MINIREVIEW

Eicosanoids: Their Function in Renal Epithelia Ion Transport (43503A)

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The arachidonic acid products that form the family of ubiquitous compounds known as eicosanoids have been of interest to renal investigators for a number of years. Their contribution to normal renal physiology and role in renal dysfunction have only recently been identified and appreciated. In this Minireview, we will attempt to cover some recent observations concerning the synthesis of eicosanoids, their actions on renal tubular epithelial ion transport mechanisms, and their possible role in renal function. Because of space limitations, it was not possible to review the entire family of the diverse group of arachidonic acid metabolites; therefore, an emphasis was placed on observations concerning the actions and role of renal prostanoids.

Eicosanoid Synthesis and Regulation

Prostaglandins have fascinated investigators ever since the initial discovery in the '30s that a substance in human semen contracted the human uterus. Subsequently, the active material was identified as a lipid-soluble acid which von Euler named prostaglandin (1). However, it wasn't until the late '70s that the actions of the prostaglandins were defined and many of this family of unique compounds isolated. Since then, a host of derivatives of the unsaturated lipid, arachidonic acid ($C_{20:4\ n\text{-}6}$), have been shown to have a variety of biological activities that appear to modulate local cellular function. Prostaglandins belong to a family of compounds known as eicosanoids, which include not only derivatives of cyclo-oxygenase, but also the lipoxygenase products, the leukotrienes, lipoxins, and various hydroxy-fatty acids. More recently, another pathway for arachidonic acid metabolism was identified that involves the cytochrome P-450-dependent monooxygenases (2). This latter pathway has received heightened interest, particularly with respect to its possible role in the kidney (3).

Figure 1 is a composite of the generalized pathways for arachidonic acid (AA) metabolism. Although arachidonic acid is ubiquitous in membrane phospholipids, it is not synthesized *de novo* in cells, but derived from dietary linoleic acid or ingested as a food constituent. There are virtually no standing intracellular pools of AA because of the activity of acyltransferases that rapidly incorporate unesterified AA into membrane phospholipids or other AA eicosanoid metabolites (4). Although AA is contained in a variety of membrane phospholipid moieties, it appears predominantly esterified at the sn-2 position of the glycerol backbone of phosphatidylinositol, phosphatidylcholine, and phosphatidylethanolamine. The release of AA in response to a stimulus occurs primarily through activation of phospholipase (PL) A_2 (5), although in some instances, AA may result from activation of diglyceride lipase following PLC actions on phosphatidylinositol 4,5-bisphosphate or phosphatidylcholine (6). The pathway for the release of AA by phospholipases is not only tissue specific, but is also dependent upon the stimulus. cDNA sequencing and immunoreactivity studies have identified at least nine distinct isozymes of PLC (7), and it would not be surprising if a similar family of isoforms of PLA_2 also exists. Indeed, both calcium-independent and -dependent forms of PLA_2 have been identified (8, 9). In whole kidney, the major PLA_2 present appears to be a soluble form that resembles the enzyme isolated

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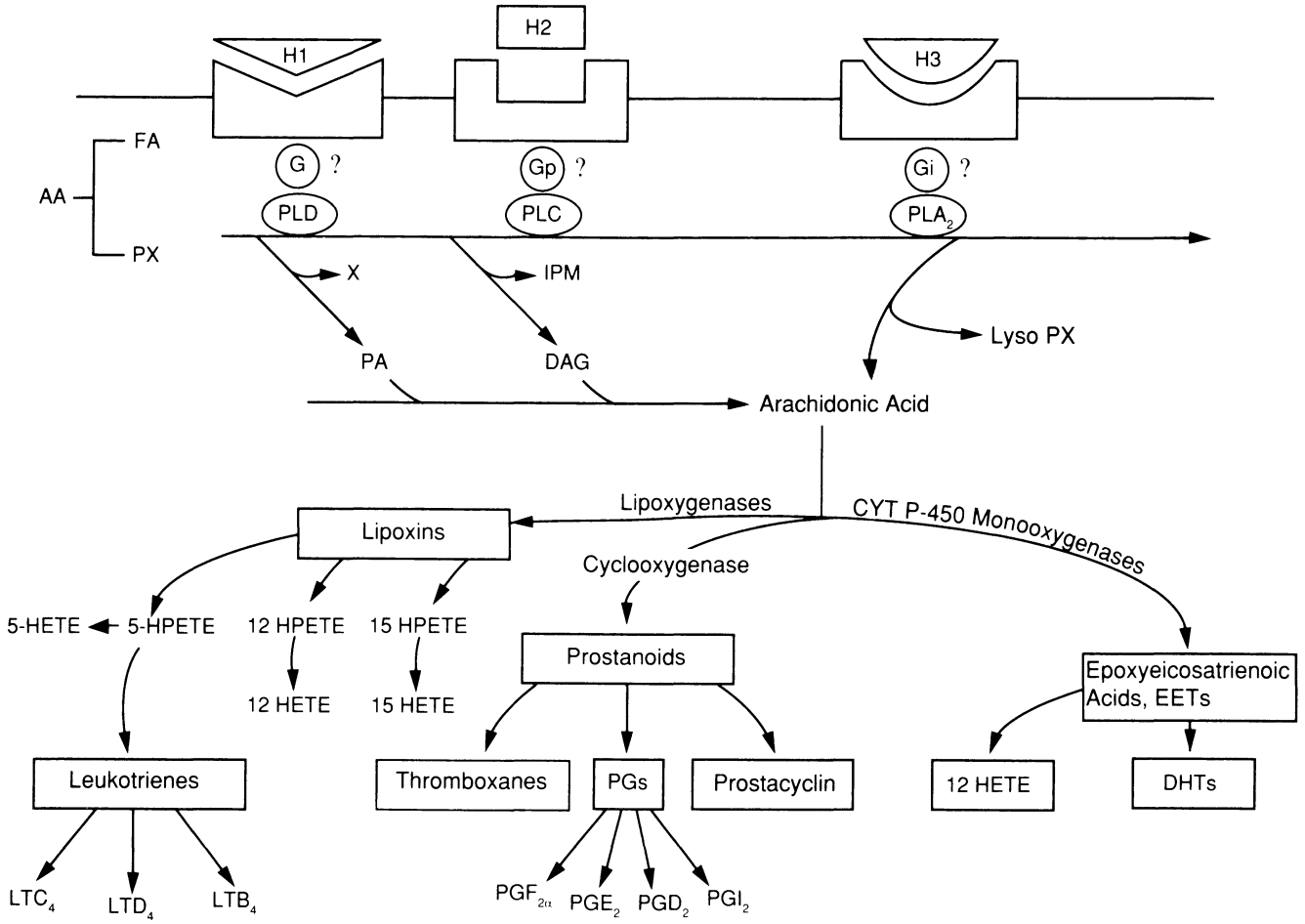

