Renal Endocrinology

Edited by
MICHAEL J. DUNN, M.D.

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Renal Endocrinology

This book is dedicated to my wife, Patricia,
and to my children,
Kathleen, Brian, Michael, Margaret, and Colleen.

Preface

The scientific disciplines of endocrinology and nephrology overlap in many areas. Although endocrinologists have traditionally concerned themselves with the physiology and pathophysiology of hormones, over the last decade there has been increasing scientific interest, on the part of nephrologists as well as renal physiologists and pharmacologists, in hormones produced by the kidney and in nonrenal hormones acting on the kidney. In addition, there has been increased attention and recognition given to autacoids such as prostaglandins and histamine which are produced in the kidney, act locally and, hence, are not considered hormones. It has also become quite clear that the kidney has a major catabolic and excretory role in the disposition of both nonrenal and renal hormones.

The purpose of this book is to authoritatively review the biochemistry, physiology, pharmacology and clinical pathophysiology of hormones and autacoids produced in the kidney and nonrenal hormones which have a significant action on the kidney. Each chapter is introduced with a basic scientific summary which serves as a background to discuss clinical derangements of hormonal action in the kidney or in the patient with renal failure. Finally, there is a chapter reviewing the renal catabolism of hormones in both health and disease. This is an initial attempt to summarize an important area, namely renal endocrinology. Hopefully, this text will have equal appeal to renal specialists and endocrinologists as well as to basic scientists who have a significant interest in the physiology, pharmacology and biochemistry of the kidney.

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Contents

SECTION 1

Hormones and Autacoids Produced in the Kidney

CHAPTER ONE

Renal Prostaglandins

MICHAEL J. DUNN, M.D.

Since the discovery in 1967 of renal medullary synthesis of prostaglandin E_2 (PGE_2) (1, 2) there has been incredible progress in the advancement of our understanding of renal prostaglandin biochemistry. The terminology of these biochemical processes is straightforward. The term "eicosanoids" refers to all oxygenated products of arachidonic acid (eicosatetraenoic acid) including prostanoids from the cyclo-oxygenase pathway and hydroxy fatty acids and leukotrienes from the lipoxygenase pathway. Prostanoids are those compounds, including prostaglandins and thromboxane, formed by cyclo-oxygenation of arachidonic acid, whereas leukotrienes and hydroxy fatty acids are lipoxygenase products of arachidonic acid oxygenation. The dienoic prostaglandins (i.e., two double bonds) are derived from arachidonic acid and have a subscript of 2. The monoenoic and trienoic prostaglandins, which are scarcely present, have subscripts of 1 and 3, respectively, and are derived from dihomo-γ-linolenic and eicosapentaenoic acids, respectively. Figure 1.1 is a summary of these pathways. Figure 1.2 presents more detail, particularly the chemical structures of the known eicosanoids except the leukotrienes. All the compounds shown in Figure 1.2 can be synthesized by renal tissue. Stimuli of renal prostaglandin synthesis generally activate an acylhydrolase, particularly phospholipase A_2, thereby providing arachidonic acid to the cyclo-oxygenase enzyme. Aspirin, indomethacin, meclofenamate and other nonsteroidal anti-inflammatory drugs inhibit the cyclo-oxygenase enzyme. Prostaglandins formed within renal cells are secreted, rather than stored intracellularly, and are thought to act locally, hence the reference to prostaglandins as autacoids. Prostaglandins are rapidly metabolized within the kidney and are also secreted into renal venous blood or excreted in the urine. Synthesis in different sections of the kidney and at different sites of the nephron varies substantially. Prostaglandin biochemistry (3) and renal prostaglandin biochemistry (4) have been expertly reviewed.

