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Physiology and Pharmacology of Prostaglandins

S.J. KONTUREK, MD, and W. PAWLIK, MD

Prostaglandins (PGs) are products of polyunsaturated acid metabolism, particularly arachidonic acid (AA) released from membrane phospholipids by the action of phospholipase A_2 in response to a variety of physical, chemical, and neurohormonal factors. AA is rapidly metabolized to oxygenated products by two distinct enzymatic pathways: cyclooxygenase and lipoxygenase. The intermediate cyclooxygenase products are converted to primary PGs, while the lipoxygenase products are converted to leukotrienes. The generation of various cyclooxygenase products varies from tissue to tissue. Aspirin and related antiinflammatory drugs reduce tissue biosynthesis of all cyclooxygenase products; their therapeutic effects and side effects parallel the inhibition of cyclooxygenase. Exogenous PGs exhibit a broad spectrum of effects. PGs of the E series and PGI_2 are generated by the endothelium and the vessel wall to maintain the microcirculation and to counteract the vasoconstrictive and proaggregatory actions of thromboxane A_2 (TXA_2). Exogenous PGs of the E and I series are potent vasodilators in various vascular beds, and result in decreased systemic blood pressure and reflex stimulation of heart rate. PGEs and PGI_2 increase renal blood flow and provoke diuresis and natriuresis, partly by modulating the renin–angiotensin–aldosterone system. PGFs contract the bronchial and gut muscle, while PGEs and PGI_2 have opposite effects. PGEs and PGFs, but not PGI_2, cause a strong contraction of the uterine muscle, hence their undesirable uterotonic effects. PGEs relax bronchial muscle, whereas PGFs cause bronchoconstriction; their imbalance may contribute to the high bronchial tone in bronchial asthma. PGs of the E and I series and TXA_2 are generated by the gastrointestinal mucosa and released into the lumen upon neural or hormonal stimulation; they probably participate in the maintenance of mucosal integrity and microcirculation. Exogenous PGs of the E and I series inhibit gastric acid secretion and stimulate alkaline secretion while increasing mucosal blood flow. All PGs, including those noninhibitory for acid secretion, are cytoprotective against various ulcerogens and necrotizing agents. The classic PGs constitute only a small fraction of biologically active products of AA metabolism, and recent studies on the lipoxygenase products emphasize their biological activity and involvement in a variety of pathological conditions.

Prostaglandins (PGs) constitute a family of chemically related lipid acids that are among the most prevalent autacoids; they seem to modulate practically every biological function in the body. They are formed by a complex of microsomal enzymes, acting on certain 20-carbon unsaturated fatty acids, particularly eicosatetraenoic or arachidonic acid (AA). Additional products of the cellular metabolism of AA, differing in structure from PGs, include the thromboxanes (TX) and leukotrienes (LT), whose physiological and pathological functions are closely interrelated with those of the PGs.

The existence of the PGs has been known for

From the Institute of Physiology, Academy of Medicine, Krakow, Poland.

Address correspondence to: Professor Dr. S.J. Konturek, Institute of Physiology, Academy of Medicine, ul. Grzegorzecka 16, 31-531 Krakow, Poland.

over half a century. Kurzok and Lieb (1) were the first to observe, in 1930, that strips of human uterus relax or contract when exposed to human semen. In the mid-1930s, von Euler (2) in Sweden, and Goldblatt (3) in England independently extracted crude PGs from the seminal fluid of man and vascular glands of sheep, and reported their smooth-muscle-contracting and vasodepressor activities. In the late 1950s, Bergstrom and Sjovall (4) isolated PGs in a pure form and, in the early 1960s, determined the chemical structure. With the identification of two unstable cyclic endoperoxides, PGG_2 (5) and PGH_2 (6), the emphasis shifted from the primary PGs (E and F series) to other biologically active products of AA metabolism, resulting in the discovery of TXA_2 (7) and prostacyclin (PGI_2) (8). In addition to the cyclooxygenase mechanism, another metabolic pathway, converting AA to hydroperoxides (HPETE and HRTE) (9, 10) and then to LTs (11), was identified. The impact of the PGs and other products of AA metabolism could be compared only to that of corticosteroids in the late 1940s and 1950s.

CHEMICAL STRUCTURE AND BIOSYNTHESIS

The natural PGs are considered analogs of prostanoic acid, a structure with a 20-carbon and 5-membered ring. They fall into several classes designated by letters, indicating different substituents on the ring, alphabetically, in order of their discovery. The main classes are subdivided according to the number of double bonds on the side chain indicated by the subscript 1, 2, or 3.

