active substances having diverse hormonelike effects in animals. Prostaglandins were discovered in human semen in 1935 by the Swedish physiologist Ulf von Euler, who named them, thinking that they were secreted by the prostate gland. The understanding of prostaglandins grew in the 1960s and ’70s with the pioneering research of Swedish biochemists Sune K. Bergström and Bengt Ingemar Samuelsson and British biochemist Sir John Robert Vane. The threesome shared the Nobel Prize for Physiology or Medicine in 1982 for their isolation, identification, and analysis of numerous prostaglandins.

Synthesis Of Prostaglandins:

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



PGE$_2$ (a prostaglandin)

Arachidonic acid is a key component of phospholipids, which are themselves integral components of cell membranes. In response to many different stimuli, including various hormonal, chemical, or physical agents, a chain of events is set in motion that results in prostaglandin formation and release. These stimuli, either directly or indirectly, result in the activation of an enzyme called phospholipase A_2. This enzyme catalyzes the release of arachidonic acid

from phospholipid molecules. Depending on the type of stimulus and the enzymes present, arachidonic acid may diverge down one of several possible pathways. One enzyme, lipoxygenase, catalyzes the conversion of arachidonic acid to one of several possible leukotrienes, which are important mediators of the inflammatory process. Another enzyme, cyclooxygenase, catalyzes the conversion of arachidonic acid to one of several possible endoperoxides. The endoperoxides undergo further modifications to form prostaglandins, prostacyclin, and thromboxanes. The thromboxanes and prostacyclin have important functions in the process of blood coagulation.

BIOSYNTHESIS AND METABOLISM

Eicosanoids exist only transiently: they are formed in a substrate-limiting environment and are rapidly metabolized. Thus, their modulation of cellular function is mostly paracrine or autocrine in fashion. The major eicosanoid precursor substrates are fatty acids, which are usually bound in the esterified form as cholesteryl esters; phospholipids; or triglycerides (see Fig. 2). The predominant prosubstrate is phospholipid, and the general consensus is that the release of free fatty acid from the prosubstrate is a major rate-limiting step in eicosanoid formation.6

Enzymes known as phospholipases split membrane-associated phospholipids by hydrolysis to give rise to many polyunsaturated free fatty acids, such as arachidonic acid, which is the main substrate for eicosanoid formation.6 Arachidonic acid is enzymatically synthesized via chain elongation and desaturation, but a major source of this fatty acid is also the diet.

The enzymes that catalyze the formation of eicosanoids exist in a substrate-limiting environment. Thus, liberation of arachidonic acid from esterified stores results in the prompt formation of these products. Release of arachidonic acid is facilitated by the hydrolytic action of phospholipases. Phospholipase C, in combination with diglyceride lipase, releases arachidonic acid from phosphatidylinositol.7 Phospholipase A2 cleaves arachidonic acid from phosphatidylcholine, as well as from phosphatidylethanolamine and phosphatidylinositol. Until recently, phospholipase A2 activity was thought to be regulated by a glucocorticoid inducible protein, originally designated lipomodulin8 but

later termed lipocortin.9 Lipocortin appeared to inhibit phospholipase A2 by forming an inactive complex with the enzyme, which could be rapidly reversed by phosphorylation of lipocortin.8 This role of lipocortin as a regulator has been challenged. Lipocortin appears to be one member of a large family of calcium- and phospholipid-binding proteins,9 which only inhibits phospholipase activity in vitro when the phospholipid substrate and/or the calcium cofactor are limited.10 Currently, the role of lipocortin as a mediator of the anti-inflammatory activity of glucocorticoids is questionable.

Prostaglandin Synthetase Pathway

Prostaglandin synthetase (cyclooxygenase moiety) is responsible for incorporating molecular oxygen into arachidonic acid (and other fatty acids), resulting in the evolution of unstable intermediate compounds referred to as prostaglandin endoperoxides (PGG2 and PGH2 [Fig. 4]).11 Currently two PGH synthases are known, which are encoded by separate genes: one is a constitutive enzyme found in virtually all tissues, referred to as PGH synthase-1 or COX-1; the second enzyme, called PGH synthase-2 or COX-2, is inducible and is often markedly upregulated during cellular differentiation by cytokines or hormones.12,13 Histologic examination of adult COX-2-deficient mice revealed tissue abnormalities restricted to the kidneys, heart, and ovaries, with homozygous (-/-) knockout female mouse offspring found to be infertile.14

