6-KETO-PROSTAGLANDIN E_1:

BIOSYNTHESIS AND CIRCULATORY EFFECTS

Eric G. Spokas, John C. McGiff
and Patrick Y-K Wong

Department of Pharmacology
New York Medical College
Valhalla, New York 10595

The changes in circulatory function induced by 6-keto-prostaglandin E_1 (6-keto-PGE_1) bear a close resemblance to the changes caused by prostacyclin (PGI_2). Like PGI_2, 6-keto-PGE_1 is potent in stimulating renin secretion [1-3], inhibiting platelet aggregation [4], and reducing blood pressure and vascular resistance in diverse regional circulations [5, 6]. In this chapter, we present evidence that 6-keto-PGE_1 may arise during the course of metabolic transformation of PGI_2 through the activity of 9-hydroxyprostaglandin dehydrogenase (9-OH PGDH) identified in various tissues, including liver, blood platelets, and renal cortex. As PGI_2 is unstable, having a half-life of approximately 3 min in aqueous solution [7], the identification of an active and stable metabolite of prostacyclin has important implications for understanding the time-dependency of prostacyclin-induced physiologic responses. In contrast to PGI_2, when 6-keto-PGE_1 is incubated in aqueous solution at pH 7.4, 37°C its platelet antiaggregatory activity remains undiminished for at least 20 min [3].

Prostacyclin and 6-keto-PGE_1 differ from the primary prostaglandins, PGE_2 and PGF_2α, in that they largely escape metabolism on passage across the pulmonary vascular bed [5], a property required for a circulating hormone. Less than 15% of PGI_2 was metabolized during one passage across the lungs; this is probably due to the low affinity of PGI_2 for the transport system of the lung as PGI_2 is rapidly metabolized by the major pulmonary degradative enzyme 15-hydroxyprostaglandin dehydrogenase (15-OH PGDH) in a cell-free preparation [8]. Between 35% to 65% of infused prostacyclin was estimated to be inactivated systemically on one circulation, presumably due to metabolism during transit through the liver, hind-
quarters, and kidney [9]. In the study of Quilley et al. [5], the effect of 6-keto-PGE₁ on blood pressure and renal blood flow in rats was shown to be equipotent by either the intravenous or intraaortic route of administration. Further, their results suggested that the duration of 6-keto-PGE₁-induced hypotension may be longer than that of PGI₂.

There are several reports of sustained biological activity of PGI₂ that are difficult to explain in view of its inherent instability. In human subjects inhalation of PGI₂ resulted in prolonged resistance of platelets to the proaggregatory action of ADP [10]. In studies using the hamster cheek pouch, ADP-induced thrombosis formation did not recover until 30 min after the infusion of PGI₂ had been stopped [11]. After addition of PGI₂ to slices of renal cortex, the release of renin was stimulated for more than 30 min [12]. These observations and similar reports are consistent with transformation of PGI₂ to a more stable substance having prolonged effects on platelet aggregation and renin secretion. As an explanation for such findings, we suggest that in certain tissues 6-keto-PGE₁ may be generated from either prostacyclin or from the hydrolysis product of prostacyclin, 6-keto-PGF₁α, via the 9-OH PGDH pathway. First demonstrated in the liver [13], this enzyme will catalyze the oxidation of the 9-OH group of 6-keto-PGF₁α to a ketone, a function similar to the enzymatic activity that converts PGF₂α directly to PGE₂. As the liver is a major site of PGI₂ clearance, the generation of a stable active metabolite of prostacyclin within the liver may be of considerable importance for cardiovascular homeostasis. However, the capacity of the renal cortex to synthesize 6-keto-PGE₁ has also been shown [3], and we speculate that under some conditions the kidney may contribute to circulating levels of 6-keto-PGE₁ as has been suggested for prostacyclin [14]. The possibility that 6-keto-PGE₁ may be an endogenous mediator of renin release from the kidney will be discussed at some length as we have recently found major differences in the in vitro renin response to PGI₂ and 6-keto-PGE₁. Before discussing the role of 6-keto-PGE₁ as a putative mediator of renin secretion, those studies which indicated its formation from PGI₂ in liver and platelets will be considered.

HEPATIC METABOLISM OF PGI₂

The generation of an active metabolite from PGI₂ was first suggested during our study of PGI₂ metabolism in the isolated perfused liver of the rabbit [13]. Hepatic metabolism of infused [9⁻³⁴S]PGI₂ was shown by a radiometric method followed by gas chromatography-mass spectroscopy (GC-MS) to be extensive, primarily through 8-oxidation and oxidative decarboxylation, resulting in the formation of dinor (C₁₀) and pentanor (C₁₅) metabolites of PGI₂ (Fig. 1). In the liver, unlike blood vessels [15], 15-OH PGDH activity was not found. Of the total radioactivity recovered in the liver perfusate, 7% was found