CHAPTER 24

Prostacyclin production by endothelial cells

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Introduction

In the early 1970's prostaglandins (PG) became recognized as important modulators of many physiologic functions including the local control of vascular tone. In 1975, while studying the role of the vessel wall in hemostasis, two independent groups of investigators noted that the vessel wall produced a material from arachidonic acid which was an extremely potent vasodilator and inhibitor of platelet aggregation (1-5). Moncada and colleagues initially called this substance PGX (1). The structure of PGX was subsequently identified and the compound renamed prostacyclin (PGI_2) (6). PGI_2 was demonstrated to be more potent than the classical prostaglandins in both its vasodilatory and platelet inhibitory actions (1, 3, 4, 7), and was subsequently shown to inhibit platelet aggregation by stimulating the synthesis of cAMP (8, 9).

It was then demonstrated that PGI_2 was the major vascular metabolite of arachidonate (6, 10) and Moncada et al. showed that of the various tissues of the vascular wall, the intima had the highest capacity to generate PGI_2 (11). At the same time, Weksler, Marcus and Jaffe demonstrated that cultured human and bovine endothelial cells synthesized PGI_2 (12) and that PGI_2 was also the major identifiable metabolite of arachidonate produced by endothelial cells (12, 13).

These findings led immediately to the hypothesis, now much embellished, that platelets and endothelial cells were natural antagonists with many opposing actions (Fig. 1). By secreting PGI_2, endothelial cells both maintain fluidity of the blood (by preventing platelet activation) and induce vasodilation. By secreting thromboxane (TXA_2), which stimulates platelet aggregation and induces vasoconstriction, platelets counter the effect of PGI_2 (1-5, 8–17). Because of the possible role of platelets and platelet-derived growth factor in the development of atherosclerosis (18), the ‘balance hypothesis’ has been extended to include atherogenesis as an expression of the interaction of platelet and endothelial PG products. Further, there is very recent evidence that the ratio of TXA_2:PGI_2 may determine the incidence of arrhythmias in myocardial ischemia – TXA_2 being arrhythmogenic and PGI_2 being antiarrhythmic (19).

Thus, there is substantial interest in the physiology and pathophysiology of endothelial cell PGI_2 production. This chapter will review what is known about the induction and regulation of endothelial cell PGI_2 synthesis by both naturally occurring substances and pharmaceuticals and also how this regulation may be altered in a variety of diseases.

Physiologic control of PGI_2 synthesis

In this section, we will show that endothelial cell PGI_2 synthesis may be modulated by a variety of biological materials and therefore may play a role in the local control of coagulation, vascular tone,
ENDOTHELIAL CELL - PLATELET BALANCE HYPOTHESIS

![Diagram of the hypothesis]

**Fig. 1.** Endothelial cell-platelet balance hypothesis. Arachidonic acid is converted to the cyclic intermediates PGG₂ and PGH₂ by the enzyme cyclo-oxygenase. This is blocked by aspirin (1). In endothelial cells PGH₂ is converted to PGI₂ by PGI₂ synthetase which is blocked by 15-hydroperoxyarachidonic acid (2). In platelets, PGH₂ is converted to TXA₂ by TXA₂ synthetase which is blocked by imidazole (3). The proposed effects of altering the ratio of PGI₂:TXA₂ toward excess of either product are listed.

and inflammation. A number of naturally occurring hormones, enzymes, peptides, and proteins have been tested to determine whether they induce or inhibit endothelial cell PGI₂ synthesis (Table 1). PGI₂ synthesis by endothelial cells in tissue culture can be demonstrated using several different assays including the inhibition of platelet aggregation or platelet serotonin release (12, 13, 20), the bioassay cascade (21), radioimmunoassay for the stable hydrolysis product of PGI₂, 6-Keto-PGF₁α (22), or combinations of thin-layer (12, 13), high-pressure-liquid, or gas chromatography and mass spectroscopy (6, 23). Further, as shown in Figure 1, the synthesis of PGI₂ should be inhibited by both aspirin (24) (a cyclooxygenase inhibitor) and 15-hydroperoxyarachidonic acid (a prostacyclin synthetase inhibitor) (2, 25). The results of a typical experiment demonstrating these findings are shown in Figure 2.

Weksler, Ley and Jaffe first demonstrated (20), and others have since confirmed (26, 27) that thrombin induces PGI₂ synthesis in human umbilical vein endothelial cells. They proposed that this synthesis may represent a physiologic control mechanism which would limit thrombus formation at a site of vascular injury. Endothelial cells become refractory to repeated thrombin stimulation and this may have physiologic significance (20, 28). Thrombin-inducible PGI₂ synthesis is apparently both species and site specific because while Hong has confirmed that human umbilical vein endothelial cells respond to thrombin, she showed that endothelial cells from calf or pig aorta do not respond to either human or bovine thrombin (27). Goldsmith and Kisker subsequently showed that though thrombin stimulated PGI₂ production by fetal sheep umbilical vein, thrombin did not affect PGI₂ production by fetal sheep aortic segments (29).

The mechanism of thrombin-induced PGI₂ synthesis is unclear. Putative thrombin binding sites on endothelial cells have been demonstrated in sev-