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Renal effects of drugs that inhibit prostaglandin synthesis

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There is extensive, clinical use of antiinflammatory drugs that inhibit prostaglandin synthesis in most, if not all, organs in the body. Much of the therapeutic efficacy of these agents depends on a reduction of prostaglandin synthesis at the site of inflammation. Not surprisingly, many of the side-effects of these drugs are secondary to decreased prostaglandin synthesis in brain, vasculature, stomach, lung, and kidney. In this review, we will focus attention on the effects of these antiinflammatory compounds on renal function, with particular emphasis on renin secretion, control of renal blood flow (RBF), and glomerular filtration rate (GFR). To describe these renal consequences of prostaglandin inhibition, we will briefly review the biochemistry of prostaglandin synthesis and the major known physiologic actions of prostaglandins in the kidney.

Renal synthesis of prostaglandins and thromboxane

Prostaglandins, endoperoxides, and thromboxanes are synthesized in the kidney. Arachidonic acid, a 20 carbon fatty acid, is the substrate for the synthesis of these products. The synthetic enzymes are collectively referred to as prostaglandin (PG) synthetase, which includes fatty acid cyclo-oxygenase (forming endoperoxides), endoperoxide isomerase (forming PGE_2), endoperoxide reductase (forming $PGF_{2\alpha}$), prostacyclin synthetase (forming PGI_2), and thomboxane synthetase (forming TxA_2) [1]. 6-keto-$PGF_{1\alpha}$ and TxB_2 are the spontaneous decomposition products of prostacyclin and TxA_2, respectively. Prostacyclin and TxA_2 are unstable in aqueous solutions at a pH of 7.4, and therefore 6-keto-$PGF_{1\alpha}$ and TxB_2 are used as stable markers of their labile precursors. Figure 1 summarizes these synthetic pathways.

These prostaglandins and thromboxanes are formed in both the renal medulla and cortex, although the activity of prostaglandin synthetase is fivefold to tenfold greater in the medulla [2]. There are differences between species as to the relative abundance of each end product of arachidonic acid oxygenation. It should be stressed that the majority of studies have used slices or microsomal extracts of renal cortex and medulla and, therefore, do not define or localize the segments of the nephron in which the prostaglandins are formed. Microsomes obtained from the medulla and cortex of human kidneys synthesize PGI_2, $PGF_{2\alpha}$, PGE_2, TxA_2, and PGD_2 [3]. In these in vitro experiments, PGI_2, PGE_2, and $PGF_{2\alpha}$ were the most abundant products; the synthesis of TxA_2 was, however, unequivocal [3]. Most prior publications have identified TxA_2 only after ureteral obstruction and not in the normal kidney [4]. In most species, PGE_2, PGI_2, and PGD_2 are vasodilatory, whereas endoperoxides and TxA_2 are vasoconstrictor [5]. $PGF_{2\alpha}$ is a weak vasoconstrictor. The in vivo measurement of renal prostaglandin synthesis has depended on the assay of renal venous plasma and urine. The prostaglandins in renal venous plasma and in urine are formed in the kidney and undoubtedly are not delivered to the kidney in the arterial blood [5, 6].

Stimulation of renal prostaglandin synthesis with bradykinin or angiotensin II (AII) increases PGE_2 and PGF_2 in both renal venous plasma and in urine [6–8]. Inhibition of renal prostaglandin synthesis with indomethacin or meclofenamate reduces renal venous and urinary concentrations of PGE_2 and $PGF_{2\alpha}$ by 50 to 75% [9]. Renal excretory rates of prostaglandins offer several advantages over renal venous plasma in the assessment of renal synthetic rates [5]. Urine collections provide an integrated measure of prostaglandin synthesis over hours to

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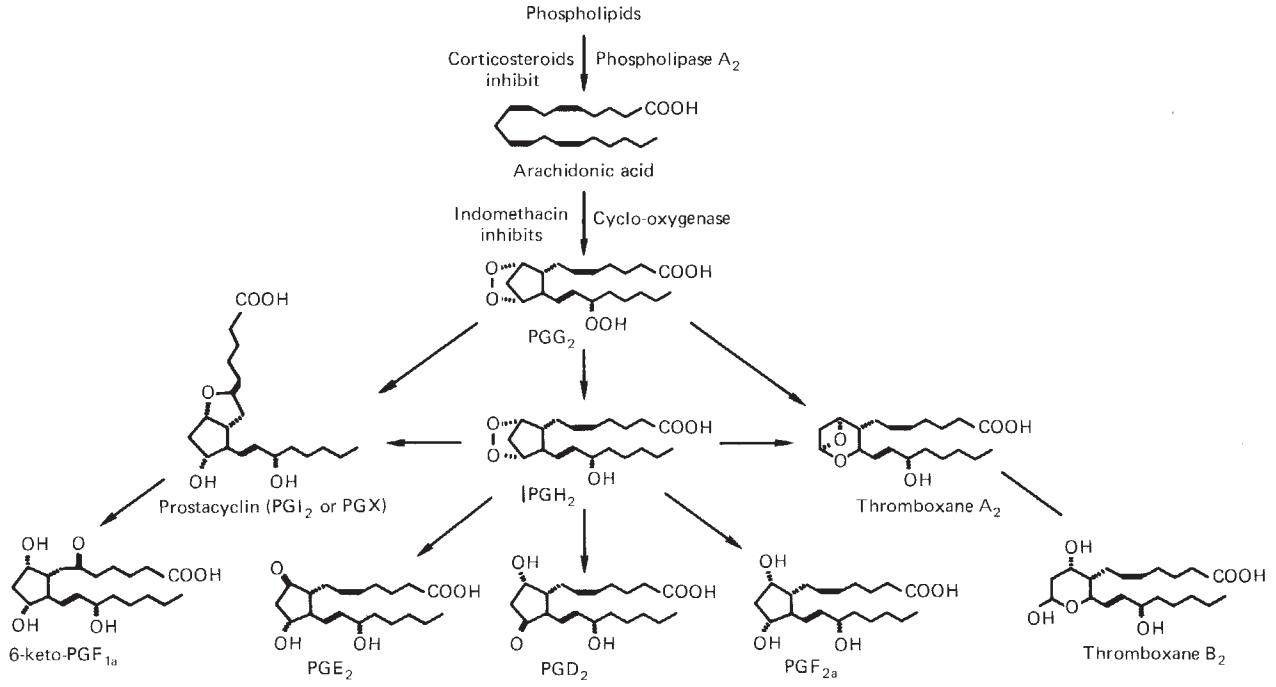

