Prostaglandins, Antidiuretic Hormone and Renin Angiotensin System

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SUMMARY Current knowledge on prostaglandin biosynthesis is reviewed, centering on how PGs participate in the regulation of vascular tone and the prevention of platelet deposition on endothelial surfaces. Discussion includes review of the vasoactivity of the PG endoperoxides, thromboxane, prostacyclin, and prostaglandin E; prostaglandin-catabolizing enzymes; polyunsaturated fatty acid precursors; nutritional factors; antidiuretic hormone; and interrelations of PGs with the renin-angiotensin system. (Hypertension 3 (suppl II): II-65-II-70, 1981)

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PROSTAGLANDINS (PGs), thromboxanes (Txs), and leukotrienes are compounds of high biological activity synthesized by all cells of the mammalian organism. The levels of PGs in biological fluids depend on experimental conditions and vary rapidly by the altering of salt and water uptake, environmental temperature, or under stress conditions. PG inhibitors are efficient in inhibiting the increase in PGs produced by endogenous or exogenous stimulus, but are not as efficient in blocking basal PG levels under normal conditions. In the in vitro system, a number of situations can drastically change the predominance of PGs, Txs, and leukotrienes, such as cofactors added to culture medium, the amount of substrate or the preparation of the specimen, i.e., slices, homogenates, or microsomal fractions. This paper reviews the current knowledge on prostaglandin biosynthesis.

Review

It has been demonstrated that PGs, synthesized by vascular tissues, partake in the regulation of vascular tone and the ability of endothelial surfaces to repel the deposition of platelets. Current evidence points to PGs (mainly PGE2) as local vasoactive hormones capable of influencing renal hemodynamics and salt and water excretion. The synthesis of renal PGs is enhanced by the kinins, and PGs actively stimulate the renin-angiotensin system and antagonize the ADH effect on the collecting duct by inhibiting cAMP formation.

Prostaglandin Endoperoxides

Prostaglandin endoperoxides, PGG2 and PGH2, formed enzymatically by the incorporation of oxygen into arachidonic acid (AA), are the immediate precursors of vasoactive substances arising through enzymatic transformation of endoperoxides in several tissues (fig. 1). Three major products of PG endoperoxides have been identified in blood vessels; these differ from each other in their biological properties as well as in their distribution in vascular tissues.

1. Thromboxane (TxA2). Primarily generated by aggregating platelets, TxA2 constricts blood vessels and aggregates platelets.
2. Prostacyclin (PGI2). The principal product of most vascular tissues, PGI2 is antiaggregatory and relaxes blood vessels.
3. Prostaglandin E2 (PGE2). PGE2 is also synthesized by blood vessels but differs from PGI2 in several ways, including its effect on platelet aggregation, renin release, salt and water excretion, and possibly in its ability to modulate the cardiovascular and renal effects of vasoactive hormones.

In contrast to other PGs, PGI2 passes through the pulmonary circulation without losing its biological activity, suggesting that PGI2 may function as a circulating hormone. The recent findings by Gryglewski et al. and Moncada et al. that there is a continuous synthesis and release of PGI2 from the lung in vivo, suggest that PGI2 acts as a circulating antiaggregatory agent, possibly through its capacity to increase cAMP. Whether PGI2 escapes pulmonary degradation is still a matter of discussion. We have evidence that PGI2 decreases considerably on passage through the fetal lung, whereas concentrations of PGI2 in inferior vena cava blood fall after ventilation and ligation of the umbilical cord, indicating net production of PGI2 by the newly ventilated lung.
Previous studies demonstrated that vascular and extravascular synthesis of PGs play a significant role in the control of blood pressure and local blood flow. Thus, the capacity of blood vessels to synthesize PGs intramurally allows these local hormones to influence vascular tone and reactivity directly by affecting the vasoconstrictor actions of angiotensin II and catecholamines, and by modulating the release of noradrenaline from adrenergic nerves.

Prostaglandin-Catabolizing Enzymes

Two major PG-catabolizing enzymes have also been reported to be present in blood vessels: 15-hydroxy-PG-dehydrogenase, which catalyzes the first step in PG degradation, and PGE 9-ketoreductase, which converts PGE to PGF. The latter can be activated in mesenteric blood vessels by vasoactive hormones. In some tissues, stimulation of PG synthesis in the presence of an activated PGE 9-keto-reductase could result primarily in pressor effects.