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BIOCHEMISTRY OF RENAL PROSTAGLANDIN SYNTHESIS

The Role of an Acylhydrolase or Phospholipase

Prostaglandin synthesis in the kidney, like prostaglandin synthesis in other organs and cells, is critically dependent on

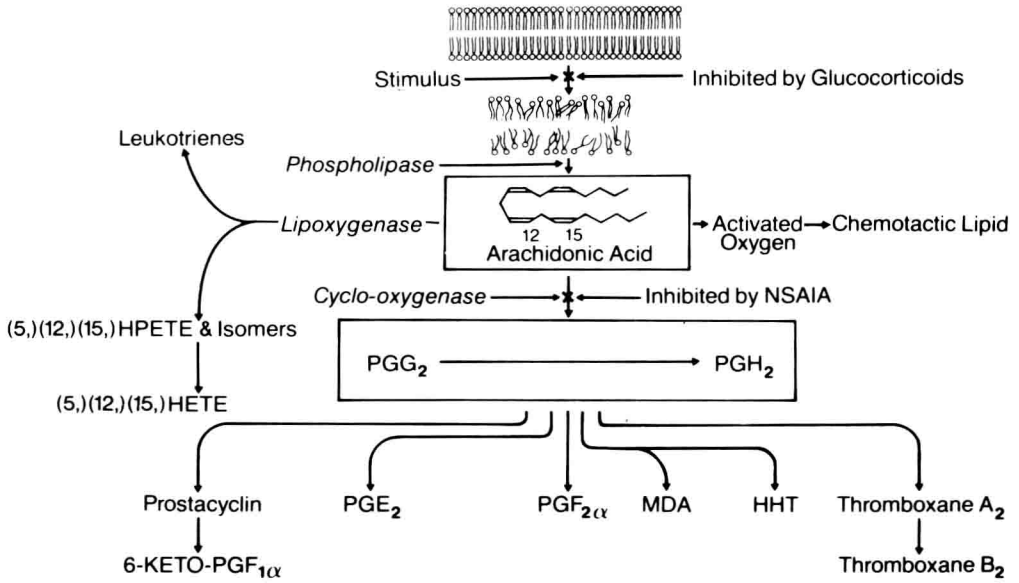

Figure 1.1. Outline of arachidonic acid conversion to oxygenated products via the lipoxygenase and cyclo-oxygenase pathways. Abbreviations: NSAIA, nonsteroidal anti-inflammatory agents; HPETE, hydroperoxyeicosatetraenoic acid; HETE, hydroxyeicosatetraenoic acid; MDA, malondialdehyde; HHT, hydroxyheptadecatrienoic acid. (Reproduced with permission from The Upjohn Company, Kalamazoo, Michigan.)