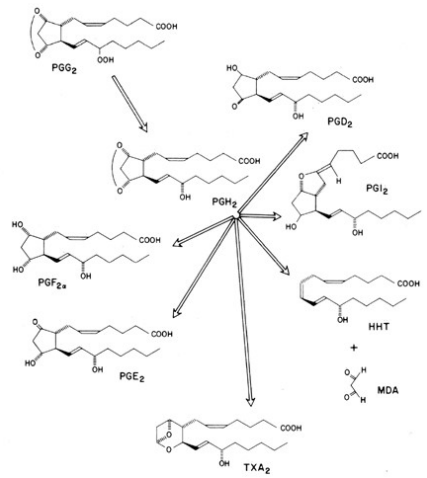


Fig. 4. Degradation of prostaglandin endoperoxides.

Prostaglandin cyclooxygenase is the site at which indomethacin and other nonsteroidal anti-inflammatory agents, such as aspirin, inhibit prostaglandin

biosynthesis. The prostaglandin endoperoxides have a transient existence and are rapidly transformed (hydrolyzed) into more stable metabolites, such as PGD2, PGF2, PGE2, PGI2 (prostacyclin), thromboxane A, thromboxane B (TXB2), and HHT (hydroxyheptadecatrienoic acid) (see Fig. 4). The end products of prostaglandin endoperoxide metabolism appear to be enzymatically directed and depend on a number of variables: the availability of reducing agents (glutathione), molecular oxygen, or cofactors such as L-tryptophan and the presence of the metabolizing enzyme.

The type of prostaglandin formed appears to be tissue specific. Platelets synthesize significant amounts of TXA2, a vasoconstrictor and platelet-aggregating substance. PGI2, a vasodilator and inhibitor of platelet aggregation, is produced by the arterial wall, corpus luteum, follicle, uterus, and ductus arteriosus. Two other major products of endoperoxide metabolism, PGE2 and PGF2, are produced in almost every tissue, including the follicle, uterus, and brain. PGE2 and PGF2α appear to have both antagonistic and agonistic interactions. In the oviduct, smooth-muscle PGE2 promotes relaxation, whereas PGF2α promotes contraction. In the uterus, however, both promote contractions.

Once secreted into the peripheral circulation, most prostaglandins (with the exception of prostacyclin and TXA2) are rapidly metabolized in the lungs by an enzyme called 15-hydroxyprostaglandin dehydrogenase (15-OH-PGDH) (Fig. 5).15 This enzyme selectively oxidizes the hydroxyl group at carbon 15 into a 15-keto moiety. This step alone results in a dramatic loss of biological activity with the formation of 15-ketoprostaglandins. It has been shown that 15-hydroxyprostaglandin dehydrogenase has a short biological half-life and is subject to rapid turnover which, in some tissues, is modulated by steroid hormones.15,16 In general, highest concentrations of 15-OH-PGDH are found in the lungs, placenta, spleen, and the kidney-cortex. The brain has relatively low levels of 15-OH-PGDH activity, as do the ovary and the testis. Substrates for 15-OH-PGDH include PGE, PGF, and PGI, but the latter prostaglandin is degraded rapidly by “facile” hydrolysis. Compounds, such as lidocaine and the diuretic drugs furosemide and ethacrynic acid can inhibit 15-OH-PGDH.17 This may explain the diuretic action of the latter drugs, since PGE2 produces diuresis through a direct action in the kidney.

Biological Activities Of Prostaglandins:

Prostaglandins have been found in almost every tissue in humans and other animals. Plants synthesize molecules similar in structure to prostaglandins, including jasmonic acid (jasmonate), which regulates processes such as plant reproduction, fruit ripening, and flowering. Prostaglandins are very potent; for example, in humans some affect blood pressure at concentrations as low as 0.1 microgram per kilogram of body weight. The structural differences between prostaglandins account for their different biological activities. Some prostaglandins act in an autocrine fashion, stimulating reactions in the same tissue in which they are synthesized, and others act in a paracrine fashion, stimulating reactions in local tissues near where they are synthesized. In addition, a given prostaglandin may have different and even opposite effects in different tissues. The ability of the same prostaglandin to stimulate a reaction in one tissue and inhibit the same reaction in another tissue is determined by the type of receptor to which the prostaglandin binds.