Polyunsaturated Fatty Acid Precursors

The synthesis of PG is often limited by the availability of a polyunsaturated fatty acid precursor, such as AA. However, these fatty acids must be in their free form; when esterified in complex tissue lipids, they are ineffective. Since the tissue phospholipids are the richest source of the precursor polyunsaturated fatty acids, it has long been suspected that the intrinsic phospholipases of the cell are essential parts of the sequence of events involved in PG biosynthesis. There is evidence suggesting that the enzyme responsible for the release of fatty acid precursors for PG biosynthesis could be phospholipase A.

In a number of tissues, arachidonate is released by the action of enzymes other than phospholipase A. In the ovary, for example, there is a high concentration of cholesterol ester containing PG precursor acids and a cholesterol esterase that can be stimulated by luteolytic hormones, leading to PG synthesis. In fat tissue and rabbit heart, a hormone-sensitive lipase may provide substrate for PG formation.

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**Figure 1.** Flow chart showing the pathways of prostaglandin biosynthesis.
Evidence has been furnished that the mechanism for arachidonate release from thrombin-stimulated human platelets involves two enzymes: a phosphatidilylinositol-specific phospholipase C, and diglyceride lipase, which specifically hydrolyzes esterified arachidonate at the C-2 position of the diglyceride. These studies demonstrate that decreased activity of phospholipase or availability of a specific lipid for PG synthesis may result in an impairment of vasoactive substances derived from AA, including cyclic endoperoxides, Txs, PGIs, and other metabolic products. It is apparent that studies on the mechanism and regulation of phospholipases in blood vessels, kidney, and other organs are lacking, and that factors controlling the release of arachidonate for PG synthesis in the vascular wall and other tissues are poorly understood.

It is likely that one or more of the aforementioned factors leading to PG synthesis will prove to be of great importance in regulating regional blood flow and vascular reactivity. We have evidence that high sodium intake in Dahl salt-sensitive and salt resistant rats modifies the activity of vascular and renal phospholipases.

However, most studies have neglected the phospholipases and the phospholipid pools, key factors in the regulation of the AA cascade, despite the well-known effect of angiotensin,[39, 40] catecholamines,[41] bradykinin,[42] and ADH[43] on phospholipase activity and arachidonic acid release. Consequently, only studies designed to explore the complete cascade of AA from acylation and deacylation to the total spectrum of metabolites will provide understanding of the dynamic interaction of PGs with vasoactive hormones.

**Nutritional Factors**

Based on the previous observations and because of the close interaction of PGs with the major blood pressure regulatory systems, it is important to carry out studies on the role of nutritional factors in the phospholipid precursor pools, cyclic endoperoxides, isomerization to the various PGs, and final metabolism into compounds identifiable in plasma and urine.

A recent comparative study performed on the Danes and the Eskimos of Greenland demonstrated delayed atherosclerosis and a low incidence of myocardial infarction in the Eskimo, and more susceptibility to vascular disease in the Dane, suggesting that the development of vascular disease might possibly be modified through diet.[44] The most important difference between Eskimos and Danes is the principal polyunsaturated fatty acid found in the diet and in lipid fractions of blood. Eicosapentaenoic acid is predominant in the Eskimo and arachidonic acid in the Dane. These differences in fatty acid, perhaps, account for the susceptibility or resistance to vascular disease among both populations. TXA₂, an eicosapentaenoic acid derivative, is reportedly unable to cause platelet aggregation.[45] On the other hand, PGI₃ maintains its antiaggregatory activity, as does PGI₁.

These studies offer the possibility that manipulation of polyunsaturated fatty acid intake and metabolism could lead to a prophylactic measure for the control of blood pressure and vascular disease.

**Prostaglandins and Antidiuretic Hormone**

PGs have been postulated to affect renal responses to ADH. PGE₃ has been shown to antagonize the increase in water permeability induced by ADH,[46] an effect mediated through the inhibition of ADH-increased cAMP. This enzyme inhibition has been demonstrated using low doses of PGs in toad bladder, rabbit renal collecting duct in vivo,[47, 48] and in the rat and hamster renal medulla.[49, 50] at high concentrations of PG, this effect was not apparent.[51]

The phospholipase inhibitors, meperidine and adrenal steroids,[52] as well as PG synthesis inhibitors, indomethacin, meclofenamate and aspirin, enhance vasopressin's effect on water reabsorption in several species, including humans.[53, 54]

PG biosynthesis is enhanced by vasopressin in renal medullary interstitial cell culture,[55] as well as in the Brattleboro vasopressin-deficient rat, as indicated by the increase in PG excretion[56, 57] and in vivo anesthetized rabbits.[58] Vasopressin stimulation of PGE synthesis can be inhibited by meperidine, a phospholipase inhibitor which decreases the availability of the substrate, suggesting that the mechanism of action of vasopressin is through the activation of phospholipases, increasing the release of AA and, subsequently, the PG formation.[59] Adrenal steroids enhance the vasopressin-stimulated transmembrane water flow indirectly through the inhibition of AA-PGE₂ release. It is clear that PGE can regulate ADH effects in water flow, but what makes this a particularly important mechanism is the fact that hormonal regulators of phospholipase activity serve as endocrine control of water reabsorption.