Fig. 1. *Biosynthesis of prostaglandins and thromboxane.* All of the products shown in this figure have been found in kidney or urine. Refer to the text for details.

days, urine can be conveniently obtained noninvasively, and urinary prostaglandin concentrations are less likely to be increased artifactually by nonrenal cells, whereas plasma concentrations may be elevated by platelet and leukocyte production of prostaglandins.

Recent work has emphasized the specific sites of prostaglandin synthesis in the kidney. Table 1 summarizes the incomplete information available from these studies. Several precautions should be expressed about this summary. The relative abundance of end products can be altered, in vitro, by cofactors and by the concentration of arachidonic acid. For example, the amount of PGE_2 formed by renal microsomes is dramatically increased by reduced glutathione [1]. The various studies summarized in Table 1 used different assays (radiometric thin-layer chromatography and radioimmunoassay), and the array of measured prostaglandins is obviously a function of assay sensitivity. Nonetheless, several conclusions seem warranted. First, cortical structures such as glomeruli and arterioles synthesize prostaglandins that are capable of controlling cortical physiologic events, including renal vascular resistance, renin secretion, and GFR. Older theories postulating that renal prostaglandins were primarily synthesized in the medulla and subsequently delivered to the cortex (via the return of urine to cortical tubules?) are unnecessary [17, 18]. It is simpler to assume that cortical functions are modulated by cortical synthesis of prostaglandins and that medullary events (medullary blood flow, collecting tubule response to vasopressin, sodium and chloride reabsorption in the Loop of Henle) are moderated by medullary synthesis of prostaglandins. Second, the prevalence of specific prostaglandins varies between different segments of the nephron. The physiologic significance of this observation is presently unknown.

The major known stimuli of renal prostaglandin synthesis are listed in Table 2. These data were ob-

Table 1. Renal sites of prostaglandin synthesis

Tissue	Products[a, b]
Glomeruli [10, 11]	$PGF_{2\alpha}$, > PGE_2, > TxA_2, > PGI_2 > PGD_2
Arterioles [12]	PGI_2
Cortical tubules [10, 11]	Trace amounts of PGE_2 and $PGF_{2\alpha}$
Collecting tubules (papillary) [13, 14]	PGE_2, > PGI_2, > $PGF_{2\alpha}$ > PGD_2
Medullary interstitial cells [15, 16]	PGE_2 >> $PGF_{2\alpha}$

[a]The relative abundance of each end product is affected in vitro by cofactors and the concentration of arachidonic acid. The prevalence of these prostaglandins, in vivo, is speculative.

[b]TxA_2 and PGI_2 synthesis were measured indirectly by the amounts of TxB_2 and 6-keto-$PGF_{1\alpha}$.

Table 2. Stimuli of prostaglandin and thromboxane synthesis in the kidney

Peptides	Angiotensin II [6, 7]
	Bradykinin [6, 8]
	Vasopressin [19–21]
Disease	Ischemia (renal arterial stenosis or hypotension) [6, 22]
	Ureteral obstruction (unilateral) [4, 23]
	Cirrhosis with ascites [24]
	Acute renal failure? [25]
	Hypertension? [26]
Miscellaneous	Catecholamines [27, 28]
	Calcium ionophore (A23187) [29]
	Furosemide [30]

tained in vivo with animals and man, in vitro with renal slices, and in vitro with cell cultures of renal medullary interstitial cells. The best documented mechanism, through which prostaglandin synthesis is stimulated, is increased availability of arachidonic acid [19]. These stimuli enhance the activity of phospholipase A_2 and thereby deacylate phospholipids to yield more arachidonic acid. The increased concentration of arachidonic acid, in the presence of an active cyclo-oxygenase, rapidly forms more prostaglandins and thromboxane, which can appear within seconds to minutes. It is probable, although unproved, that diseases such as unilateral ureteral obstruction and renal ischemia stimulate the synthesis of prostaglandins and/or thromboxane through the intrarenal release of AII, bradykinin, or catecholamines. Indirect evidence suggests that blockade of AII and of alpha adrenergic receptors will substantially reduce the compensatory release of renal prostaglandins in response to decreased renal perfusion [31]. Several different experiments also suggest that ureteral obstruction and chronic vasopressin administration can stimulate increased enzyme synthesis of either phospholipase, cyclo-oxygenase, or thromboxane synthetase [32, 33]. It seems likely that increased synthesis of enzymes beyond the phospholipase step may play an important role in the more chronic responses of the prostaglandin and thromboxane pathways.