Figure 1. Diagram of the pathways leading to the genesis of arachidonic acid and its subsequent metabolism through three enzymatic pathways: (i) the cyclo-oxygenase; (ii) lipoxygenases; and (iii) cytochrome P-450 mono-oxygenases. H1, H2, and H3 represent three different hormones, each capable of releasing AA by activation of phospholipases. PLA_2 can release AA directly from membrane phospholipids (H3) or, following PLD activation, a phosphatidic acid-specific PLA_2 (H1) could release AA. In addition, AA can be generated by the sequential activation of PLC and DAG-lipase (H2). Once released, AA can be metabolized by the common cyclo-oxygenase pathway leading to the prostanoids (PGE_2, $PGF_{2\alpha}$, TXA_2, PGI_2, PGD_2) or it can be metabolized by the lipoxygenases to form lipoxins and, subsequently, leukotrienes (LTC_4, LTD_4, LTB_4). Some tissues also contain the P-450 mono-oxygenase system, thus allowing for another pathway for AA to take. This system generates a series of compounds, including the epoxyeicosatrienoic acids and the dihydroxyeicosatetraenoic acids (DHT). FA, fatty acid; X, N-base; PX, phosphorylated N-base; PA, phosphatidic acid; DAG, diacylglycerol; IPM, inositol monophosphate.

from renal mesangial cells, which has been found to associate with membrane fractions in a calcium-dependent manner (9, 10). Thus, those hormones that produce an increase in intracellular calcium could cause PLA_2 to translocate to the membrane as part of the hormone signal transduction process and provide a mechanism for PLA_2 regulation. Because the rate-limiting step in the synthesis of prostaglandins and other eicosanoids is the release of AA (11–13), attention has been placed on understanding the regulation and activation of PLA_2. Recently, a family of intracellular calcium-phospholipid-binding proteins called lipocortins, lipomodulins, or renocortins, thought to be induced by glucocorticoids, has been shown to inhibit PLA_2 activity *in vitro* (14, 15). Such proteins were also identified in renal mesangial cells (16). Although initial studies thought these proteins interacted directly with PLA_2 (17), recent observations suggest that these proteins and others called calpactins may bind to the phospholipid substrate and indirectly prevent PLA_2 activity (18). However, even this latter action has been questioned, as a number of observations have shown a lack of effect of these proteins on PLA_2 activity and their inability to be induced by glucocorticoids (19, 20). Clearly, much has yet to be determined before a specific action is identified for these proteins; however, a role for intracellular modulatory proteins that regulate PLA_2 activity remains a viable possibility. Such proteins could play an important role in the regulation of AA release and subsequent eicosanoid production.

Phospholipase A_2 activity and the formation of prostaglandins through the cyclo-oxygenase pathway have been demonstrated in the mammalian kidney (21, 22) and in renal-like epithelia, the frog skin and toad

urinary bladder (23, 24). Interestingly, our laboratory proposed some 14 years ago that the regulation of sodium transport by aldosterone involved activation of phospholipase A_2 (23). Observations in support of this were that mepacrine, a PLA_2 inhibitor, decreased PLA_2 activity by 35% and completely prevented the increase in sodium transport that normally accompanies aldosterone addition (23). Recently, the apical sodium channel in renal epithelia was shown to be under the control of G proteins and that $G\alpha_{i\text{-}3}$ tonically maintains sodium channels open (25). It was also observed that mepacrine decreased GTPγS-stimulated activity of the sodium channel and that the addition of AA, even in the presence of mepacrine, induced channel activity (26). These results suggested that the apical sodium channel on renal epithelia is regulated by a G protein-activated PLA_2 activity (27). These observations were consistent with our previous findings concerning the role of PLA_2 in the mechanism of action of aldosterone (23). These studies further indicated that AA or one of its metabolites was altering the activity of the sodium channel.

Cyclo-oxygenase Pathway. Because of the relatively low intracellular concentration of AA, the release of AA from membrane phospholipids is rate limiting (11). However, once released, arachidonic acid is rapidly metabolized by either of three distinct pathways (Fig. 1), each producing unique compounds with diverse biological activities. The first involves the more common cyclo-oxygenase enzyme, also know as prostaglandin endoperoxide synthetase (EC 1.14.99.1), and catalyzes the oxygenation and cyclization of AA leading to the formation of the unstable intermediates prostaglandin (PG) G_2 and PGH_2. Most of the prostaglandin endoperoxide synthetase activity in the kidney is found in the microsomal fraction of the papilla (28), with decreasing activity in the medulla and cortex (29, 30). Immunohistochemical staining for the synthase in human kidney has localized the enzyme to the collecting duct, the thin ascending limb epithelial cells, and the mesangial cells (31). The PGH_2 intermediate serves as a substrate for several other enzyme systems ultimately responsible for the formation of prostaglandins, thromboxanes, or prostacyclin. The enzyme prostaglandin endoperoxide E isomerase (EC 5.3.99.3) converts PGH_2 into PGE_2 and is dependent upon reduced glutathione (32). A reduction in intracellular reduced glutathione would result in an attenuated PGE_2 production, even in the presence of normal PGH_2 concentrations. A shift in prostaglandin products will be seen depending upon the activity of other prostanoid enzymes in the pathway. Besides PGE_2, PGH_2 can be transformed into PGD_2 by enzymatic and nonenzymatic processes (33). What role PGD_2 plays in renal function is not known; however, PGD_2 has been shown to be released from renal cells following a variety of stimuli (34). $PGF_{2\alpha}$ is probably nonenzymatically formed, although several proteins have been purified that have enzyme activity of a PGF reductase (35). PGH_2 can also be enzymatically transformed either into prostacyclin (PGI_2) or thromboxane A_2 (TXA_2), which involves the cell-specific enzymes prostacyclin and thromboxane synthetase. PGI_2 and TXA_2 are unstable and are rapidly converted to the stable, yet inactive, metabolites 6-ketoprostaglandin $F_{1\alpha}$ and thromboxane B_2, respectively. In studies in which tissue production of PGI_2 and TXA_2 is evaluated, it is their stable metabolites that are measured.