The common precursors of PGs, TXs, and LTs are three naturally occurring eicosapolyenoic acids: trienoic (dihomo-γ-linolenic) acid, tetraenoic (arachidonic) acid, and pentaenoic acid (12). In man, tetraenoic acid (AA) is by far the most common, giving rise to the PGs of the subscript-2 series. It is either derived from dietary linoleic acid or ingested as a constituent of food. After absorption from the gut, it is esterified and present ubiquitously in the body as a component of phospholipids of cell membranes and of other complex lipids.

The hydrolysis of esterified AA provides the first rate-controlling step in PG formation. Dihomo-γ-linolenic acid, which has one less double bond than AA, gives rise to PGs of the subscript-1 series. Pentaenoic acid is very rare, derives from fatty acid with three double bonds, and is converted to PGs of the subscript-3 series.

In mammalian tissues, PGs and their precursor acids occur in appreciable quantities only in seminal, menstrual, and amniotic fluids. The precursor acids are present as phospholipids in cell membranes. A wide variety of divergent physical, chemical, and neurohormonal factors may activate the enzyme phospholipase A_2, setting free the precursor acids to gain access to enzyme complexes present in most tissues. Once released, fatty acids can follow two pathways: the cyclooxygenase pathway gives rise to the PGs and TXs, while the lipoxygenase pathway gives rise to the LTs and other unsaturated hydroxy acids. The metabolic pathway for AA and the structures of selected metabolites are shown in Figure 1.

The specific metabolites of the AA cascade formed *in vivo* vary according to the tissue and species. The first product of cyclooxygenase is an unstable cyclic endoperoxide derivative, PGG_2, which can proceed either spontaneously or by way of a peroxidase to PGH_2. PGH_2 is the common intermediate for TXA_2, PGD_2, PGE_2, $PGF_{2\alpha}$ and PGI_2. An endoperoxide isomerase can convert PGH_2 to either PGE_2 or its isomer PGD_2. The combined action of this isomerase and reductase yields $PGF_{2\alpha}$. In some tissues, a 9-keto-reductase catalyzes the interconversion of PGE_2 and $PGF_{2\alpha}$. PGE_2 may then undergo dehydration to PGA_2 and isomerization to PGB_2. In the plasma of some species, an enzyme isomerizes PGA_2 to PGC_2.

PGH_2 may be converted by prostacyclin synthetase into PGI_2, first discovered in the vascular wall. PGI_2 is unstable under physiological conditions, hydrolyzing to a stable compound, 6-keto-$PGF_{1\alpha}$ (12–14).

The other route of PGH_2 metabolism is to TXA_2, yet another unstable and highly active compound formed by an enzyme complex, thromboxane synthetase. TXA_2 is hydrolyzed nonenzymatically to the hemiacetal oxane TXB_2.

The details and significance of the lipoxygenase pathway are still under intensive investigation. As in the cyclooxygenase pathway, the first products formed are hydroxyperoxides (HPET), which are then converted by peroxidases to the corresponding hydroxides (HETE), giving rise to the LTs (15). (These products will not be discussed in this review.)

The chain of events leading to the release and metabolism of AA from the membrane phospholipids can be initiated by a number of factors: nerve stimulation, neurotransmitters (eg, norepineph-