Table 3. Inhibitors of fatty acid cyclo-oxygenase

Aspirin type	Acetylsalicyclic acid
	Salicyclic acid[a]
	Phenacetin[a]
Nonsteroidal antiinflammatory drugs	Indomethacin (Indocin®)
	Meclofenamate
	Phenylbutazone (Butazolidin®)
	Ibuprofen (Motrin®)
	Naproxen (Naprosyn®)
	Tolmetin (Tolectin®)
	Fenoprofen (Nalfon®)
	Sulindac (Clinoril®)

[a] Salicyclic acid must be converted, in vivo, to gentisic acid; phenacetin is converted to acetaminophen. These metabolites are active inhibitors of prostaglandin synthesis [35].

Inhibitors of prostaglandin synthesis. Since the original observation by Vane [34] and Flower and Vane [35] that aspirin inhibited prostaglandin synthesis, a large number of compounds have been discovered that inhibit the fatty acid cyclo-oxygenase. Table 3 enumerates many of the compounds commercially available and used in clinical medicine. Many other congeners are available for laboratory use. The efficacy of these drugs, as inhibitors of prostaglandin synthesis, varies between different organs (that is, different sources of microsomal cyclo-oxygenase studied in vitro) [35]. There are also in vivo differences by virtue of metabolism and excretion of the drug and perhaps because of limited access to the intracellular cyclo-oxygenase enzyme. Acetylsalicyclic acid acetylates the cyclo-oxygenase protein and thereby irreversibly inhibits this enzyme [36]. The effect of aspirin is dissipated only after the synthesis of new enzyme. Unlike the platelet cyclo-oxygenase, which is inhibited by aspirin for the life of the cell, renal cyclo-oxygenase turnover or synthetic rates are rapid, and the aspirin-mediated inhibition disappears after 24 to 48 hours [37]. The "nonaspirin," nonsteroidal, antiinflammatory drugs inhibit reversibly the cyclo-oxygenase. These drugs apparently dissociate from the cyclo-oxygenase protein, and consequently, their inhibitory effects are progressively attenuated over 8 to 24 hours. After in vivo administration, these agents rarely inhibit prostaglandin synthesis by more than 80% [9]. It is unknown whether the residual, uninhibited 20% of prostaglandin secretion by the kidney is sufficient to support prostaglandin-dependent processes. Many investigators, possibly erroneously, have concluded that indomethacin and related compounds inhibit all prostaglandin production and therefore any physiologic function remaining after indomethacin is independent of prostaglandins. There may be pitfalls in this type of reasoning. An additional shortcoming of some studies, especially those using chronic therapy with indomethacin and its analogues, is the failure to document the extent of fatty acid cyclo-oxygenase inhibition. We have recently reported that the inhibition of renal excretion of PGE_2 and PGF_2, after chronic administration of indomethacin to diabetes insipidus rats, was progressively and completely overcome by coadministration of the vasopressin analogue, 1-desamino-*d*-arginine vasopressin (dDAVP) [33].

Stated differently, renal excretion of PGE_2 and $PGF_{2\alpha}$ increased tenfold and returned to normal values in indomethacin-treated rats with diabetes insipidus who recived 12 to 16 days therapy with dDAVP [33]. Any experimental protocol, whether in animals or man, using nonsteroidal inhibitors of prostaglandin synthesis should document the extent of inhibition by measurement of one or more of the prostaglandin or thromboxane end products.

These nonsteroidal agents are not selective inhibitors of fatty acid cyclo-oxygenase [5]. Indomethacin, the best studied prototype, has many other actions, some of which have no direct bearing on prostaglandin metabolism. Table 4 lists these effects. Because of these multiple actions, especially at high doses of indomethacin, one must be cautious in the interpretation that any physiologic function is prostaglandin-mediated if it is attenuated after indomethacin. The dependence of any process on prostaglandin synthesis should be examined with several prostaglandin inhibitors, evaluated after infusions of arachidonic acid, and examined after replacement of specific prostaglandins in the presence of cyclo-oxygenase blockade. With this approach, the nonspecific (and "nonprostaglandin") actions of indomethacin will be recognized, and misinterpretation will be minimized.

Table 4. Actions of indomethacin

A. Prostaglandin-related actions
   1. Inhibit prostaglandin synthesis (cyclo-oxygenase) [35]
   2. Reduce prostaglandin degradation (15-hydroxy-dehydrogenase) [38]
   3. Reduce conversion of PGE_2 to $PGF_{2\alpha}$ (9-ketoreductase) [39]
   4. Reduce arachidonic acid release (phospholipase A_2) [40]
   5. Inhibit renal tubular transport of prostaglandins [41]

B. Prostaglandin-unrelated actions
   1. Inhibit cyclic AMP degradation (phosphodiesterase) [42]
   2. Decrease cellular efflux of cyclic AMP [43]
   3. Inhibit cyclic AMP-stimulated protein kinase [44]
   4. Compete with aldosterone for mineralocorticoid receptors [45]
   5. Reduce angiotensin II binding to adrenal cells [46]
   6. Alter smooth muscle contractility by inhibition of calcium transport [47]