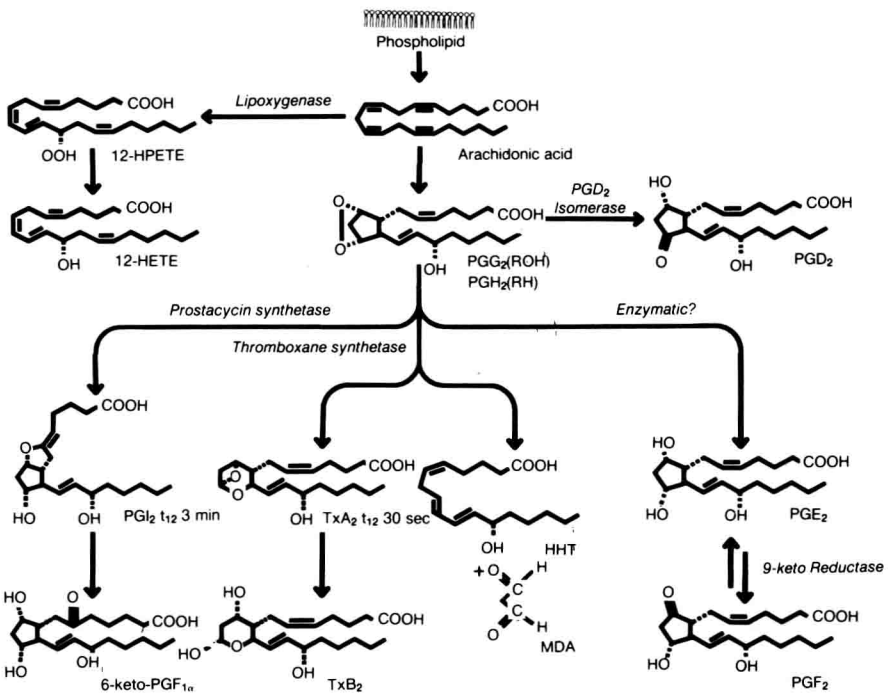

Figure 1.2. Chemical structures of the products of arachidonic acid oxygenation in the kidney. All products shown have been demonstrated in renal tissue. $PGF_{2\alpha}$ can be directly formed from PGH_2 as well as from PGE_2 through the 9-ketoreductase. 6-Keto-$PGF_{1\alpha}$ and thromboxane B_2 are the inactive, stable hydrolysis products of PGI_2 and thromboxane A_2, respectively. (Reproduced with permission from The Upjohn Company, Kalamazoo, Michigan.)

acylhydrolases which deacylate arachidonic acid from phospholipids, especially phosphatidylcholine and phosphatidylinositol. Figure 1.3 depicts these steps. If ^{14}C-arachidonic acid is incorporated into the renal phospholipids of the isolated, perfused rabbit kidney, stimulation of prostaglandin production by bradykinin releases ^{14}C-PGE_2 (5). Subsequently, Isakson and his co-workers were able to show, using albumin containing perfusate, that bradykinin enhanced radiolabeled arachidonic acid release from ^{14}C-arachidonic acid-labeled kidneys and that substantially more arachidonate was released than was cyclo-oxygenated to prostaglandins (6). Ischemia had roughly similar effects and phosphatidylcholine appeared to be the major source of arachidonate (7). Arachidonic acid which is released from phospholipids after a stimulus is, by and large, reacylated into the phospholipids and a small fraction (<5–10%) is converted to prostaglandins (5–7). If animals are maintained on a fatty acid-deficient diet, not only does the arachidonic acid content of the kidney decrease, but prostaglandin synthesis also diminishes (8).

Most stimuli of prostaglandin synthesis, in the kidney and in other tissues, stimulate the release of arachidonic acid from phospholipids either by directly stimulating phospholipase activity or by somehow enhancing the susceptibility of phospholipid substrate to the enzyme. This is true for peptide stimuli (angiotensin II, bradykinin and vasopressin), ischemia and calcium (Table 1.1). Although peptide and other stimuli of prostaglandin synthesis will be discussed subsequently, I will focus some attention on their actions in this section in order to emphasize the importance of phospholipase. Zusman and Keiser, using rabbit renomedullary interstitial cells in culture, demonstrated angiotensin, bradykinin and vasopressin augmentation of PGE_2 synthesis and concomitant stimulation of arachidonic acid release (9). Mepacrine, a known inhibitor of phospholipase, blunted the release of

