A Two-Receptor Model for the Mechanism of Action of Prostaglandins in the Renal Collecting Tubule

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1. INTRODUCTION

Studies on the mechanism of action of steroid hormones have led to the concept that different steroids act through different receptors present in different target cells to elicit a common biochemical response, namely, regulation of transcription. One might presume that different prostaglandins also operate through different receptors to cause some common response. However, this response is still not defined. In this chapter we summarize our recent studies on the metabolism and function of prostaglandins by the renal collecting tubule (Garcia-Perez and Smith, 1983, 1984). Our major focus is to describe the development of a two-receptor model for the actions of prostaglandins in these cells.

Briefly, we propose that prostaglandins operate in the collecting tubule through two distinct receptor populations having different specificities to elicit two different biochemical responses. Binding of a prostaglandin to one type of receptor (type I) leads to the activation of adenylate cyclase and rapid elevation of cAMP levels in collecting tubule cells. We suggest that this increase in cAMP leads to inhibition of the release of arachidonic acid from phosphoglycerides. Thus, occupancy of this type I prostaglandin receptor leads to feedback inhibition of prostaglandin formation. A second type of prostaglandin receptor (type II) in collecting tubule cells is coupled
to the desensitization of adenylate cyclase to circulating hormones. The major circulating hormone to which collecting tubules respond is antidiuretic hormone (ADH).

2. RESULTS AND DISCUSSION

2.1. Renal Collecting Tubules as a Model for Studies of the Mechanism of Prostaglandin Action

We begin our discussion of the mechanism of action of prostaglandins in collecting tubules by indicating why these cells are an appropriate model for looking at a physiological action of prostaglandins. Diagrammed in Fig. 1 are the major functional units of the kidney and the cellular sites at which prostaglandins are formed by the kidney. The renal collecting tubule is the terminal part of the tubule. Immunocytochemical studies in our laboratory (Smith and Bell, 1978; Smith et al., 1979) and microdissection studies by Currie and Needleman (1982) have demonstrated that the thin limb and the collecting tubule are the only sites of prostaglandin synthesis in the renal tubule. Thus, collecting tubules are clearly capable of producing prostaglandins.

Early studies by Grantham and Orloff (1968), which have since been confirmed by many other workers (Handler and Orloff, 1981), have established that addition of low concentrations of PGE$_2$ (ca. $10^{-9}$ M) inhibits the hydroosmotic effect of ADH on rabbit cortical collecting tubules in vitro. That is, treatment of isolated perfused collecting tubules with PGE$_2$ prevents the ADH-induced transcellular movement of water from the lumen of the tubule to the surrounding interstitium. This hydroosmotic effect of ADH is known to be mediated by cAMP (Handler and Orloff, 1981). However, Grantham and Orloff demonstrated that PGE$_2$ does not prevent the hydroosmotic effect of cAMP itself, suggesting that PGE$_2$ inhibits ADH-induced cAMP formation. Paradoxically, Grantham and Orloff found that high concentrations of prostaglandins (ca. $10^{-7}$ M), when used alone, actually cause a hydroosmotic effect in rabbit collecting tubules.

Inhibition of the hydroosmotic response to ADH by PGE$_2$ is not simply a pharmacological curiosity observed with isolated perfused tubules but also appears to occur in vivo. Animals treated with cyclooxygenase inhibitors or subjected to essential fatty acid deficiency produce a hyperosmotic urine (Anderson et al., 1975; Fejes-Toth et al., 1977; Hansen, 1981). Moreover, the medullas of rats fed with cyclooxygenase inhibitors contain elevated levels of cAMP (Lum et al., 1977). One would expect these results if no prostaglandins were being produced by the collecting tubule to blunt the cAMP-elevating effect of ADH. The fact that collecting tubules form prostaglandins, coupled with evidence that prostaglandins inhibit the hydroosmotic response of ADH both in isolated tubules and in intact animals, argues strongly that prostaglandins normally play a physiological role in modulating the response of collecting tubule cells to ADH.