ACTIONS OF PROSTAGLANDINS

Prostaglandins exhibit a wide range of biological effects, and their actions are among the most varied of any naturally occurring compounds. Despite this observation, this group of lipids displays a marked structure-activity specificity, which is determined mainly by cyclopentanone ring substitutions and the degree of unsaturation of the prostanoic acid side chains. The cellular response to prostaglandins is mediated by their interaction with plasma membrane receptors.

PG receptors were initially classified on the basis of functional activities of natural and synthetic agonists, and antagonists were classified into the following categories: DP, EP, FP, IP, and TP. The first letter denotes the prostaglandin type, and the letter P stands for “prostanoid.”30 Later, studies by binding analysis and molecular cloning confirmed the presence of distinct receptor types as well as three or four subtypes of EP (EP1–4). Plasma membrane prostaglandin receptors belong to the superfamily of G-protein-coupled receptors characterized by seven transmembrane-spanning regions.31 Intracellular second messengers of prostaglandin receptors include cAMP, protein kinase C, and calcium.30,31 The various receptors show remarkable specificity for the eicosanoid, with at least a 100-fold preference for the ligand. At high concentrations, PGE2 and PGF2α interact with the DP receptor; similarly, PGF2α will activate the EP receptor, whereas PGD2 and PGE2 will interact with the

FP receptor at high concentrations. Most tissues contain a mixture of receptors, which appears to be the basis for the often opposite effects of a particular prostaglandin at different doses.

Role of Prostaglandins in Gonadotropin Secretion

Recent data implicating a physiologic role of prostaglandins in the regulation of gonadotropin-releasing hormone (GnRH) secretion have been published.32,33 A number of reports now suggest that prostaglandins, particularly PGE2, exert stimulatory influences on gonadotropin release, an effect that appears to be mediated by an action at the level of the hypothalamus. PGE2 has been shown to stimulate the release of GnRH from the hypothalamus, and pretreatment of animals with antisera to neutralize endogeneous GnRH prevents the PGE2-induced release of LH.34 In addition, PGE1 and PGE2 appear to be the most potent stimulators of growth hormone release from cultured adenohypophyseal cells.35 PGB, PGA1, PGA2, PGB2, PGF1, and PGF2 are also active stimulators, but their effects are not seen at physiologic doses. In general, prostaglandins appear not to stimulate gonadotropin secretion by a direct action on the pituitary.

Further evidence suggesting that prostaglandins might affect gonadotropin secretion (by acting directly on the hypothalamus) is supplied from studies using prostaglandin synthetase inhibitors, such as indomethacin, which apparently reduce gonadotropin secretion.36 That prostaglandins act by way of hypothalamic-releasing factors is evident on the basis of two observations:

1. Pretreatment of female and male rats with antiserum to LH-releasing hormone (LHRH) impaired the ability of PGE2 (100 mg per rat) to increase LH secretion.36
2. Direct administration of PGE2 into the ventricle of the brain of the rat mimicked the intravenous effect of prostaglandins on the stimulation of gonadotropin secretion.36

Additional findings provide compelling support for the concept that PGE2 acts at the level of the median eminence to elicit release of LHRH. This contention is further corroborated by the finding that median eminence tissue contains greater amounts of endogenous prostaglandins than basal hypothalamic regions. Data obtained from in

vitro incubations of median eminence fragments obtained from male rats have shown that norepinephrine and dopamine stimulate the simultaneous release of LHRH and PGF2α. This effect is blocked by indomethacin, suggesting that intraneuronally produced prostaglandins are the mediators of catecholamine-stimulated LHRH release. These interesting findings are discussed in greater detail in a review by Ojeda and co-workers.36

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 PGF2α 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 mediate the 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 secretion of 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 shown in Figure .