PGs also stimulate vasopressin release from the central nervous system. Intracarotid, intracisternal, and intravenous infusion of PGE₂ and PGE₃ in rats and dogs increase ADH release.[55, 56] Furthermore, the antiuretic effect produced in dogs by intravenous administration of PGE₂ could be inhibited by hypophysectomy.[57]

The physiological control of ADH appears influenced by hormones capable of regulating phospholipase activity. Bradykinin, angiotensin II, and adrenal steroids are ideal candidates for this function since they are capable of regulating the release of fatty acid substrate for PG synthesis, controlling through this PG-mediated mechanism the effect of ADH on water reabsorption (fig. 2).

**Interrelation of PGs with the Renin-Angiotensin System**

PGs regulate renin release from the kidney, as well as modulate the action of angiotensins.

There are regional differences in PGs in the kidney; vascular tissues synthesize primarily PGI₃, whereas
Figure 2. Schematic interaction of PGE, with antidiuretic hormone. PL = phospholipids; AA = arachidonic acid; PGE, = prostaglandin E,; ADH = antidiuretic hormone; ATP = adenosine triphosphate. Solid line with arrow represents stimulation; broken line with arrow represents inhibition.

PGE, is the predominant renomedullary PG. The effect of PGs on renin release was first demonstrated by Larsson et al. in 1974, who showed an increase in plasma renin activity following AA administration into the rabbit renal artery. This effect can be prevented by indomethacin.

The PG influence on renin release is not independent of tubular, neural, or mechanical factors; it may represent the final common pathway for the expression of multiple signals influencing renin release.

PGI, is the major product of AA metabolism in all renal blood vessels examined, including interlobular and afferent arterioles. It has been proposed that renal cortical formation of PGI, may influence renin secretion. This finding raises the possibility that AA metabolites from the cortical blood vessel influence renin release directly by stimulation of juxtaglomerular cells, or indirectly by interaction with adrenergic transmission and other vasoactive hormones acting at the level of the vascular wall of the afferent arteriole.

These properties of PGs, especially the E, series in the kidney, which antagonize the vasoconstrictor effect of pressor stimuli, have been clearly demonstrated in the anesthetized dog during intraarterial infusion of angiotensin II. PG synthetase inhibitors substantially potentiated the vasoconstrictor and antidiuretic effects of angiotensin.

The interactions of PGs with the renin-angiotensin system serve as a primary defensive mechanism that protects local blood flow in the face of increased activity of the renin-angiotensin system. In the dog subjected to the stress of anesthesia and laparotomy, PGE, levels in renal venous blood greatly increased and positively correlated with the plasma renin levels. The contribution of PGs in supporting the renal circulation following stimulation of the renin-angiotensin by acute stress was demonstrated by the inhibition of PG synthesis. Administration of indomethacin to the stressed animal caused a precipitous reduction in renal blood flow, which correlated with a decline in the efflux of PGE, into the renal vein. In contrast, in the resting dog not subjected to trauma, administration of indomethacin did not affect renal blood flow or renal venous PG. This observation indicates that renal circulation is maintained under stress conditions by a major PG component, abolition of which results in a rapid decline of renal blood flow.

The intrarenal blood flow distribution is also dependent on a PG mechanism providing another example of their generally accepted role as local hormones. These studies indicate that activation of the renin-angiotensin system cannot necessarily result in the elevation of blood pressure unless other PG-dependent mechanisms that contribute to the circulatory regulation are compromised.

Most of the controversies and difficulties in studying the PG system derive from the lack of methods to analyze concomitantly, in the same biological sample, all the products of AA cascade, including PGs and their metabolites. The use of PG synthesis inhibitors to investigate the role of PGs is very unspecific and requires qualitative and quantitative analysis of the AA products to assess inhibition. The lack of relevant measurement of PG parameters often yields to no more than a descriptive effect of a pharmacologic agent. The use of PG synthetase inhibitors, or intravascular infusion of PGs, has severe limitations; both maneuvers affect a number of physiologic processes, and the infusion of various chemically synthetized PGs in several vascular beds stimulates the production of endogenous PGs. The potential contribution of endogenous PGs to the changes under investigation could be of significant importance.

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