A number of observations have indicated that different segments of the nephron synthesize different prostaglandins. The primary prostaglandins produced in isolated nephron segments of the renal cortex are PGI_2 and PGE_2, whereas PGE_2 and $PGF_{2\alpha}$ are the major products of the medulla. Most investigators agree that the renal medullary area of the nephron synthesis of prostaglandins exceeds that of the renal cortex, although the cortex does make appreciable quantities of prostaglandins. A progressive increase in PG biosynthesis occurs along the nephron, with the collecting tubule demonstrating the greatest activity (36). Schlondorff *et al.* (37) observed that PGE_2 synthesis increased from the branched collecting tubule to the medullary and cortical collecting tubules. Likewise, addition of the calcium ionophore A23187, which activates PLA_2, enhanced PGE_2 production consistent with its basal concentrations along the nephron (37). PGI_2 is synthesized by the glomerulus (38), predominantly by the epithelial cell, whereas the mesangial cell produces PGE_2 (39). The major prostaglandin product of the cortical collecting tubule is PGE_2; however, $PGF_{2\alpha}$ and PGD_2 may also be formed. Of the more proximal nephron segments, only the thin descending limb has significant prostaglandin biosynthesis (36). In most instances, PGE_2 is produced approximately 100 times more than is $PGF_{2\alpha}$ in each segment, except for the glomerulus, in which $PGF_{2\alpha}$ may have a greater role and is synthesized to the same extent as PGE_2. The stable thromboxane metabolite TXB_2 has as its major site of synthesis the glomerulus, with the cortical and medullary collecting tubules also capable of thromboxane synthesis. In addition, the medullary interstitial cells are also capable of producing prostaglandins (40) and contribute significantly to the overall production of prostanoids by the kidney. Prostaglandins, once formed, are often released from cells and act as local messengers interacting with specific receptors (see below) localized in neighboring cells or within the cell of origin.

Lipoxygenase Pathway. Another important pathway for the oxidation of arachidonic acid involves the lipoxygenase enzymes that catalyze the oxidation of AA to hydroxy- and hydroxyperoxy-unsaturated fatty acids (the lipoxins) (Fig. 1). In contrast to the cyclo-oxygenase pathway discussed above, in which stable products have three atoms of oxygen covalently attached to AA, li-

poxygenases insert a single oxygen atom into the molecular structure of AA. The family of lipoxygenase enzymes were initially described in plants, where they are responsible for lipid peroxidation-producing inactive products. A major difference in plant versus mammalian lipoxygenases, is that the plant lipoxygenases can add a hydroperoxy radical to almost any position on a fatty acid, whereas the mammalian enzymes are restricted to certain positions on the fatty acid. As a result, mammalian lipoxygenases catalyze the formation of either a 5-hydroperoxy-, a 12-hydroperoxy-, or a 15-hydroperoxyeicosatetraenoic acid (HPETE) (35). A peroxidase reaction reduces HPETE to hydroxyeicosatetraenoic acid (HETE) while generating oxygen free radicals. The production of oxygen free radicals contributes to tissue injury during inflammatory reactions in which the peroxidase reaction is induced. Protection against such damage is usually provided by superoxide dismutase and catalase. The 5-lipoxygenase pathway that produces 5-HPETE leads to the formation of the leukotrienes (LT) (Fig. 1). The leukotriene LTA_4 contains a reactive epoxide ring that reacts with glutathione at the C-6 position to yield the three common thionyl-peptide leukotrienes, LTC_4 (which contains the tripeptide glutathione), LTD_4 (which contains glycine and cysteine), and LTE_4 (which contains only cysteine). These leukotrienes all possess proinflammatory properties and the latter three compounds account for the activity of slow-reacting substance of anaphylaxis (41), which makes them important components in immune-mediated inflammatory reactions. Currently, there are no reports of 5-lipoxygenase activity and subsequent leukotriene production by renal tissue. However, recently, Cantiello *et al.* (26) and Cantiello and Ausiello (27) indirectly implicated the 5-lipoxygenase pathway and LTD_4 in the regulation of apical sodium channels in cultured A6 amphibian kidney cells. These authors have data that support the conclusion that the apical sodium channel can be activated by the $\alpha_{i\text{-}3}$ subunit of the G_i protein that stimulates PLA_2 activity. The released AA undergoes conversion via the 5-lipoxygenase pathway to LTD_4, which either directly or through an as yet undefined pathway activates amiloride-sensitive channels in this renal epithelial cell. However, their conclusion has been based on experiments using patch clamp techniques and pharmacological probes. Additional studies are needed to identify the enzyme pathways and AA products responsible for this sodium channel regulation.

The 12-lipoxygenase pathway leads to 12-HPETE formation, which is metabolized into 12-hydroxyeicosatetraenoic acid (12-HETE). Likewise, the 15-lipoxygenase pathway gives rise to compounds similar to those found in the 12-lipoxygenase pathway (for instance 15-HPETE and 15-HETE). Some of these compounds appear to have some proinflammatory activity, and may be important signaling molecules in the nervous system. There have been reports of 12-HETE production in guinea pig kidney homogenates and 12- and 15-HETE formation by soluble fractions of rabbit medullary homogenates (42). Lipoxygenase activity has also been observed in the cortex of rat kidney, where 12-HETE was produced by homogenized glomeruli, glomerular epithelial cells in culture, and cortical tubules (43). In addition, 12- and 15-HETE have been reported to be produced by cultured mesangial cells (44).

How these lipoxygenase products alter renal function is not clear; however, it has been suggested that they may alter activity of ion channels, as observed in atrial cells, where lipoxygenase intermediates activated potassium channels (45). Scherer and Breitwieser (46) have also found that AA modifies the affinity of activation of acetylcholine-mediated K^+ channel activity, an effect that is also present when activation is achieved by GTPγS turning on the $G_{\alpha i}$ subunit, independent of muscarinic receptor occupancy. The inhibition by AA was blocked by nordihydroguaiaretic acid, a 5-lipoxygenase inhibitor, and re-established by LTC_4, thereby implicating a modulatory role of the 5-lipoxygenase pathway in the regulation of the K^+ channel. The initial observations reported above concerning the role of lipoxygenase products in the regulation of the Na^+ channel in A6 kidney cells (26, 27) and the observation that the Na^+ channel of LLC-PK_1 cells, a model of proximal tubule transport, is also regulated by G proteins in a fashion similar to that described for the A6 kidney cells (47) suggest that regulation of ion channel activity may be a common mechanism shared by some lipoxygenase products.

Cytochrome P-450 Pathway. The cytochrome P-450-dependent mono-oxygenases represent the third pathway of AA metabolism that we will consider (Fig. 1). This family of mixed-function oxidases involves hemoprotein, cytochrome P-450, NADPH cytochrome reductase, and phosphatidylcholine (48). Cytochrome P-450 metabolism of AA requires molecular oxygen and NADPH in a 1:1 stoichiometry; however, other polyunsaturated fatty acids may substitute for AA as a substrate in this reaction (49). Thus, the substrate specificity requirements of this P-450 system are not as stringent as the enzymes of the cyclo-oxygenase and lipoxygenase pathways. The oxidation of AA by this P-450 system involves three types of reactions (Fig. 1): (i) epoxidation, which gives rise to epoxyeicosatrienoic acids (EET) that can be converted by epoxide hydrolases to vicinal diols, the dihydroxyeicosatetraenoic acids (50); (ii) allylic oxidation, to form 5-, 8-, 9-, 11-, 12-, and 15-HETE (51); and (iii) ω- and ω-1 hydroxylation of AA giving rise to 20- and 19-HETE (2).

