INTRODUCTION

The biosynthetic capacity of the mammalian kidney to produce prostaglandins is exceeded only by the seminal vesicles. Although the medulla is the major site of synthesis in the kidney, an appreciable and physiologically important synthesis also occurs in the glomeruli, arterioles and collecting ducts. Aspirin and the non-steroidal anti-inflammatory (NSAI) agents are potent inhibitors of prostaglandin synthase. Vane suggested that most of the side effects produced by this class of drugs were a consequence of the decreased tissue production of specific prostaglandins, which normally exerted protective effects. It has since been assumed that the renal toxicity of NSAIs arises from the inhibition of renal prostaglandin production. Accordingly, renal prostaglandins should also protect the kidney from the effects of non-NSAI drug or disease-induced renal damage. In recent years other metabolites of arachidonic acid have been discovered with a wide range of biological activities. The diversity of products complicates our understanding of their role in renal function, especially when we try to explore their role in nephrotoxicity. In this chapter our present understanding of the function of the renal prostaglandins will be reviewed, and related to various animal models of nephrotoxicity and human renal disease.

RENAL EICOSANOIDs

Prostaglandins are autocoids (local hormones) which are synthesized near their site of action and then enzymatically inactivated. Arachidonic acid is the major substrate for the synthesis of prostaglandins. This essential fatty acid is an important constituent of cell membrane phospholipids, where it is present in high concentrations. Arachidonic acid can be released by the action of
of two calcium-dependent phospholipases; phospholipase A2 which acts on phosphatidylcholine and phospholipase C which acts on phosphatidylinositol. The two major pathways for the conversion of the arachidonic acid to prostaglandins and other products are shown in Figure 1. In recent years these products have been termed eicosanoids, and include all the oxygenated products of arachidonic acid produced both from the cyclo-oxygenase and lipoxygenase pathways. More recently a series of epoxygenase enzymes have been identified in the cells of the thin ascending limb of Henle which form a series of stable arachidonic acid epoxides and their related dihydroxy-arachidonic acids. Since the biological actions of these products have not yet been fully defined, they will not be discussed.

The cyclo-oxygenase enzyme converts arachidonic acid to two very potent endoperoxides, PGG2 and PGH2. Although these two compounds have biological activities their physiological importance is that they are short-lived intermediates, with a half-life of several minutes, and are substrates for the three different enzymes which form the prostaglandins (PGE2, PGD2 and PGF2α), the thromboxanes (TxA2) and prostacyclin (PGI2).

The isolation and identification of PGE2 and PGF2α from rabbit renal medulla was first reported by Lee et al. Although PGF2α is a potent vasoconstrictor in other organs, it has no effect on blood flow in the kidney, and no renal role has been found for it to date. The major haemodynamic action of PGE2 in the renal medulla arises from its profound vasodilatation of blood vessels and its ability to modulate the effect of vasoconstrictor stimuli. Prostaglandin E2 is also involved in the regulation of sodium and chloride excretion, and in the modulation of water excretion.

The two major sites of medullary synthesis of PGE2 are the interstitial cells and the collecting tubules, both of which synthesize very large quantities of this stable prostaglandin. In addition, the medullary microvasculature synthesizes much smaller quantities of prostacyclin.

The pattern of synthesis of eicosanoids in the cortex is different both qualitatively and quantitatively. Depending on the species the cortex produces between 1 and 10% of the quantities of PGE2 and PGF2α synthesized by the medulla. The most important difference involves the cortical glomeruli. Human glomeruli synthesize PGI2 predominantly, in contrast to rat glomeruli which produce more PGE2 than prostacyclin. The most important role of this glomerular prostacyclin is the stimulation of renin secretion by the juxtaglomerular cells. The cortical collecting duct produces mainly PGE2 and the arterioles produce prostacyclin. These smaller quantities of PGE2 and PGI2 probably contribute to the control of cortical blood flow and glomerular filtration rate.

### EFFECT OF NSAIs ON RENAL FUNCTION

Experiments in anaesthetized dogs showed a relationship between renal blood flow and synthesis of renal of PGE2 as measured in the renal venous blood, but Zins did not observe changed renal blood flow in indomethacin-treated, conscious dogs. Neither in-

---

360