Prostaglandins, RBF, GFR, and drug-induced renal failure

Animal studies. Renal prostaglandins exert little or no important control over resting or basal RBF in conscious animals. These conclusions are based on the inability of indomethacin or meclofenamate to reduce RBF despite significant reductions of prostaglandin synthesis [9, 48, 49]. We found that inhibition of renal prostaglandin synthesis did not alter RBF or renal vascular resistance in unanesthetized dogs. These results contrast with earlier work demonstrating that inhibition of prostaglandin synthesis with indomethacin, meclofenamate, ibuprofen, and tolmetin reduces RBF in anesthetized and instrumented animals and in isolated perfused kidneys [50–54]. The role of renal prostaglandins in the control of resting RBF in man remains an open question. Nowak and Wennmalm have reported that 50 mg of indomethacin, given i.v., acutely increased renal vascular as well as splanchnic resistance (30% and 16%) [55]. Infusion of PGE_1, 4 to 8 mg/min, returned renal vascular resistance and RBF to normal. Whether these increments of renal vascular resistance, after indomethacin, are directly related to prostaglandin inhibition remains unclear, because nonvisceral resistance did not rise after indomethacin and yet PGE_1 infusion also increased nonvisceral blood flow. The changes of RBF in response to both indomethacin and PGE_1 were observed acutely, over 1 hour. It seems clear that renal ischemia or renal vasoconstriction will stimulate renal prostaglandin synthesis. This release of PGE_2 (? PGI_2 also) is compensatory and homeostatically modulates the extent of vasoconstriction. Figure 2 shows that the effects of AII or of renal arterial constriction on RBF in the dog kidney are inversely related to the compensatory response of the PGE_2 secretory rate as measured by renal venous concentrations of PGE_2. In these dogs, the compensatory return of RBF towards control levels, after the onset of renal arterial constriction or renal arterial infusion of AII, was positively correlated with the increment of renal venous PGE_2. More severe ischemia, induced by complete occlusion of the renal artery for 1 to 3 min, leads to postocclusive hyperemia with a predominant increase of RBF to the inner cortex. Indomethacin significantly reduces this reactive hyperemia in the dog [55a] and the cat [56] but not in the rabbit [57]. In contrast, prostaglandins may not be important in the autoregulatory control of GFR and RBF to alterations of perfusion pressure between 75 and 150 mm Hg because indomethacin and meclofenamate do not interfere with autoregulation in the dog [52, 58] or the rat [59]. It is important to also note several studies showing that sodium depletion, in the dog, sensitizes the animal to deleterious renal effects of prostaglandin inhibition; that is, decreased GFR, RBF, and sodium excretion [60, 61]. If renal synthesis of vasodilatory prostaglandins is blocked by indomethacin or meclofenamate, then vasoconstrictor effects of intra-

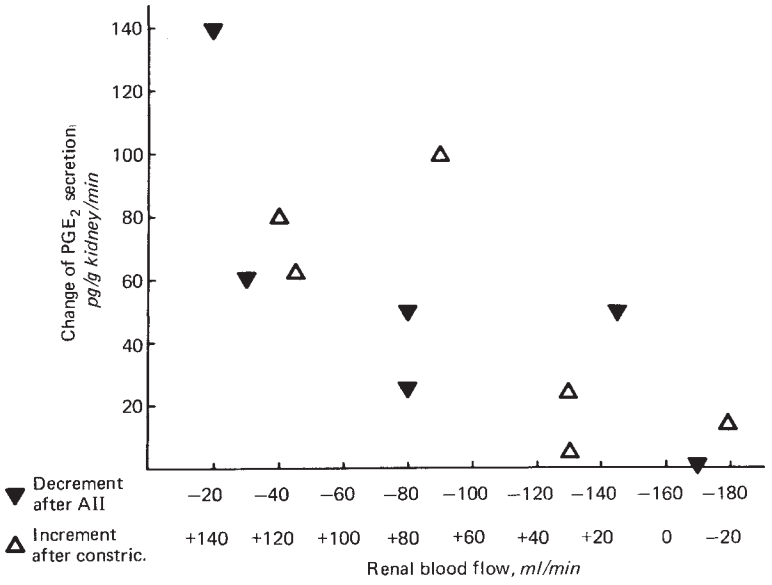

Fig. 2. *Relation between PGE_2 secretion and RBF.* The renal artery was partially constricted for 12 min or angiotensin II was infused, intrarenally, at 50 ng/min for 15 min. The values for RBF are shown as decrements or increments. These changes actually depict the compensatory return of RBF from the nadir after constriction (△) or the extent of the decrement after angiotensin II (▼). (From *Kidney Int* 13:136–143, 1978)

renal AII or norepinephrine, and renal neural stimulation are enhanced in dogs and cats [59, 62–65]. Hemorrhagic hypotension in dogs and baboons, when combined with cyclo-oxygenase blockade by indomethacin, meclofenamate, or R020-5720, induces more severe decrements of GFR and RBF than were observed in untreated, hemorrhaged animals [66, 67]. These observations in vasoconstricted animals are very important in our interpretations of the deleterious effects of indomethacin on GFR and RBF in vasoconstricted patients.

Baylis et al have demonstrated effects of PGE on the glomerular microcirculation. Infusions of PGE_1 into the rat renal artery reduced the glomerular ultrafiltration coefficient and increased glomerular plasma flow. The net effect was no change in the single nephron GFR [68]. It is well established that infusions of PGE_2 and PGI_2 do not alter the whole kidney GFR in normal animals. The response of the glomerulus to AII is also affected by the synthesis of prostaglandins [69]. Rats treated with cyclo-oxygenase inhibitors, prior to the infusion of AII, showed greater decrements of single nephron GFR and plasma flow and greater increments of afferent or efferent arteriolar resistance [69]. Inhibition of prostaglandin synthesis in rats with chronic (4 week) unilateral partial occlusion of the ureter increased arteriolar resistance and decreased glomerular plasma flow and GFR [70]. These studies clearly indicate a significant "protective" role for renal prostaglandins (vasodilatory) to preserve normal glomerular dynamics in the face of vasoconstrictor influences.