Only recently have the products of the cytochrome P-450 system been identified and potential sites of action described. Early observations concerning the

presence of this system in the kidney included incubating AA with rabbit renal cortical supernatants and microsomes and demonstrating the production of dihydroxyeicosatetraenoic acids as well as 19- and 20-HETE (52). Coincident with this observation was the reports that the renal cortex contained an active NADPH-dependent mono-oxygenase that metabolized AA into 19- and 20-HETE (53, 54). Subsequently it was reported that isolated thick ascending limb cells from the rabbit outer medulla produced two compounds that differed from lipoxygenase products when they were incubated with radiolabeled AA (55). It was also found that the product formation was inhibited by SKF-525A, an inhibitor of the cytochrome P-450 system, and increased when the P-450 system was induced (56). One of the products contained vasodilator activity, while the second compound was capable of inhibiting Na^+-K^+-ATPase (57). Two principal AA products, 20-HETE and 20-COOH-AA, were identified in the medullary thick ascending limb of the loop of Henle (58).

The effects of P-450 AA metabolism on ion transport have been determined by measuring ^{86}Rb uptake in the medullary thick ascending limb of the loop of Henle cells as a means to assess K^+ uptake (58). The addition of AA produced a concentration-dependent inhibition of Rb uptake that was prevented by the blockade of AA metabolism by the P-450 pathway. This blockade could be overcome by the addition of P-450 products. The reduction in Rb uptake by AA and P-450 products could be interpreted as either an inhibition of Na^+-K^+-ATPase activity or a reduction in the Na^+-$2Cl^-$-K^+ co-transporter. The authors suggested that the AA-derived product generated by the P-450 pathway probably inhibited Na^+-K^+-ATPase and was either 20-HETE or 20-COOH-AA. In another transporting epithelium, the cornea, a P-450 product generated by corneal microsomes also inhibited Na^+-K^+-ATPase (59). Mass spectral analysis revealed the product to be 12-HETE; however, further stereochemical analysis demonstrated that the active inhibitor of the Na^+-K^+-ATPase was 12(R)-HETE (59). The availability of 12-HETE stereoisomers has allowed these compounds to be tested on other tissues, including the kidney. Major differences were noted when the isomers 12(S)- and 12(R)-HETE were tested on renal function. 12(R)-HETE produced an extended natriuretic activity and inhibited renin release, whereas the 12(S) isomer had only transient effects on sodium excretion and renin release (60). In addition to their known actions on Na^+-K^+-ATPase, P-450 products have been shown to have other physiological roles. The epoxyeicosatrienoic acids (5,6-, 11,12- and 14,15-EET) have been shown to inhibit vasopressin-mediated osmotic water flow in the renal model epithelium, the toad urinary bladder (61). The vicinal diol products of these compounds also produced inhibitory effects on hormone-induced osmotic water flow (61). The mechanism for the inhibition appeared to be mediated at the level of adenylate cyclase, as the EET prevented hormone-induced increases in cyclic AMP concentrations in tissue as well as prevented the stimulation of adenylate cyclase by vasopressin in broken cell preparations (61). In mesangial cells, antagonists of the P-450 pathway attenuated cell proliferation and mRNA levels of the immediate early genes, *Egr*-1 and c-*fos*, suggesting a role for endogenous cytochrome P-450 AA products in the regulation of cell growth (62). Much has yet to be learned about the range of activities of the vast number of potential cytochrome P-450 products that may be produced not only in the kidney, but in other tissues where AA has been shown to be released following a variety of stimuli. To further complicate the eicosanoid picture, it has been shown that many of the P-450 metabolites may also be candidates for action by the cyclo-oxygenase pathway, thus producing another class of prostaglandin analogs with potential biological activity (see [2]).

Eicosanoid Receptors

Although the pathways for eicosanoid biosynthesis and metabolism have been determined for a number of products and a physiological role has been identified, there has been limited progress in the classification of eicosanoid receptors. Part of the problem has been the limited availability of stable agonists and selective antagonists to properly define tissue receptors. The problem is further confounded by the fact that the eicosanoids encompass a wide spectrum of biological activity, with the ability in some cases to produce opposing actions within the same tissue, as can be seen with PGE_2, which can produce either contraction or relaxation of airway smooth muscle (63). Such diverse activity has led to immense technical problems in the identification of specific eicosanoid receptors. Methods that have been utilized for the preliminary identification of eicosanoid receptors have been (i) to compare rank order of potency of the natural agonists; (ii) to compare, using competitive antagonists, potencies (pK_B) on a range of tissues; and (iii) to identify and characterize binding sites using radiolabeled ligands, either as agonists or antagonists.

Using the first method described above in comparing rank order of potency, a systematic test of a wide range of tissues resulted in the identification of several prostanoid receptors in which one prostanoid appeared to predominate over the others. For example, a PGE_2 receptor had the following rank order of potency: $PGE_2 > PGI_2 > PGF_{2\alpha} > PGD_2 >$ U46619 (a stable thromboxane agonist) (64); a $PGF_{2\alpha}$ receptor had: $PGF_{2\alpha} > PGD_2 > PGE_2 > PGI_2 >$ U46619; a thromboxane receptor had: U46619 $>> PGD_2 > PGF_{2\alpha} = PGI_2 > PGE_2$; and a prostacyclin receptor had: $PGI_2 >> PGD_2$

>> PGE_2 = $PGF_{2\alpha}$ >> U46619 (zero activity) (65). Although a PGD_2 receptor has been identified, the rank order of potency has not been determined. The problem with this approach is that more than one receptor for the prostanoids may exist in the tissue. Also, some prostanoids may interact with other classes of prostanoid receptors. As a result, the finding that a prostanoid may be active on a tissue does not indicate that its specific receptor is present. Other findings utilizing selective antagonists have helped in confirming the existence of distinct types of prostanoid receptors (Table I).