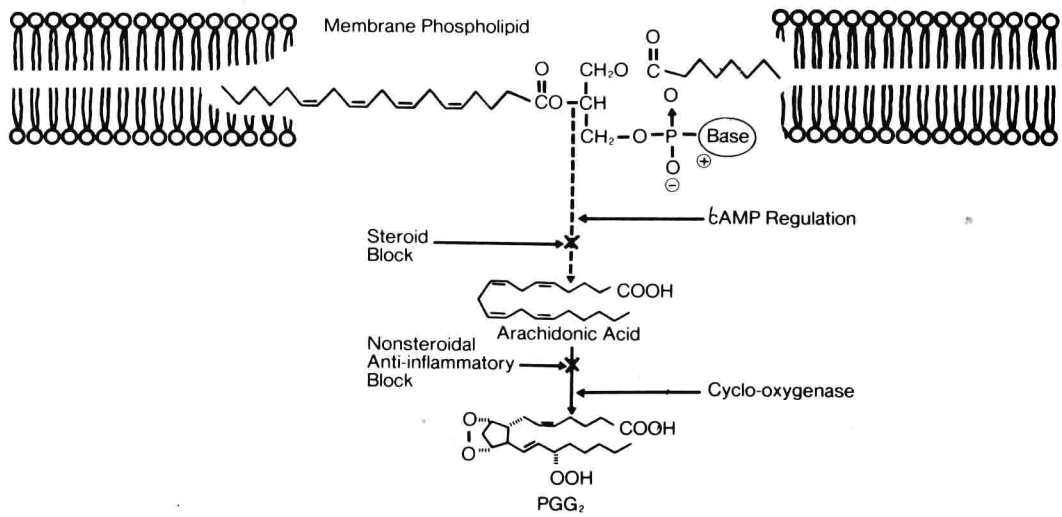

Figure 1.3. Phospholipid deacylation in the modulation of arachidonic acid availability. Renal membranes, containing phospholipids such as phosphatidylcholine and phosphatidylinositol, have arachidonic acid acylated to the second carbon of the triglyceride backbone. Phospholipase A_2 releases arachidonic acid after a variety of stimuli (see text). In addition, diglyceride lipase may release arachidonate after phosphatidylinositol has been converted to the diglyceride through the action of phospholipase C. Cyclic AMP and anti-inflammatory cortical steroids inhibit phospholipase activity and thereby reduce arachidonate acid availability as substrate for cyclo-oxygenation to prostaglandins. (Reproduced with permission from The Upjohn Company, Kalamazoo, Michigan.)

Table 1.1.
Stimuli of renal prostaglandin synthesis

Peptides
Angiotensin II, III
Bradykinin
Vasopressin
Miscellaneous
Calcium
Catecholamines
Adenosine triphosphate
Diuretics
Diseases
Bartter's syndrome
Hypertension (SHR)
Ischemia
Ureteral or renal venous obstruction
Glomerulonephritis

SHR: spontaneously hypertensive rat

arachidonic acid and reduced synthesis of PGE_2 (10). Schwartzman and Raz, in a series of experiments, have utilized the isolated and perfused rabbit kidney to further study the role of phospholipase in the control of prostaglandin release. They have shown that the release of arachidonic acid from phospholipids exceeds the conversion of arachidonate to prostanoids by 15- to 20-fold in the basal state, but bradykinin stimulation enhances the coupling between released arachidonate and cyclo-oxygenation (11–13). In other words, after peptide stimulation with bradykinin and angiotensin, greater amounts of arachidonate, deacylated from phospholipids, are converted to PGE_2. Other fatty acids were not deacylated. Schwartzman and her co-workers have hypothesized that there is hormone-sensitive and a hormone-insensitive lipid pool within renal cells. Peptide hormonal activation of prostaglandin biosynthesis is mediated through the hormone-sensitive lipid pool, and this is more tightly coupled to the cyclo-oxygenase than the hormone-insensitive pool which can be stimulated by ischemia or provision of exogenous arachidonic acid (13).

Phospholipase A_2 and phospholipase C are calcium-dependent enzymes and abundant evidence now exists that renal acylhydrolases are calcium-dependent. Experiments using renal medullary slices or homogenates have demonstrated the calcium dependence of prostaglandin synthesis and have shown substantial stimulation of prostaglandin production after exposure to the divalent cation ionophore, A23187, when extracellular calcium was present (14–17). The enhancement of prostaglandin production after calcium stimulation was accompanied by enhanced release of arachidonic acid (16, 17). It is noteworthy, and possibly physiologically important, that urea suppressed the calcium-induced medullary release of arachidonic acid and PGE_2 (18, 19). Craven and DeRubertis have highlighted the importance of calcium and calcium calmodulin for the medullary synthesis of PGE_2, especially in response to vasopressin, and documented that urea inhibited the vasopressin-stimulated release of PGE_2 (18, 19). Calmodulin, the calcium regulatory protein present in most cells, may be a ubiquitous protein which is critically important in controlling phospholipase activity and phospholipase responsiveness. Okahara and his co-workers have extended the aforementioned *in vitro* studies by showing that the infusion of A23187 or calcium into the renal artery of dogs increased by 10 fold the secretion of PGE_2 and concomitantly augmented renal blood flow and renin release (20, 21).