Because sustained, severe cortical vasoconstriction is observed in most, if not all, forms of both experimental and human acute renal failure, some studies have attempted to potentiate or exacerbate the development of renal failure by prior administration of indomethacin. Experiments in rats, using glycerol or mercuric chloride, showed no potentiation or renal injury after prior inhibition of prostaglandin synthesis [71]. Similar results were obtained in rabbits given mercuric chloride [72]. Rabbits given glycerol and huge doses of indomethacin (24 mg/kg over 6.5 hours) developed a more severe renal failure [72]. These experiments in animals do not establish any clear relationship between inhibition of prostaglandin synthesis and an increased risk of acute renal failure.

Because of our belief that intrarenal prostaglandins serve a protective role under conditions of ineffective circulating volume and high levels of AII, we designed experiments in dogs in which hepatic disease was induced by chronic bile duct ligation and renal function was then measured 36 to 78 days later, before and after an acute dose of indomethacin. RBF and GFR decreased and renal vascular resistance increased in all bile duct-ligated dogs after

the inhibition of renal prostaglandin synthesis. Changes in RBF and GFR were greater in dogs with ascites. There were no significant changes of RBF in the sham-operated controls. Indomethacin produced a 90 to 95% reduction in the renal excretion of both PGE_2 and $PGF_{2\alpha}$ in both the sham-operated controls and the bile-duct-ligated experimental animals. The accompanying changes in plasma renin activity, and fractional sodium excretion were variable and did not achieve statistical significance. Nevertheless, the hypothesis warrants further exploration that hepatic disease may stimulate the renal synthesis of prostaglandins in some animals and that when this augmented synthetic rate is inhibited by indomethacin, this may have a deleterious effect on renal function.

Human studies. Indomethacin, 150 mg/day for 3 days, reversibly reduced GFR in normal volunteers who were sodium restricted (50 mEq/day for 4 days) [73]. Although the GFR fell in 7 of 7 subjects (mean decrease of 9 ml/min) the effective renal plasma flow was unchanged. In the same study, in 10 of 10 patients with renal parenchymal disease or a solitary kidney, indomethacin reduced GFR and renal plasma flow (16 ml/min and 30 ml/min mean reduction) during sodium restriction. Other reports of the effects of indomethacin in normal subjects have shown no changes of GFR despite restriction of sodium to 9 mEq/day for 7 days and indomethacin, 150 mg/day [24, 74]. In 19 nephrotic patients, the GFR decreased 35% (19 of 19 decreased) and renal plasma flow fell 23% (16 of 19) [75]. Two patients dropped their GFR by 65% and 76% during indomethacin therapy. These changes appeared within 24 hours and disappeared rapidly after cessation of drug administration, suggesting a functional rather than a structural alteration [75]. These patients received a diet of 20 mEq of sodium per day, and it is not known whether equally severe changes would occur with higher sodium intakes. Interestingly, the proteinuria diminished 55% during indomethacin therapy. The reduced effective circulating plasma volume, a consequence of hypoalbuminemia, undoubtedly predisposes nephrotic patients to reductions of GFR and RBF after inhibition of renal prostaglandin synthesis. Two recent reports reenforce the importance of ineffective circulatory volume and impaired cardiovascular function as predisposing factors for renal toxicity of nonsteroidal antiinflammatory drugs. Zipser et al administered indomethacin or ibuprofen to 12 patients with severe hepatic disease and ascites [24]. Urinary levels of PGE_2 were increased prior to indomethacin, indicative of a compensatory role for renal prostaglandins in the maintenance of RBF in the presence of renal vasoconstrictor factors. Creatinine clearance decreased from 73 to 32 ml/min for the 12 patients, and serum creatinine rose from 0.7 to 1.2 mg/dl after 200 mg of indomethacin (10 cases) or 2000 mg of ibuprofen (2 cases) over 24 hours. The patients with the more severe hyperreninism dropped GFR from 68 to 18 ml/min [24]. Indomethacin has also been reported to cause decompensation of renal function in a patient with severe congestive heart failure [76]. Patients with ineffective circulating plasma volume, high plasma renin and AII, increased alpha adrenergic neural activity, and renal vasoconstriction depend on cortical synthesis of prostaglandins to modulate the vasoconstriction. Their response to indomethacin undoubtedly resembles the response of animals infused with AII or subjected to hemorrhage or chronic bile duct-ligation (that is, significant decrements of GFR and RBF and increments of afferent and efferent arteriolar resistance). Figure 3 summarizes these interactions.

The initial reports describing the effectiveness of indomethacin to induce closure of a patent ductus arteriosus in infants also noted the risk of transient oliguric acute renal failure [77, 78]. These early studies used higher doses of indomethacin (up to 5 mg/kg) than are used presently. At dosages of 0.2 mg/kg per 24 hours, 59 preterm infants responded favorably, showing transient decreases of urine output but no changes of serum creatinine [79]. Therefore, it appears that inhibition of fatty acid cyclooxygenase will close a patent ductus arteriosus in almost all infants, and the risk of renal failure is quite small.