The pharmacology of PGE is quite diverse. In the kidney, PGE_2 can increase sodium excretion and decrease vasopressin-mediated water reabsorption (66). Both of these responses appear to involve interactions with adenylate cyclase. It has been proposed that PGE receptors are coupled to guanine nucleotide regulatory proteins or G proteins (67). PGE receptors coupled to G_s proteins are involved in the stimulation of adenylate cyclase, whereas PGE receptors coupled to G_i proteins are inhibitory on adenylate cyclase activity (68). The presence of two types of receptors coupled to adenylate cyclase could help explain early observations by our laboratory that PGE_2 produced dose-dependent effects on cyclic AMP formation in a renal-like epithelium, the toad urinary bladder, where it was demonstrated that low doses of PGE_2 inhibited cyclic AMP formation and high doses stimulated it (69). The PGE receptor has been partially purified from the canine renal medulla (70), where it was found to be associated with a guanine nucleotide regulatory protein of the G_i type. These authors also demonstrated that PGE_2 inhibits cyclic AMP formation in this region of the kidney. In the rabbit cortical collecting tubule, PGE in low concentrations inhibited vasopressin-stimulated water flow, whereas at higher concentrations, water reabsorption was enhanced (71), similar to what was reported for the amphibian urinary bladder (69). It was further found in membranes prepared from collecting tubules that low PGE_2 concentrations inhibited vasopressin-induced increases in cyclic AMP that had been blocked by pertussis toxin pretreatment (72). These results were consistent with the contention that PGE_2 can act through receptors coupled to inhibitory guanine nucleotide regulatory proteins. Using radioligand binding studies, it was also shown that PGE binding to its receptor can be reduced by guanine nucleotides (73). In addition, down-regulation of PGE_2 receptors has been demonstrated in the rat renal medulla (74), similar to what has been observed for other G protein-coupled receptors. The PGE receptor is the only prostanoid receptor in the kidney that has been isolated and classified and for which radioligand binding studies have been performed, whereas information on other prostanoid receptors comes mainly from pharmacological studies in the kidney and from ligand binding studies in other tissues. Table I is a summary of some of the

Table I. Classification of Eicosanoid Receptors[a]

Receptor	Eicosanoid	Selective agonist	Selective antagonist	Effector pathway
EP_1	PGE	17-Phenyl-o-trinor-PGE_2 Sulprostone	SC19220 AH6809	IP_3/DG
EP_2	PGE	Butaprost AY 23636 AH 13205	None	Increase cAMP
EP_3	PGE	GR 63799 Enprostil	None	IP_3/DG Decrease cAMP
FP	PGF	Fluprostenol	None	IP_3/DG
IP	Prostacyclin	Cicaprost	None	Increase cAMP
DP	PGD	BW 245C 2K110841	BW A868C	Increase cAMP
TP_{1-3}	Thromboxane TXA_2/PGH_2	I-BOP U 46619 STA_2	Bay U3405 AH 19437 GR 32191	IP_3/DG
pLT_1	Leukotrienes	LTC_4	None	
pLT_{2c}		$LTC_4 = D_4 \geq E_4$	FPL 55712 SKF104,353 ICI 198,615 ICI 240,219	IP_3/DG
pLT_{2b}	Leukotrienes	LTD_4/E_4	Low affinity FPL 55712	IP_3/DG
pLT_{2a}		LTD_4/E_4	High affinity FPL 55712	
pLT_{2d}		LTD_4/E_4	FPL 55712 LY 171,883	

[a] The information in the above table was taken from Refs. 55 and 79.

prostanoid receptors that have been classified. Included in this table are some agonists and antagonists that have been useful in delineating the relative selectiveness of the receptor. Additional information regarding prostanoid receptors can be obtained in an excellent review by Halushka *et al.* (75).

The peptidyl leukotrienes have profound effects on a variety of tissues, and these effects are also mediated through specific receptors (76). The heterogeneity of leukotriene receptors has been appreciated for many years. With the advent of new and selective antagonists and techniques of molecular biology, the diversity of this family of receptors will become clearer. Table I contains information on the receptor classification of leukotrienes based on a number of different observations and techniques from a variety of tissues. As the peptidyl leukotrienes have been shown to be the components of slow-reacting substance of anaphylaxis and to produce biological effects common to allergic asthma (e.g., bronchoconstriction, pulmonary edema, and mucus secretion), a great interest in finding compounds that modulate the activity of leukotrienes has been launched. As a result, a number of receptor antagonists have been developed against leukotrienes, thereby making identification of leukotriene classes of receptors possible. Much of the studies of leukotrienes in the kidney have come from either identification of synthetic pathways (77) (see above) or pharmacological profiles. It appears that leukotriene receptors may be linked to regulation of ion channels; however, no direct measurements are available. For instance, the $\beta\gamma$-subunits of G proteins have been reported to activate potassium channels by stimulating the production of lipoxygenase intermediates (45); they have also been reported in renal epithelial cells in the regulation of the sodium channel (78). Likewise, receptors for cytochrome P-450 products have yet to be defined. However, as these substances appear to have profound effects in the kidney (see above), receptor identification will surely follow.

Effects of PG on Hemodynamic Parameters of the Kidney

The major pathway for metabolism of AA in the kidney is the cyclo-oxygenase enzyme system (80). The cyclo-oxygenase activity is reported to be present in the arterial and arteriolar efferent and afferent vessels of the glomerulus. This activity seems to be relegated to the endothelial cells of these structures and the predominant product appears to be PGI_2 (81). In addition, it has also been reported that mesangial cells from the rat and human are capable of producing PGE_2 (82, 83). Also, cultured human mesangial cells have been shown to synthesize $PGF_{2\alpha}$ and PGI_2 (84). By far the most prevalent receptor type for PG is the E_2 receptor in kidney. The greatest concentration of E_2 receptors has been found in the outer medulla, with lesser numbers in the inner medulla and cortex. Additionally, significant numbers of receptors for $PGF_{2\alpha}$, PGI_2, and TXA_2 occur throughout the cortex and outer medulla (85).

Some of the earlier studies focused on the vasodilator actions of prostaglandins in the kidney. Johnston *et al.* (86) and Vander (87) in 1967 and 1968, respectively, were among the first to report on this action. Much work has followed since that time and several good reviews are available on the PG effects on renal vasodilator actions (88, 89). In all animal studies, with the exception of the rat, the PGE series and PGI have been shown to induce vasodilation. Even the precursor of prostaglandins, arachidonic acid, when infused into the renal artery of the dog in very high concentrations, was found to cause vasodilation (90). Studies in the rat kidney have been conflicting with regard to PG effects. Gerber and Nies (91) have reported that the only PG that was an effective vasodilator in the rat kidney was PGI_2. A more recent report (92) in the rat indicated that both PGE_2 and PGI_2 increased renal vascular resistance, causing substantial reductions in renal blood flow with no change in systemic blood pressure. At the present time, the difference in response between the rat kidney and dog, rabbit, and human kidney to various PG is not apparent. It may be that the difference is quantitative rather than qualitative, as it first appears.