Little is known about endogenous inhibitors of phospholipase although the recent work of Hassid suggests that intracellular cyclic adenosine monophosphate (AMP) inhibits phospholipase activity of cultured kidney cells, thereby down-regulating prostaglandin synthesis in a manner similar to the well-documented inhibitory effect of cyclic AMP on thromboxane A_2 (TxA_2) synthesis in the platelet (22). Since PGE_2 and PGI_2 stimulate adenylate cyclase activity in most renal cells, the inhibitory actions of cyclic AMP on the release of arachidonic acid serves a down-regulatory function to reduce PG synthesis. Anti-inflammatory adrenal ste-

roids also reduce arachidonate release through the synthesis of a protein called macrocortin (23) or lipomodulin (24), which inhibits acylhydrolase activity. Renal medullary interstitial cells contain steroid receptors and glucocorticoids reduce PG synthesis presumably through the synthesis of an inhibitory protein such as lipomodulin (25).

Fatty Acid Cyclo-Oxygenase and Renal Prostaglandin Synthesis

The initial work by Lee (1), Daniels (2), Hamberg (26) and Crowshaw (27, 28) documented significant synthesis of PGE_2 and $PGF_{2\alpha}$ in renal medullary tissue. In 1972, Änggård and his co-workers isolated prostaglandin synthetase (i.e., cyclo-oxygenase) from renal microsomes (29). Although some prostaglandin synthesis may occur in plasma membranes and mitochondria, the majority of synthetic enzyme can be found in the endoplasmic reticulum which is the predominant component of isolated microsomes (30). Although prostaglandin synthesis and microsomal cyclo-oxygenase is most abundant in the renal medulla (30, 31), cortical tissue also possesses prostaglandin synthetic capacity (31, 32). The regional localization of prostaglandin synthesis within the kidney will be discussed subsequently at greater length. The renal fatty acid cyclo-oxygenase, like cyclo-oxygenases isolated from other tissues, is inhibited by aspirin and indomethacin (33). Renal microsomal enzymes synthesizing prostaglandins are stimulated by glutathione and catecholamines *in vitro*; however, the *in vivo* significance of these co-factors is unknown (33, 34). Renal cyclo-oxygenase, like other cyclo-oxygenases, probably undergoes a process characterized as self-catalyzed destruction and, hence, automatic deactivation of enzymic activity after initial activation (35). It is interesting that the cyclo-oxygenase, which forms prostaglandins, can also co-oxygenate various compounds such as benzedine and may be an important mechanism of inner medullary drug metabolism (36). Although most stimuli of PG synthesis appear to act on phospholipase, and hence on availability of arachidonic acid, there are several circumstances in which cyclo-oxygenase activity may be increased. Enhancement of renal prostaglandin and thromboxane synthesis after ureteral obstruction is accompanied by increased amounts of cortical cyclo-oxygenase (37, 38). Administration of a vasopressin analogue, 1-desamino-8-D-arginine vasopressin (dDAVP), also increased cyclo-oxygenase in microsomes obtained from the renal medullae of diabetes insipidus rats (39).

After cyclo-oxygenation of arachidonate to endoperoxides, the kidney is capable of synthesizing not only PGE_2 and $PGF_{2\alpha}$, but also thromboxane A_2 and PGI_2 (Figs. 1.1 and 1.2). PGI_2 synthesis has been documented in isolated, perfused rabbit kidney (40) and in cortical slices from the rabbit (41). Other studies, however, have shown that prostacyclin synthesis is not restricted to the cortex and can be demonstrated in the medulla of the rat (42), rabbit (43) and dog (44). Although limited in number, studies using human tissue have verified the aforementioned experiments with animals. Hassid and I, using cortical and medullary microsomes from human kidneys, were able to show not only synthesis of PGE_2 and $PGF_{2\alpha}$, but also the production of large amounts of PGI_2, particularly in the medulla (45). Thromboxane synthesis could also be measured, although thromboxane was the least prevalent prostanoid measured in this study. Others have also measured medullary as well as cortical synthesis of PGE_2 and $PGF_{2\alpha}$ using human neonatal tissue (46). Nowak and Wennmalm (47) infused radioactive arachidonic acid into the renal artery in volunteers and showed the appearance of radiolabeled PGE_2, $PGF_{2\alpha}$, PGD_2 and 6-keto-PGF_1 (stable metabolite of PGI_2) in renal venous blood. The same prostanoids were synthesized from ^{14}C-arachidonate by human medullary ho-

mogenates (48). Human tissue, like animal tissue, showed 10 to 20 times more prostaglandin synthesis in the medulla than in the cortex (45).