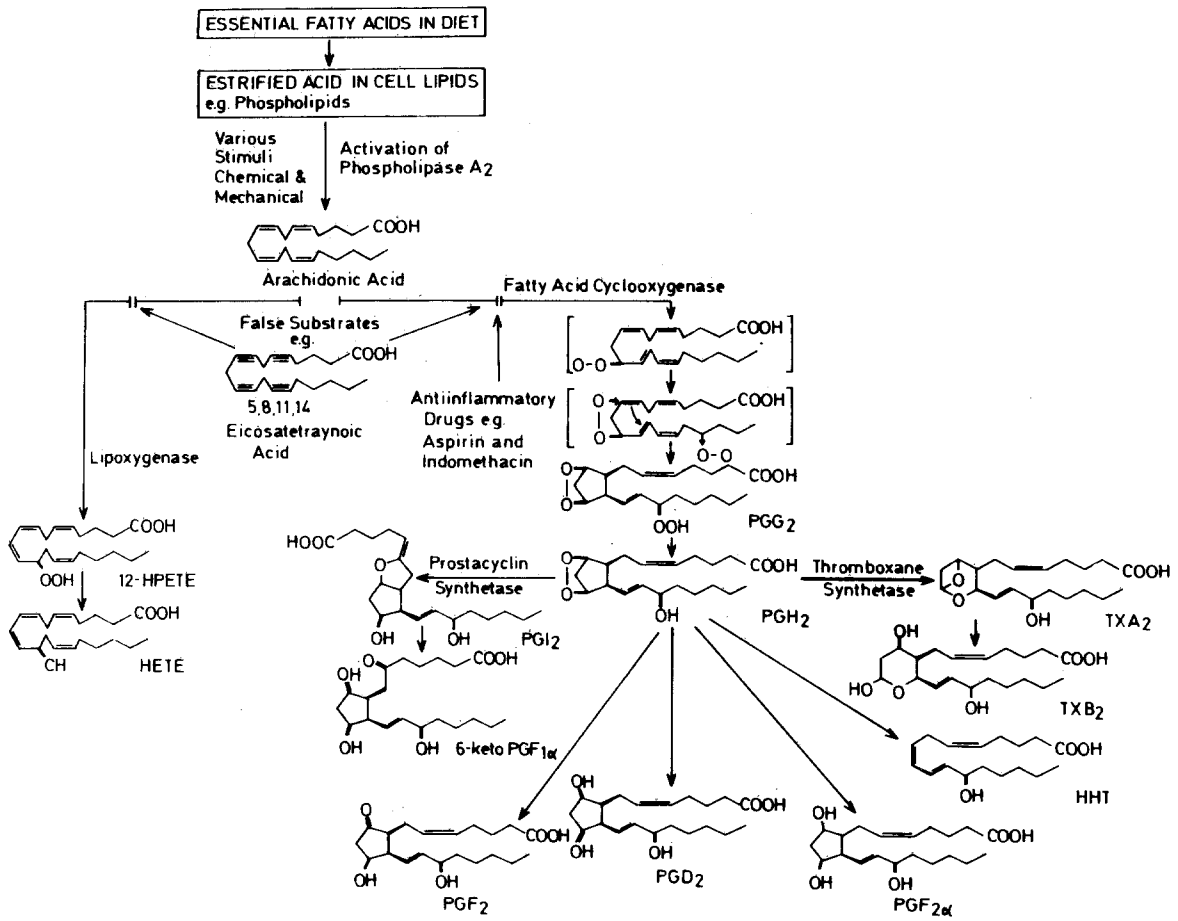

Fig 1. Biosynthesis of the products of arachidonic acid.

rine), neuropeptides (eg, somatostatin), various humoral agents (eg, bradykinin), hyperosmolar solutions, and even mechanical strain. Indeed, almost any deformation of cell membrane, such as stretching a blood vessel, inflation of the lung or contraction of the intestine, may lead to increased PG formation under physiological conditions (16–21). Numerous pathological conditions may increase PG or TX synthesis. Any damage of tissue, apart from frank trauma, increases the generation of cyclooxygenase products (22). Acute cardiac ischemia favors the synthesis of vasoconstrictor products over normal vasodilator metabolites of AA. Tissue injury from an anaphylactic reaction or edema may augment PG formation (eg, in the lungs) and may contribute to increased vascular permeability. Acute hypoxia or exposure to tobacco smoke in the lungs also increases PG synthesis.

Thus, many kinds of tissue injury may lead to increased generation of PGs and LT products (23). Breakdown of lysosomes will release, among other enzymes, phospholipases, which may hydrolyze AA from the membrane phospholipids.

Not all metabolites are formed in every tissue when AA is released; it depends on the most active enzymes in the tissue involved. All cells contain phospholipids and at least some cyclooxygenease and lipoxygenase. Most tissues seem able to synthesize PG endoperoxides from free AA, but the factors controlling their further steps have not been defined. Certain tissues (such as lung, spleen, gastrointestinal tract, thyroid, and adrenals) are able to synthesize the whole range of products, whereas other tissues predominantly produce PGD_2 (mast cells), PGE_2 (seminal vesicles), PGI_2 (vessel wall), or TXA_2 (platelets).

Antiinflammatory steroids appear to reduce PG biosynthesis by lowering the availability of the substrate acid to the cyclooxygenase or by blocking the efflux of PGs from their biosynthetic site (Figure 2). They seem to act by inducing the synthesis and release of proteins (lipomodulin) that possess