Reduction in cardiac output, hemorrhaging, and sodium depletion have all been reported to increase levels of PG. In 1981, Oliver *et al.* (93), using the anesthetized dog, were able to show a direct correlation of PGE_2 production in the kidney to a change in cardiac output and peripheral resistance. By partially obstructing the inferior vena cava, they were able to cause a slight reduction in cardiac output and arterial pressure with an accompanying elevation in peripheral resistance. However, renal blood flow and renal vascular resistance remained constant. During this period, a 4-fold increase in renal venous PGE_2 was found. This study suggested that PGE_2 produced by the kidney acts as a vasodilator in maintaining renal blood flow and the glomerular filtration rate in light of reductions in cardiac output. Likewise, following a classic study by Vatner in 1974 (94), using both dogs and baboons, an entire body of evidence has accumulated indicating that during moderate hemorrhaging, renal blood flow increases in response to blood pressure decreases of upward of 25%. Reports by two groups (95, 96) indicate that sodium depletion in rabbits and dogs increased urinary PGE_2 excretion and renal venous PGE_2 concentration, respectively. These studies suggested that activation of the renal vasodilator prostaglandin system modulates or neutralizes the activation of the renal vasoconstrictor renin-angiotensin system.

At least three other actions of PG in the kidney should be mentioned. Prostaglandins, primarily PGE_2

and PGI_2, maintain a functional glomerular filtration rate by mediating mesangial cell relaxation in a modulatory response to hormone-induced mesangial cell contraction from both angiotensin II and vasopressin (97, 98). PG have been reported to stimulate renin secretion (99), and this stimulation appears to be independent of sympathetic stimulation and mediated through increases in adenylate cyclase in the juxtaglomerular apparatus of the kidney (100). And finally, even though the functional significance is not clear at this time, $PGF_{2\alpha}$ and TXA_2 both mediate vasoconstriction of the renal vasculature (101, 102).

In summary, it appears that renal PG, specifically PGE and PGI_2, are vasodilators of the renal arterioles. Their primary role in renal hemodynamics seems to be to dampen the effect of vasoconstrictor renal nerves and angiotensin II. Increases in either renal nerve activity or the renin-angiotensin system stimulate the kidney to synthesize and release vasodilator prostaglandins, which in turn modulates the vasoconstrictor activity of the sympathetic nerves and angiotensin II. This mechanism ensures that the kidney will get a proper amount of blood flow in light of increased peripheral vasoconstrictive and angiotensin II activity. PG have also been reported to influence electrolyte and water excretion by the kidney. In the past, many of these actions were attributed to the hemodynamic changes of the PG. However, over the last few years, much evidence has accumulated that demonstrates conclusively that PG have a direct effect on renal tubular electrolyte and water metabolism. This will be discussed in the next section.

Effects of PG on Renal Epithelial Electrolyte Transport

There is now overwhelming evidence that the eicosanoids have important regulatory effects on the transport of many electrolytes across renal epithelia (Fig. 2). These various actions of PG on epithelia transport are clearly independent of their actions on renal hemodynamics. In most mammalian species studied thus far, the distal part of the nephron, e.g., the collecting ducts, appears to be the major site for PG synthesis (36, 37, 103, 104). Additionally, the thick ascending limb of Henle (TALH) has significant numbers of PGE_2 receptors (105).

Sodium Ion. In an early study by Stokes and Kokko (106), it was shown that PGE_2 inhibits Na^+ transport in the medullary portion of TALH. However, in the cortical TALH this action of PG is apparently not present (107). The functional significance of the PGE_2 effect in the medullary TALH is not clear at this time.

Even though the proximal tubule has a insignificant amount of biologically active PG synthesis, it has been reported that PGE_1 has an effect on Na^+ reabsorption in this area. A study by Standhoy *et al.* (108), using micropuncture techniques in dogs, has reported that proximal tubular fractional reabsorption of Na^+ is significantly reduced by PGE_1, but not affected by PGE_2. Given the paucity of experimental evidence for PG action on the proximal tubule, this reported effect might have been due to a nonspecific action of PGE_1 on this part of this dog nephron.

One of the primary effects of endogenous PG is to produce a natriuretic effect by increasing Na^+ and Cl^- excretion in the kidney. Several groups have shown that when PGE_2 is added to the medium bathing isolated perfused segments of rabbit cortical and medullary collecting tubules, there is a reduction in the rate of Na^+ reabsorption from tubule lumen to bath as well as a significant decrease in transmembrane potential difference (106, 109, 110). Na^+ transport in renal epithelia is electrogenic and occurs primarily via the principal cell of this tissue. Na^+ enters the cell across the apical membrane by a passive conductive Na^+ channel and exits across the basolateral membrane via an electrogenic Na-K-ATPase. Recent reports indicated that the inhibitory effect of PG may be mediated indirectly through actions on the basolateral Na-K-ATPase by blocking Na^+ conductance on the apical membrane (110, 111). Recently, it was shown that PGE_2 can stimulate intracellular Ca^{2+} and activate protein kinase C in *in vitro* perfused cortical collecting ducts (112). It is also possible then that inhibition of Na^+ could be accomplished via this latter mechanism.

Frazier *et al.* (113) were the first to demonstrate the effects of exogenous PG on transepithelial Na^+ transport in amphibian epithelia. Later reports demonstrated that PGE_1, PGE_2, $PGF_{2\alpha}$, and PGI_2 increase the short-circuit current, a measure of active Na^+ transport, across toad urinary bladder and frog skin epithelia (114–117). The toad bladder and frog skin have been used in many studies over the past several decades on epithelial transport and are accepted models of the mammalian distal nephron epithelial cell. Obviously, this stimulation of Na^+ transport in the amphibian skin by PG is opposite that seen in the mammalian nephron, where they are inhibitory in nature. The action of PG on Na^+ transport in toad bladder and frog skin is believed to occur by stimulating activity of the adenyl cyclase system (116).

Calcium and Phosphate Ions. There seem to be very few reports in the literature regarding the action of PG on Ca^{2+} and $PO_4^=$. In an early experiment (118) using thyroparathyroidectomized dogs, PGE_2 was found to block the phosphaturic action of parathyroid hormone. In later studies (119) using perfused rabbit proximal straight tubules, PGE_2 was found to have a mild inhibitory effect on NaCl and phosphate absorption. Preliminary studies from this same laboratory suggest that the action of PGE_2 may be by blocking the activation of adenyl cyclase by parathyroid hormone