Prostaglandin Metabolic Degradation

The major PG degradative pathways are summarized in Figure 1.4. The initial degradative step is catalyzed by a cytosolic 15-hydroxyprostaglandin dehydrogenase which forms inactive 15-ketoprostaglandins. The 15-hydroxyprostaglandin dehydrogenase from kidney has been isolated and purified into a type 1 enzyme, requiring oxidized nicotinamide adenine dinucleotide (NAD^+), and a type 2 enzyme stimulated primarily by $NADP^+$ (49–51). There is substantially more degradative enzyme in the cortex than in the medulla of the kidney. Little is known about physiologic control of the degradative enzymes except that enzymic catabolic activity changes rapidly with age in neonatal rat kidney (52). Further degradation of the 15-ketoprostaglandins is achieved by a prostaglandin reductase which reduces the 13–14 double bond. PGI_2 and TxA_2 are very unstable and spontaneously convert to hydrolysis products 6-keto-$PGF_{1\alpha}$ and TxB_2. The kidney is a major degradative site, along with the liver, for PGI_2 (53). Several PG interconverting enzymes have also been found, namely prostaglandin 9-ketoreductase and prostaglandin 9-hydroxydehydrogenase, which have been found in animal and human kidney cytosol (54–61). 9-Ketoreductase converts PGE_2 to $PGF_{2\alpha}$, whereas 9-hydroxydehydrogenase converts $PGF_{2\alpha}$ to PGE_2 and changes 6-keto-$PGF_{1\alpha}$ and PGI_2 to 6-keto-PGE_1. Virtually nothing is known about the physiologic or pharmacologic impor-

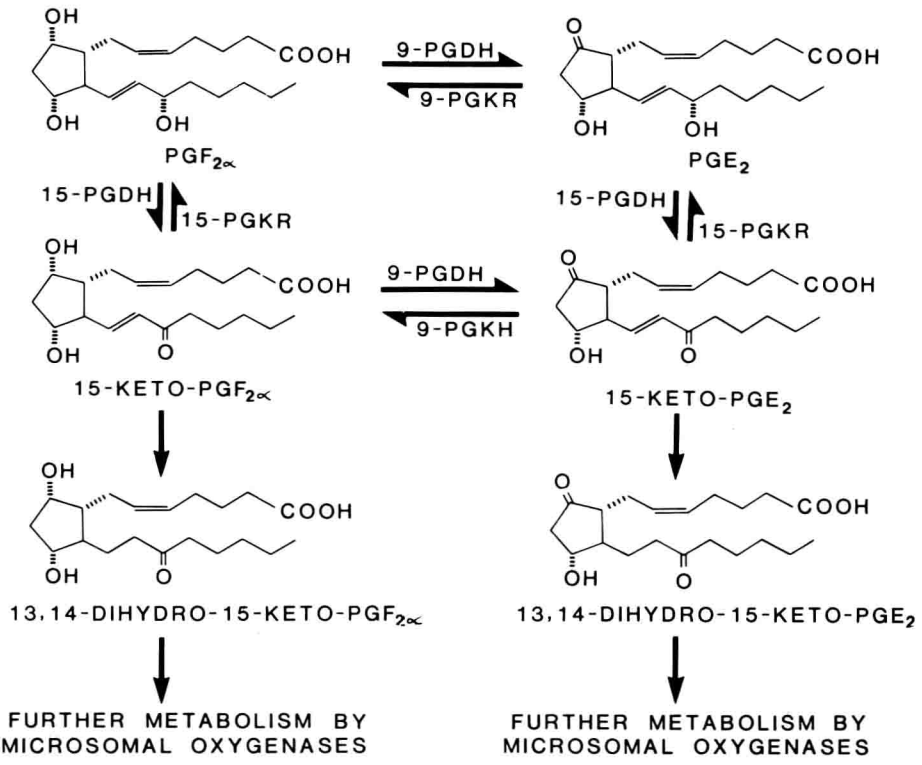

Figure 1.4. Prostaglandin metabolic degradative pathways. Abbreviations: 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; 15-PGKR, 15-ketoprostaglandin ketoreductase; 9-PGDH, 9-hydroxyprostaglandin dehydrogenase; 9-PGKR, 9-ketoprostaglandin ketoreductase (see text for details).