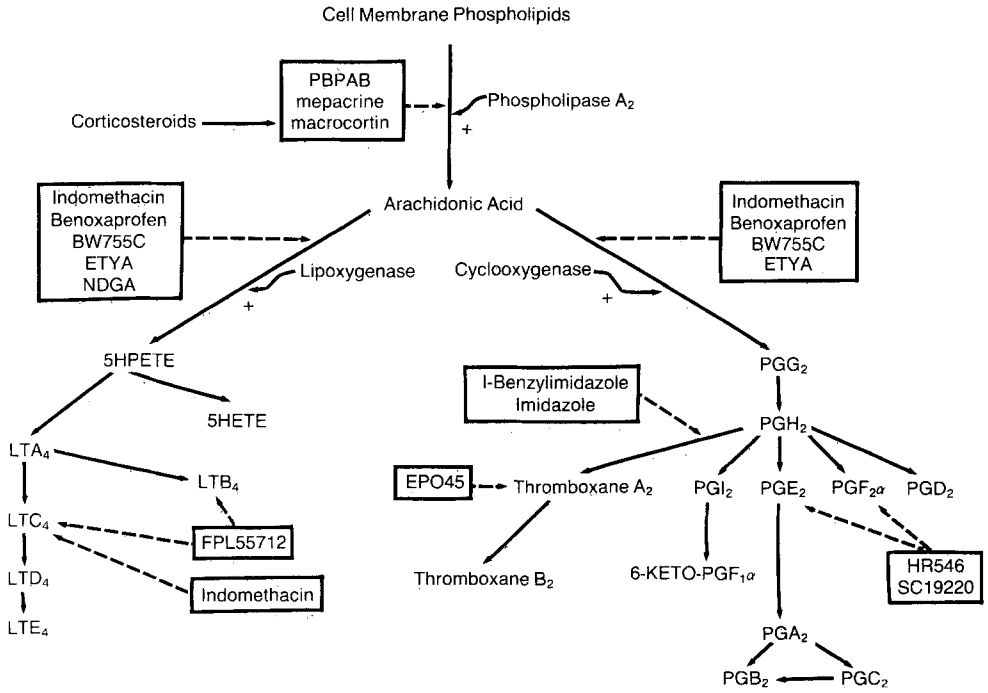

Fig 2. Cascade of arachidonic acid, showing blockade at different steps of metabolism.

antiphospholipase properties. Aspirin and related nonsteroidal antiinflammatory drugs (NSAIDs) are very potent inhibitors of PG biosynthesis; they work by preventing the production of PG endoperoxides. Vane (24) proposed that the inhibition of PG biosynthesis by NSAIDs may account for their therapeutic effects, and this has been confirmed by direct measurements of PGs in various tissues and fluids in animals and humans treated with conventional NSAIDs. The sensitivity of cyclooxygenase to NSAIDs varies from tissue to tissue (25). Unlike in other tissues, the biosynthesis of PG endoperoxides in platelets can be suppressed by low doses of aspirin, resulting in the reduction of TXA_2 formation, which may be useful in reducing TX biosynthesis in platelets without affecting PGI production by the vessel wall. Products of lipoxygenase are direct inhibitors of the cyclooxygenase pathway, suggesting the existence of a negative feedback relationship between these two pathways. Similarly, the inhibition of TX biosynthesis (eg, by imidazole derivatives) leads to increased formation of primary PGs (26).

Several efficient mechanisms catabolize and inactivate biologically active metabolites of AA. The PG intermediates, PGG_2 and PGH_2, are highly unstable, apparently existing only momentarily *in vivo*. PGs are rapidly inactivated, the first step being the oxidation of the C-15 hydroxyl group by 15-hydroxy-PG-dehydrogenase (PGDH). This enzyme is widely distributed in many tissues, especially the lungs; consequently, about 95% of PGs of the E and F series, but not D or I, are metabolized during a single passage through the lungs. The 15-keto compound is then reduced by a Δ^3 reductase (PGR) to the 13,14-dihydro Δ^3 derivatives. Subsequent beta-oxidation and omega-oxidation of the side chains causes further degradation, giving rise to the dicarboxylic acids in the urine. Both PGDH and PGR are intracellular soluble enzymes, so that the substrate must pass through the cell membrane before degradation can proceed. Natural PGE_2 and $PGF_{2\alpha}$ pass through the membrane and are quickly inactivated. In contrast, methylated PGs (eg, 16,16-dimethyl PGE_2) also cross the membrane but are not the substrate for PGDH; therefore, they are taken up by lung tissue and then slowly released unchanged into the circulation. This results in prolonged biological activity. PGI_2, which is the substrate for PGDH *in vitro* but not for transfer into lung cells, can pass unchanged from the venous to the arterial blood. Such selectivity in PG inactivation is not seen in the gastrointestinal mucosa or in the liver, where all natural PGs are inactivated on passage through the portal circulation. However, methylated PGs can escape inacti-

vation, being resistant to the mucosal or hepatic PGDH; they are active orally and, in part, act from the gastric lumen directly on the gastric glands. PGD_2 and TXA_2 are not degraded by PGD_2, although they possess a 15-hydroxyl group. TXA_2 is very unstable and spontaneously converts to TXB_2, which follows the catabolic route of other PGs. PGI_2 is also hydrolyzed spontaneously to inactive 6-keto-$PGF_{1\alpha}$.