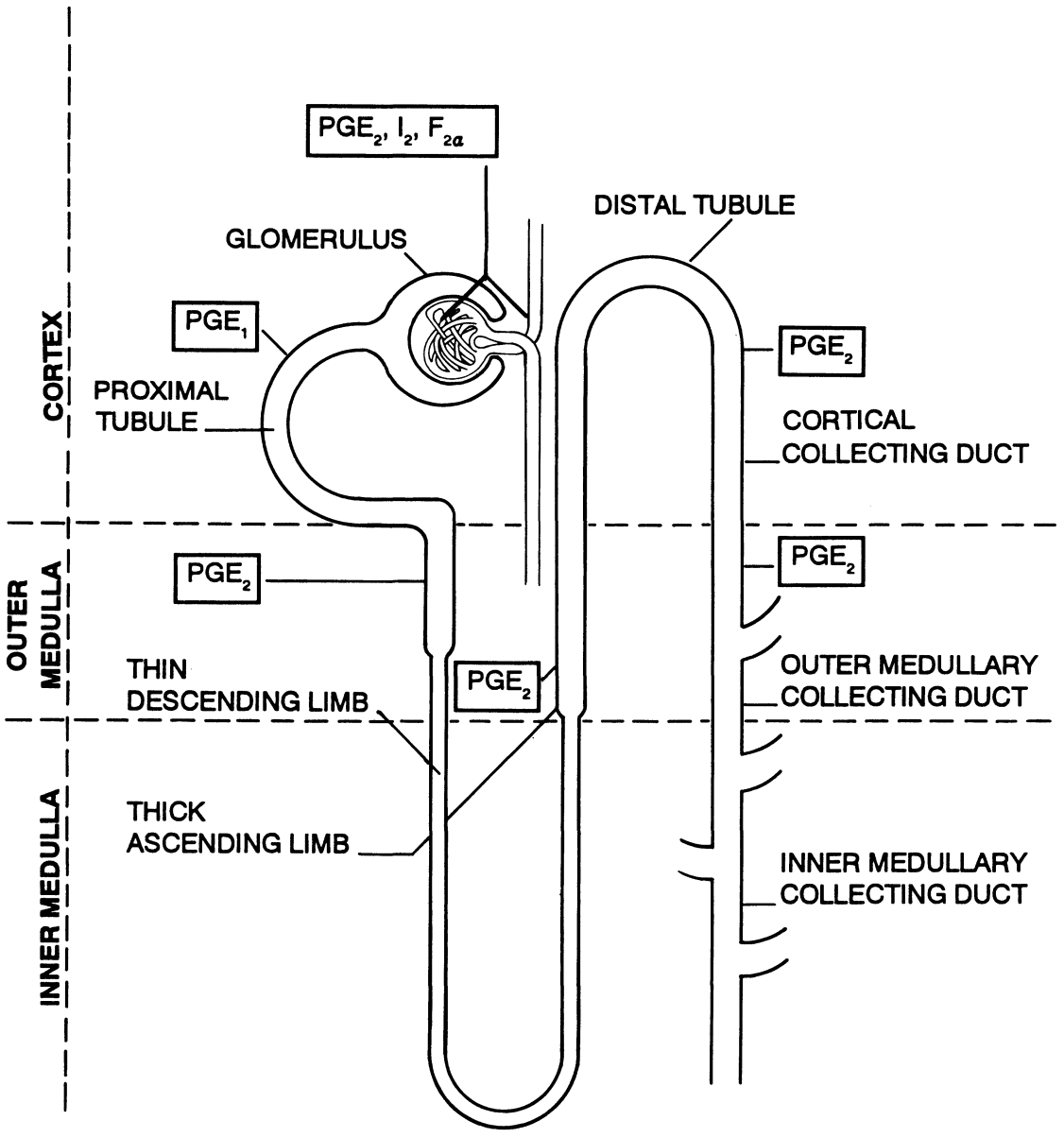

Figure 2. Diagram of mammalian nephron showing sites of action of various PG. The predominate effects on electrolyte transport are in the collecting duct and mediated by the PGE series.

via interaction at the inhibitory guanine nucleotide regulatory protein (120). Holt and Lechene (121) demonstrated that PGE_2, in the perfused rabbit cortical collecting duct, inhibited the reabsorption and, in some cases, actually stimulated the secretion of Ca^{2+} and $PO_4^{=}$. This experiment was performed in the absence of ADH, since ADH itself inhibits Ca^{2+} and $PO_4^{=}$ reabsorption distally. Therefore, these studies suggest that PGE_2 may mediate this inhibitory effect of ADH.

Amphibian skin and toad urinary bladder have both been shown to increase efflux of Ca^{2+} in response to PGE_1. Cuthbert and Wong (122) demonstrated in the toad urinary bladder that PGE_1 stimulates mucosal Ca^{2+} efflux. This increased efflux was attributed to increased permeability of the mucosal membrane by PGE_1. Likewise, the frog skin (123) has been shown to respond to PGE_1 in a similar manner.

Hydrogen and Ammonium Ions. There has been much less work done on the regulatory role of PG in the proton (H^+)-secreting tissues like the distal nephron. In a recent review, Schlondorff and Ardaillou (80) suggested, from a teleological point of view, that prostaglandins could well be important in the overall acid-base balance by the kidney cells. In 1987 (124), a study using conscious dogs reported that the urinary excretion of PG is dependent upon the acid-base state and urine acidity. This strongly suggested the possibility that PG and other eicosanoids contribute to the regulation or urine acidification. In a later study, Hays *et al.* (125), using rabbit medullary collecting ducts and microper-

fusion, were able to demonstrate a 12–15% reduction in H^+ excretion after exposure to PGE_2. In the same study, they also demonstrated that indomethacin, a PG synthesis blocker, was able to stimulate H^+ excretion by approximately 14%. Additionally, Stone *et al.* (126) showed that collecting ducts from adrenalectomized rabbits have a reduced H^+ excretion rate. The importance of this finding is based on the fact that desoxycorticosterone decreases PG production in rabbit cortical collecting tubules (127). Collectively, this body of evidence strongly suggests a role of PG in acid-base balance by the kidney.

Prostaglandins have also been implicated in the control of NH_4^+ excretion in the kidney. $PGF_{2\alpha}$ has been shown to inhibit the ammoniagenic response to acute acidosis in LLC-PK_1 cells through the stimulation of phosphoinositide turnover followed in part by the activation of protein kinase C (128). In addition, Kapoor *et al.* (129), using clearance studies in the intact rat, were able to show a stimulation of total ammonia production in the kidney by meclofenamate in both normal and metabolic acidotic rats. Since meclofenamate is an inhibitor of PG synthesis, this was taken as presumptive evidence of PG inhibition of total NH_4^+ production in the kidney.

Prostaglandins have also been shown to be important mediators of H^+ excretion in amphibian tissue, including toad urinary bladder, turtle urinary bladder, and frog skin. All three of these tissues excrete H^+ and this H^+ excretion is increased by a metabolic acidosis (130–132). Recent studies by Frazier and Yorio (24) using toad urinary bladder have demonstrated that PGE_2 at a concentration of 10^{-5} *M* and 10^{-6} *M* stimulates H^+ excretion by 2-fold in the normal toad. PGE_2 at these same concentrations had no effect on NH_4^+ excretion. In this same study, it was found that the toad bladder contains PGE_2, $PGF_{2\alpha}$, PGI_2, and 6-keto-$PGF_{1\alpha}$. Using labeling studies with ^3H-arachidonic acid, it was shown that the turnover rate of all four PG was increased by a chronic metabolic acidosis. However, only the concentration (ng (mg tissue)$^{-1}$) of PGE_2 was found to be significantly increased by metabolic acidosis. The authors were further able to show, by preloading the animals with mepacrine, an inhibitor of phospholipase A_2, that this prevented the increase in PGE_2 normally seen with acidosis (24). This finding implies that metabolic acidosis stimulates phospholipase A_2 activity in this tissue.