Because the nonsteroidal antiinflammatory drugs are used primarily in patients with arthritic diseases, much attention has been paid to possible deleterious actions of these compounds on the kidneys. There is no clear relation between aspirin therapy and renal dysfunction in patients with rheumatoid arthritis. Epidemiologic studies of patients with rheumatoid arthritis, treated with salicylates, have not demonstrated an increased risk of renal damage [80]. Nonetheless, there are definite nephrotoxic changes after salicylate therapy; it is not known, however, whether this results from a direct toxic action of salicylates or from the reduction of prostaglandin synthesis. Salicylates can increase renal epithelial cell excretion, increase excretion of enzymes presumably derived from tubular cells, and decrease renal concentrating and acidifying

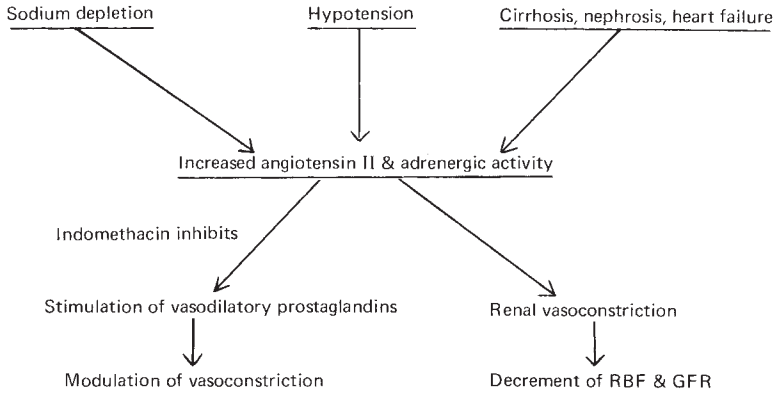

Fig. 3. *Balance between vasoconstrictor and vasodilator factors in the kidney.* Sodium depletion, hypotension, or an ineffective circulatory volume due to cirrhosis, nephrosis, or heart failure exert vasoconstrictor effects on the kidney that are modulated by release of vasodilatory prostaglandins (PGE_2 and PGI_2). If prostaglandin synthesis is inhibited with an antiinflammatory drug, then renal vasoconstriction is exaggerated, and GFR and RBF decrease significantly.

function [81]. After acute i.v. administration of acetylsalicyclic acid to dogs, significant reductions of RBF occurred when plasma salicylate concentrations were 27.5 to 50.0 mg/dl, but no reductions of GFR were observed [82]. Berg has reported significant renal alterations after oral or i.v. administration of acetysalicyclic acid to normal subjects [83] or to patients with chronic renal insufficiency [84]. In normal persons, aspirin transiently reduced sodium excretion, whereas in patients with reduced GFR (23 ± 7 ml/min) aspirin, 750 mg i.v., reduced GFR, RBF, and sodium excretion by approximately 50% [84]. These changes disappeared after 6 to 10 hours.

Kimberly et al have published a series of papers on their studies of the effects of aspirin and other inhibitors of prostaglandin synthesis on renal function in patients with systemic lupus erythematosus [85–87]. Approximately 50% of treated patients with plasma salicylate concentrations of 27 ± 1 mg/dl showed increments of blood urea nitrogen and serum creatinine after 7 or more days of aspirin therapy [85]. The occurrence of aspirin-induced renal dysfunction was strongly associated with preexistent glomerulonephritis and hypocomplementemia secondary to systemic lupus erythematosus. More detailed studies in 7 women with systemic lupus erythematosus, treated with aspirin to achieve serum salicylate levels of 25 to 30 mg/dl for 1 week, confirmed the original report [86]. Creatinine clearance and inulin clearance decreased 18% and 14%, respectively, and RBF (para-aminohippurate clearance) decreased 29%. Most of these patients had previous evidence of lupus nephritis. It is important to note that these patients had increased excretory rates for PGE_2 prior to aspirin therapy and, in this regard, are similar to cirrhotic patients in whom indomethacin caused severe reductions of GFR. Other nonsteroidal inhibitors of prostaglandin synthesis can induce similar decrements of GFR in patients with systemic lupus erythematosus [87].

Prostaglandin, renin release, and Bartter's syndrome

Prostaglandins and prostaglandin precursors are potent stimuli of renin release. Arachidonic acid, infused into the renal artery of experimental animals, stimulates renin secretion [88–90]. This stimulation of renin is dependent on the conversion of arachidonic acid to prostaglandin end products because indomethacin blocks the response [88–90]. There is substantial disagreement over the exact prostaglandin(s) responsible for stimulating renin secretion [91]. Studies of PGI_2 (prostacyclin), whether infused into the renal artery or added to cortical slices, have shown renin stimulation [92, 93]. PGE_2 has enhanced renin release in vivo [93–95], but does not directly stimulate renin release from cortical slices [91]. $PGF_{2\alpha}$ has generally exerted no effects on renin secretion [94, 95]. The renin-stimulatory actions of PGI_2 and PGE_2 are probably a direct action on the juxtaglomerular cells, because the nonfiltering kidney, with no distal delivery of filtrate to the macula densa, releases renin in response to arachidonic acid or prostaglandins [95–97]. Indomethacin and other inhibitors of prostaglandin synthesis inhibit but do not obliterate the response of renin to stimuli. The experimental studies with indomethacin and other inhibitors of prostaglandin synthesis have produced areas of agreement as well