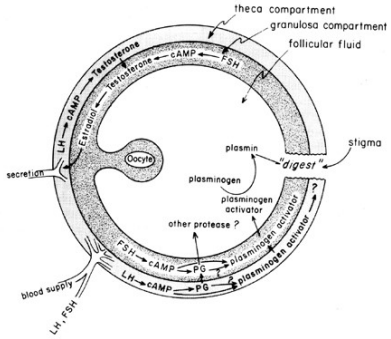


Fig.. Possible mechanism of prostaglandin action in follicular rupture.(Behrman HR: Prostaglandins in hypothalamo-pituitary and ovarian function. Ann Rev Physiol 41:685, 1979)

Role of Prostaglandins in Luteal Function: Luteolysis and Menstruation

The mechanism by which the human corpus luteum regresses 10 to 12 days after its formation is a mystery. Since the early finding that PGF2α was luteolytic in the rat and many other subprimate species,43 a major research effort has been made to investigate the possibility of menstrual regulation with PGF2α.PGF2α induces functional regression of the corpus luteum by a receptor-mediated process, independent initially of changes in ovarian or luteal blood flow.32 Within minutes, PGF2α depletes ascorbic acid,44 uncouples the occupied LH receptor from adenylate cyclase, and decreases transport of gonadotropin from capillaries to the luteal cell.

Other functions:

1 Vasodilation and blood clotting:

Most prostaglandins act locally; for instance, they are powerful locally acting vasodilators. Vasodilation occurs when the muscles in the walls of blood vessels relax so that the vessels dilate. This creates less resistance to blood flow and allows blood flow to increase and blood pressure to decrease. An important example of the vasodilatory action of prostaglandins is found in the kidneys, in which widespread vasodilation leads to an increase in the flow of blood to the kidneys and an increase in the excretion of sodium in the urine. Thromboxanes, on the other hand, are powerful vasoconstrictors that cause a decrease in blood flow and an increase in blood pressure.

Thromboxanes and prostacyclins play an important role in the formation of blood clots. The process of clot formation begins with an aggregation of blood platelets. This process is strongly stimulated by thromboxanes and inhibited by prostacyclin. Prostacyclin is synthesized in the walls of blood vessels and serves the physiological

function of preventing needless clot formation. In contrast, thromboxanes are synthesized within platelets, and, in response to vessel injury, which causes platelets to adhere to one another and to the walls of blood vessels thromboxanes are released to promote clot formation. Platelet adherence is increased in arteries that are affected by the process of atherosclerosis. In affected vessels the platelets aggregate into a plaque called a thrombus along the interior surface of the vessel wall. A thrombus may partially or completely block (occlude) blood flow through a vessel or may break off from the vessel wall and travel through the bloodstream, at which point it is called an embolus. When an embolus becomes lodged in another vessel where it completely occludes blood flow, it causes an embolism. Thrombi and emboli are the most common causes of heart attack (myocardial infarction). Therapy with daily low doses of aspirin (an inhibitor of cyclooxygenase) has had some success as a preventive measure for people who are at high risk of heart attack.

2 Inflammation:

Prostaglandins play a pivotal role in inflammation, a process characterized by redness (*rubor*), heat (*calor*), pain (*dolor*), and swelling (*tumor*). The changes associated with inflammation are due to dilation of local blood vessels that permits increased blood flow to the affected area. The blood vessels also become more permeable, leading to the escape of white blood cells (leukocytes) from the blood into the inflamed tissues. Thus, drugs such as aspirin or ibuprofen that inhibit prostaglandin synthesis are effective in suppressing inflammation in patients with inflammatory but noninfectious diseases, such as rheumatoid arthritis.

3 Smooth muscle contraction:

Although prostaglandins were first detected in semen, no clear role in reproduction has been established for them in males. This is not true in women, however. Prostaglandins play a role in ovulation, and they stimulate uterine muscle contraction—a discovery that led to the successful treatment of menstrual cramps (dysmenorrhea) with inhibitors of prostaglandin synthesis, such as ibuprofen. Prostaglandins also play a role in inducing labour in pregnant women at term, and they are given to induce therapeutic abortions.

The function of the digestive tract is also affected by prostaglandins, with prostaglandins either stimulating or inhibiting contraction of the smooth muscles of the intestinal walls. In addition, prostaglandins inhibit the secretion of gastric acid, and therefore it is not surprising that drugs such as aspirin that inhibit prostaglandin synthesis may lead to peptic ulcers. Prostaglandin action on the digestive tract may also cause severe watery diarrhea and may mediate the effects of vasoactive intestinal polypeptide in Verner-Morrison syndrome, as well as the effects of cholera toxin.