tance of these enzymes. It is noteworthy that 6-keto-PGE_1, like PGI_2, has antiplatelet and vasodilatory actions (62). All of the prostaglandin degradative enzymes are cytosolic in contradistinction to the synthetic enzymes which are microsomal. Cytosolic fraction of rabbit cortex has 10 times more 9-ketoreductase activity than medulla (56). Hassid and I have recently found that human renal cortex and medulla contains all of the aforementioned prostaglandin degradative enzymes including 9-hydroxydehydrogenase, 9-ketoreductase, 15-hydroxydehydrogenase, and 13, 14-reductase (63).

Localization of Prostaglandin Synthesis Within the Kidney

Since 1967, (1, 2) when the first reports were published documenting renal medullary prostaglandin synthesis, there was an initial impression that prostaglandin synthesis occurred exclusively in the renal medulla (27, 28). In 1973, Larrson and Änggård showed cortical synthesis of PGE_2, albeit in substantially smaller amounts than in the medulla, and subsequently confirmed the presence of PGE_2 and $PGF_{2\alpha}$ from cortical tissue using gas chromatography-mass spectroscopy (31, 32). Whereas previous reports used cortical slices or homogenates, Larrson and Änggård utilized cortical microsomes which eliminated the cytosolic degradative enzymes (31). Nonetheless, all species including man show substantially greater medullary than cortical synthesis of most prostaglandins with the possible exception of PGI_2 (45). Many of the dominant renal physiologic actions of prostaglandins require a cortical site of synthesis, since the original hypothesis that medullary prostaglandins might be secreted into the tubular lumen, and thereby transported to the cortex, seems untenable. The current belief is that cortical synthesis of prostaglandins subserves cortical physiologic functions and medullary synthesis regulates medullary functions. Specific localization of prostaglandin synthesis to nephron segments and components of the kidney have utilized three techniques: namely, specific histochemical and immunofluorescent stains, separation of nephron segments, and cell culture of specific components of the nephron. These three techniques have yielded significant agreement about localization of renal prostaglandin synthesis to the various components of the kidney. Table 1.2 summarizes the results of these studies.

Cortical Sites of Synthesis

Cortical synthesis of prostaglandins occurs primarily in glomeruli, arterioles and cortical collecting tubules. Smith and coworkers, utilizing an antibody to cyclooxygenase, have shown immunofluorescent staining of glomerular tissue (64, 65). Mori and Mine have recently confirmed these observations using indirect immunofluorescent microscopy of glomeruli with antibodies to PGE_2, $PGF_{2\alpha}$ and 6-keto-$PGF_{1\alpha}$ (66). We (67) and others (68,

Table 1.2.
Renal cellular sites of prostaglandin synthesis

Glomeruli (whole)	$PGF_{2\alpha} \geq PGE_2 > T\times A_2 > PGI_2$
Glomerular epithelial cells	$PGE_2 \gg T\times A_2 > PGF_{2\alpha} > PGI_2$
Glomerular mesangial cells	$PGE_2 \gg PGF_{2\alpha} > PGI_2 > T\times A_2$
Arterioles (cortical)	PGI_2
Cortical tubules (mixed)	Negligible
Collecting tubule	
Cortical	PGE_2
Papillary	$PGE_2 \gg PGF_{2\alpha} > T\times A_2$, PGI_2
Medullary thick ascending limb	$PGE_2 \gg PGF_{2\alpha}$
Medullary interstitial cells	$PGE_2 \gg PGF_{2\alpha}$

Data are based on microdissection and cell culture studies of rat and rabbit.