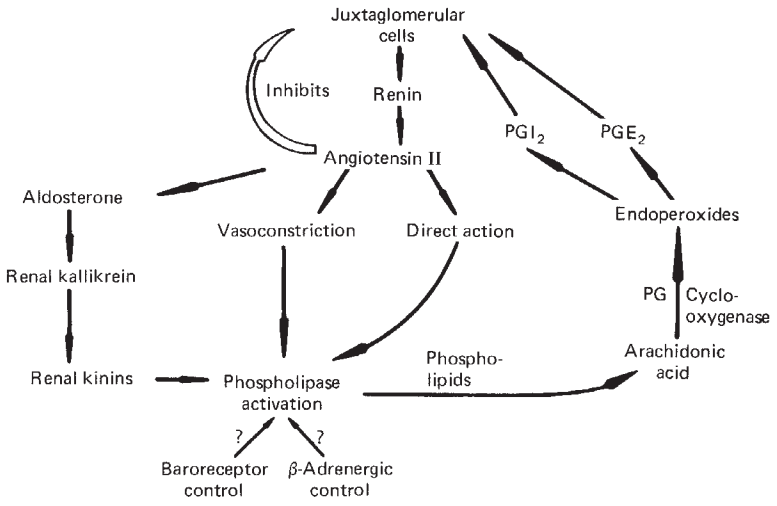

Fig. 4. *Prostaglandins and renin release.* This schema depicts our understanding of the literature on the subject of the renin-prostaglandin interaction. Other stimuli, besides those shown, do increase prostaglandin synthesis. The site at which baroreceptor and beta adrenergic receptor stimulation trigger prostaglandin synthesis is conjectural. Because indomethacin inhibits the cyclo-oxygenase enzyme, renin secretion is reduced in response to most stimuli.

as contradictory results and divergent interpretations. There is general agreement that indomethacin blocks basal renin release in man and animals [98–101]. Furthermore, most investigators agree that the macula densa is of minor or minimal importance in the prostaglandin-control of renin secretion [95–97]. Virtually all studies also demonstrated significant reduction or abolition by indomethacin of furosemide-stimulated renin secretion in animals and man [97, 98, 100, 102–104]. Disagreement is focused on the effects of indomethacin, and hence on the role of prostaglandins, in baroreceptor and in beta adrenergic receptor control of renin secretion by renal juxtaglomerular cells. Several studies in dogs showed no effect of indomethacin on renin release after reduced renal perfusion pressure [31, 97], whereas two other reports of experiments in dogs documented indomethacin blockade of renin release after reduction of renal perfusion pressure [96, 105]. Beta adrenergic stimulation of renin secretion was reduced or blocked by indomethacin in two studies (dog and rat [97, 106]), whereas indomethacin had little effect in other experiments (dog and man on low sodium intake [100, 105, 107]). Although a synthesis of these papers is risky, we believe the following schema is reasonable. Prostaglandins produced in the renal cortex, in glomeruli, and in arterioles stimulate renin release. The order of stimulatory potency is $PGI_2 > PGE_2 > PGD_2$. Renin release in basal and stimulated states are affected by these prostaglandins. Prostaglandins may serve an intracellular role related to cyclic AMP formation in the juxtaglomerular and glomerular cells. Although renin secretion is linked to these prostaglandins, this is not an all or none response, and parallel or alternative pathways of activating renin secretion exist. Therefore both baroreceptor and beta adrenergic receptor stimulation can be blunted by indomethacin but can persist if adequately activated. One must remember, when interpreting the indomethacin papers, that indomethacin has at least three actions on cyclic AMP systems (phosphodiesterase, protein kinase, and cyclic AMP transport; see Table 4). Consequently, some of its actions on renin release, a cyclic AMP-controlled event, could be independent of prostaglandins. Figure 4 summarizes the interrelations between renin, AII, kinins, and prostaglandin synthesis.

Recently, there has been renewed interest in Bartter's syndrome because of the discovery of increased renal excretion of PGE_2 and beneficial results after treatment with inhibitors of prostaglandin synthesis [74, 108–112].

Bartter's syndrome consists of many or all of the following: hypokalemia, inappropriate renal losses of potassium, sodium and chloride, metabolic alkalosis, hyperreninemia associated with juxtaglomerular cellular hyperplasia, hyperaldosteronism, reduced pressor responsiveness to AII, elevated urine and plasma levels of prostaglandins (PGE_2 and PGI_2), and normotension. The initiating defect in these patients is unknown, but Gill and Bartter have recently concluded that defective chloride reabsorption in the ascending limb of Henle's loop

triggers distal tubular potassium losses, secondary overproduction of prostaglandins, renin, and aldosterone, and further losses of potassium and chloride [113]. The evidence that potassium depletion can induce secondary overproduction of prostaglandins by the kidney is contradictory. Although potassium depletion in dogs apparently enhances urinary excretion of PGE [114] studies in potassium-depleted rats offer no supporting evidence that renal synthesis of PGE_2 or $PGF_{2\alpha}$ is increased [115]. Treatment of these patients with indomethacin, ibuprofen, naproxen, or aspirin has been beneficial. These drugs differ only in their potency, and indomethacin appears most potent and has been the preferred drug [112]. These inhibitors of fatty acid cyclo-oxygenase have the following beneficial effects in Bartter's syndrome: reductions of plasma and urine prostaglandins as well as aldosterone and renin, decreases of renal losses of potassium, sodium, and chloride, improvement of metabolic alkalosis, hypokalemia, and angiotensin resistance, and improved sense of health and well-being [74, 108–112]. These patients also have abnormalities of the kallikrein-kinin system with increased urine kallikrein, increased plasma bradykinin, and decreased kinins [74, 110]. Indomethacin reduces urine kallikrein, plasma kinins, and urine PGE_2 in parallel, whereas kinin excretion increases in patients with Bartter's syndrome. Normal subjects under severe sodium restriction (to raise aldosterone and urine kallikrein) did not, however, change urine or plasma kinins after indomethacin despite a 40 to 50% decrement of urine kallikrein [74]. It is unknown how prostaglandins affect renal synthesis of kallikrein, although it is presumed that overproduction of prostaglandins, in the kidney and systemically, stimulates urine kallikrein and plasma kinin because indomethacin suppresses these parameters. A direct action of indomethacin on the kallikrein-kinin system has not been ruled out. It is noteworthy that most cases of Bartter's syndrome respond to indomethacin with a decrease of creatinine clearance of 15 to 30%, which is transient and improves over 3 to 5 days [74] or is persistent at least for 1 week [112].