PHYSIOLOGICAL FUNCTIONS AND PHARMACOLOGICAL PROPERTIES

The biological actions of PGs comprise a wide spectrum of effects. Some have directly opposing actions in many systems, and prostanoid-mediated control of cellular, tissue, or organ functions reflects the interactions between different PGs, TXs, and LTs.

Cardiovascular System and Platelets. The major cyclooxygenase product in the wall of all arteries and veins so far examined, and also in the microcirculation, is prostacyclin (27). The generating capacity for PGI_2 was found to be greatest in the endothelium, progressively decreasing toward the adventitia (28). *In vitro,* the endothelial cells are the most active producers of PGI_2 (29). Because of its resistance to inactivation in the pulmonary circulation, investigators have proposed that PGI_2 may function as a circulating hormone, but its biological instability suggests that it is most likely a local factor (30). Various data indicate that the vessel wall can synthesize PGI_2 not only from its endogenous precursors but also from PG endoperoxides released by the platelets, suggesting a biochemical cooperation between the platelets and the vessel wall. PGI_2 produced by the vessel is a strong vasodilator and also the most potent known inhibitor of platelet aggregation known (31) (Figure 3).

On the other hand, the major product of AA metabolism in platelets is TXA_2. It appears that when platelets are activated and the endogenous AA cascade is triggered, the PG endoperoxides thus generated are converted predominantly to TXA_2, the most potent stimulant of platelet aggregation known and a very strong vasoconstrictor. PGI_2 and TXA_2 show opposite effects on cyclic AMP concentrations in their target cells, thereby giving a balanced control mechanism affecting both the platelets and the vessels.

PGI_2 is not only the most potent inhibitor of platelet aggregation among the naturally occurring

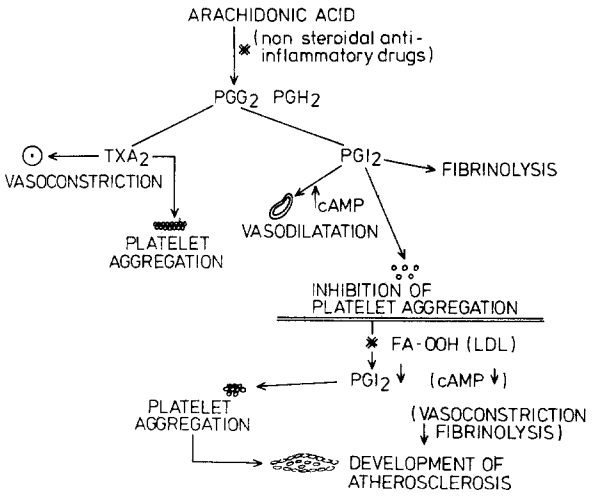

Fig 3. The interaction of TXA_2 and PGI_2 on platelet aggregation, vessel diameter, and fibrynolysis.

PGs, but also the most potent endogenous antiaggregating agent described. Since it is generated in large amounts by the endothelial cells, its likely physiological role is to inhibit platelet adhesion to the endothelium and the formation of thrombus. It can also inhibit the mobilization of fibrinogen-binding sites on human platelets *in vitro,* and thus may limit the extent of fibrinogen–platelet interaction. Furthermore, it may enhance fibrinolytic activity in the lung (31–33).

PGI_2 is a potent vasodilator in the mesenteric vascular bed, the gastric mucosal circulation (34), and in pulmonary (35), coronary (36), and renal (37) vessels. It is also active in the microcirculation and causes pronounced vasodilation of both large and small arteries. Because of the potent vasodilator activity in many microvascular beds, PGI_2 generation may be involved in the modulation of local blood flow and in the functional hyperemic responses of the tissues (38).

Since TXA_2 is highly unstable, studies of its vascular effects are difficult. TXA_2 causes an immediate and brief vasoconstriction in various vascular beds, such as the mesenteric and femoral vessels. As with platelet function, the directly opposing vasoactive properties of TXA_2 and PGI_2 may play an important role in the regulation of vascular tone and tissue blood perfusion under physiological and pathological conditions. Several diseases have been related to imbalance between PGI_2 and TXA_2 systems. In general, in thrombotic diseases (eg, arterial or venous thrombosis, or myocardial infarction), TXA_2 production is increased or PGI_2 generation is

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