A previous study by Frazier (133) has also shown that vasopressin-stimulated water flow response in toad urinary bladder was reduced by inducing a chronic metabolic acidosis in the animal. This study suggested that the acidosis brings about an increased production of PG, which in turn inhibits the bladder's response to vasopressin. This also supports the hypothesis that PG synthesis may be increased by an acidic pH and hence could lead to PG stimulation of H^+ excretion.

Prostaglandins also appear to be important in controlling H^+ excretion in frog skin, a tissue similar to toad urinary bladder. In frog skin epithelia, it has been found that exogenous $PGF_{2\alpha}$ inhibits H^+ excretion at low concentrations ($ED_{50} = 5 \times 10^{-8}$ *M*) (134). This same study revealed that $PGF_{2\alpha}$, but not PGE_2, produced a dose-dependent inhibition of proton excretion that was still observed even when the animals were in metabolic acidosis. PGE_2 in toad bladder stimulated H^+ excretion at high doses, but at lower doses, it inhibited H^+ excretion (134). This latter response in toad bladder is similar to that observed above for $PGF_{2\alpha}$ in frog skin. It is possible that certain PG, like $PGF_{2\alpha}$, maintain low levels of H^+ excretion, and when the animal is in a state of acidosis, another PG, such as PGE_2, is stimulated and released at concentrations that will elicit increased H^+ excretion.

It has also been reported that PGE_2 inhibits H^+ excretion in the turtle urinary bladder (135). The investigators report an inhibitory dose-response for PGE_2 effect on H^+ excretion similar to that for $PGF_{2\alpha}$ in the frog skin. The reasons why PGE_2 stimulates H^+ excretion in toad urinary bladders and approximately the same concentrations inhibit H^+ excretion in turtle urinary bladder are not clear. This is most likely due to a species difference and/or a difference in predominate receptor type.

Potassium Ion. There is very little evidence that PG play any direct role on the metabolism of K by the renal tubular cells. PG, particularly PGE_2 and PGI_2, are overproduced and excretion is greatly enhanced in several hypokalemic disorders, including Bartter's syndrome (136). However, the failure of treatment with prostaglandin inhibitors in patients with Bartter's syndrome suggests that PG are not important in correcting the K^+ imbalance that is present (137).

Chloride and Bicarbonate Ions. In the above section, we examined the multiplicity of effects that eicosanoids exert primarily on cation transport processes. However, much less is known concerning eicosanoid actions on anion transport mechanisms and, more importantly, very few observations have been made concerning eicosanoid regulation of anion transport in the kidney. Early reports concerning prostaglandin effects on anion transport have come primarily from observations on chloride-secreting epithelia, such as the mammalian intestine (138) and the amphibian cornea (139). In the latter study, it was shown that administration of arachidonic acid to the bathing media of corneas mounted in Using chambers resulted in an increase in chloride transport (139). Further investigations revealed that the cornea was able to synthesize PGE_2 utilizing the exogenous AA, and there was a simultaneous increase in cyclic AMP after AA addition. It was subse-

Table II. Actions of PG on Electrolyte Transport in Renal Epithelia[a]

Ion activity	Tissue	PG					Ref.
		E_1	E_2	$F_{1\alpha}$	$F_{2\alpha}$	I_2	
Na^+ reabsorption	Rabbit proximal tubule		↓				104
	Rabbit medullary TALH		↓				106
	Rabbit cortical collecting duct		↓				109
	Rabbit medullary collecting duct		↓				110
	Dog proximal tubule	↓	→				108
	Toad urinary bladder	↑	↑			↑	115, 116, 117
	Frog skin	↑					114
Ca^{2+} reabsorption	Rabbit cortical collecting duct		↓				121
	Toad urinary bladder	↓					122
	Frog skin	↓					123
$PO_4^=$ reabsorption	Rabbit cortical collecting duct		↓				119
Cl^-/HCO_3^- reabsorption	MDCK cells		↑				88
	Frog skin				↓		148
H^+ excretion	Rabbit medullary collecting duct		↓				125
	Toad urinary bladder		↑	(high doses)	→		24
	Toad urinary bladder		↓	(low doses)			24
	Frog skin		→	→	↓		134
	Turtle bladder		↓				135
NH_4^+ excretion	LLC-PK_1				↓		128
	Rat kidney				↓		129
	Toad urinary bladder		→		→		24

[a] ↑, Increased activity; ↓, decreased activity; →, no change in activity. MDCK, Mardin-Darby canine kidney.

quently demonstrated that the increase in cyclic AMP was mediated by PGE_2, as indomethacin blocked the increase in cyclic AMP by AA (140). However, indomethacin did not totally block the increase in chloride transport. This observation led these investigators to consider alternative AA metabolites as contributing to the stimulation of chloride transport in this epithelial cell. In the ensuing studies, the lipoxygenase products LTC_4 and LTB_4 were found to have profound modulatory effects on chloride transport (141). Similar observations concerning AA stimulation of chloride transport have been reported in the small intestine (142) and colonic mucosa (143). Recently, apical chloride channels were also observed in cortical collecting duct cells in culture (144) and active chloride secretion was identified in rabbit cortical collecting duct (145). Most recently, chloride secretion in a renal-derived cultured epithelium, Madin-Darby canine kidney cells, was demonstrated (146). More importantly, PGE_1 stimulated this transport (146) and enhanced the acetylcholine and bradykinin increases in chloride transport (147). Our laboratory, using the renal-like epithelia, the frog skin, demonstrated that $PGF_{2\alpha}$ decreased mucosal to serosal bicarbonate transport, possibly by interfering with the conversion of CO_2 into bicarbonate (148). Additional studies are underway to further describe this mechanism. However, substantial work still remains with regard to the role of eicosanoids in anion transport.

In summary, it is quite clear that PG play a large role in control of electrolyte metabolism and acid-base balance by the kidney and other renal epithelia tissue. Table II is a summary of the different action of PG on the various electrolytes in renal tissue.

The pharmacological, biochemical, and structural characteristics of eicosanoid receptors are only now beginning to be unraveled. With the tools of molecular biology, pharmacological antagonists, and photoaffinity ligands, the facilitation of the identification and characterization of eicosanoid receptors will be forthcoming. As receptors are purified and sequences determined, comparisons of structural homology and binding domains can be described, allowing for the development of future therapeutic agents.

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