Renal prostaglandins, renin, aldosterone, and potassium may also be interrelated in the syndrome of hyporeninemic hypoaldosteronism [116]. Urine PGE_2 and $PGF_{2\alpha}$ were reported to be decreased in two cases of hyporeninemic hypoaldosteronism [116, 117]. Indomethacin induced this syndrome in a patient with mild chronic renal insufficiency [117], and the hyperkalemia improved after stopping indomethacin. Vinci et al observed no increases of serum potassium in indomethacin-treated normal subjects despite a small decrease of renal potassium excretion [74]. Hyperkalemia after indomethacin is probably rare and restricted to cases with hyporeninemic hyposldosteronism.

Prostaglandin inhibition: Sodium and water excretion. We will not attempt to review the complex and contradictory literature concerning the response of renal prostaglandins to the alteration of sodium intake or the interrelation between natriuresis and renal secretion or excretion of prostaglandins. Many reports have been published on the effects of aspirin, indomethacin, and related drugs on sodium and water balance in man and animals [5, 118]. There is no unanimity among these papers. Antiinflammatory drugs can alter sodium excretion through a direct action by removal of the effects of prostaglandins on tubular sodium reabsorption [119–121], reduction of RBF with secondary effects on sodium excretion, or competition for mineralocorticoid receptors [122]. The direct removal of a prostaglandin action on sodium transport seems the most plausible explanation for the majority of studies showing a decrement of sodium excretion after indomethacin. Acute administration of aspirin, indomethacin, or meclofenamate reduced renal excretion of sodium and water in dogs [82, 123], rats [122, 124], and man [24, 73, 75, 84, 125] either in the basal state or in some experiments only after sodium loading or sodium depletion. Other experiments with indomethacin have not shown alterations of sodium excretion [74, 99, 126]. We found no effects of indomethacin or meclofenamate on sodium excretion in the conscious dog [9]. Oliw et al found that indomethacin potentiated the natriuretic response to sodium loading in rabbits [127]. Many of these responses are acute and transient, and it appears that the chronic effects of these drugs are less dramatic [74, 99]. Although inhibition of renal prostaglandin synthesis augments, acutely, the renal response to vasopressin [128, 129], there is no clinical or experimental evidence of chronic retention of water or dilutional hyponatremia.

Because furosemide, given i.v., stimulated renal excretion (that is, synthesis) of PGE_2 and $PGF_{2\alpha}$ in animals and man [130–133], many investigators have evaluated the interactions of furosemide and other diuretics with indomethacin. Indomethacin reduced the acute natriuretic response to furosemide in the dog, rabbit, and man [99, 134–137]. Similar results were seen with MK447 and indomethacin in rats [138] and bumetanide and indomethacin in dogs [139]. Other authors report no significant

negative interaction between diuretics and indomethacin [100, 126].

It seems reasonable to conclude that prostaglandin inhibitory drugs can acutely reduce renal excretion of sodium and water and attenuate the renal response to diuretics. It is also likely that this action is entirely dissipated after several days unless the patient has a disease characterized by severe sodium retention (cirrhosis, heart failure, nephrotic syndrome). The recent reports of antagonism of the chronic antihypertensive actions of beta adrenergic blockers and diuretics by indomethacin are undoubtedly multifactoral and not simply secondary to a reduction of sodium excretion [140, 141].

Summary. The kidney synthesizes all known prostaglandins and thromboxanes, namely, PGE_2, PGI_2, $PGF_{2\alpha}$, PGD_2, and TxA_2. The major physiologic functions of these products of arachidonate oxygenation are control of RBF and GFR, stimulation of renin secretion, and modulation of sodium and water excretion. Indomethacin, aspirin, and related drugs inhibit fatty acid cyclo-oxygenase and thereby inhibit prostaglandin synthesis. Indomethacin in conventional doses, reduces renal synthesis of prostaglandins by greater than 75% within 1 hour of parenteral administration. These inhibitory drugs exert few, if any, deleterious effects on renal function in normal man or conscious, normal animals. If animals are volume-depleted, vasoconstricted, or bile-duct-ligated, then indomethacin can significantly decrease RBF, GFR, and sodium and water excretion. Patients with severe liver disease and ascites, lupus erythematosus, primary glomerular disease with and without the nephrotic syndrome, and advanced congestive heart failure will often respond to prostaglandin-synthesis-inhibitors with reductions of GFR and decrements of salt excretion. Suppression of renal prostaglandin synthesis in patients with Bartter's syndrome exerts salutary changes in the clinical course.

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