CHAPTER

32 Nephrotoxicity of Nonsteroidal Anti-inflammatory Agents, Analgesics, and Inhibitors of the Renin-Angiotensin System

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NEPHROTOXICITY OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs (NSAIDs) are some of the most widely used therapeutic agents in clinical practice today. Although the gastrointestinal toxicity of these medications is well known, it has become increasingly apparent that the kidney is also an important target for untoward clinical events. The renal toxicity associated with the use of NSAIDs can be divided into one of several distinct clinical syndromes. These include a form of vasomotor acute renal failure, nephrotic syndrome associated with interstitial nephritis, chronic renal injury, and abnormalities in sodium, water, and potassium homeostasis. The common link in these syndromes is a disruption in prostaglandin metabolism, the class of compounds whose synthesis is inhibited by these agents.

PROSTAGLANDIN BIOSYNTHESIS AND COMPARTMENTALIZATION

Prostaglandins are members of a class of compounds termed eicosanoids. Eicosanoids are biologically active fatty acids that are all derived from the oxygenation of arachidonic acid. The particular enzyme involved in the oxygenation process dictates which class of eicosanoid will be synthesized. Oxygenation of arachidonic acid by the enzyme cyclooxygenase is responsible for prostaglandin and thromboxane synthesis (Fig. 32.1). The enzyme lipoxygenase converts arachidonic acid to leukotrienes, lipoxins, and eventually, to hydro fatty acid derivatives such as hydroxyeicosatetraenoic acid (HETE). Finally, oxygenation by the cytochrome P-450 system generates epoxyeicosatrienoic acids (EETs).

The availability of free arachidonic acid is the rate-limiting step in eicosanoid biosynthesis. Normally, arachidonic acid is found esterified to membrane phospholipids, where it undergoes deacylation primarily under the influence of phospholipase A_2. Phospholipase A_2–mediated arachidonic acid release is a calcium-calmodulin–dependent step that is stimulated by vasopressin, bradykinin, angiotensin, and norepinephrine.[1] Once released, free arachidonic acid is either re-esterified back into membrane lipids or is converted into one of the biologically active eicosanoids.

The first step in the synthesis of prostaglandins and thromboxanes is a cyclooxygenase reaction in which arachidonic acid is converted into the cyclic endoperoxide prostaglandin G_2 (PGG_2). PGG_2 then undergoes a peroxidase reaction to form a second endoperoxide called PGH_2, which is accompanied by the formation of a superoxide radical. Both of these reactions are catalyzed by the enzyme cyclooxygenase (COX), also known as prostaglandin endoperoxide H synthase.[2,3] The cyclooxygenase and peroxidase reactions occur on distinct but neighboring sites on the COX enzyme. Once formed, PGH_2 has a short half-life and is rapidly acted on by a series of enzymes that produce biologically active prostaglandins or thromboxane. Prostacyclin synthase acts to form prostacyclin (PGI_2), thromboxane synthase forms thromboxane A_2, and isomerases are responsible for the formation of PGE_2, PGD_2, and $PGF_{2\alpha}$.

Prostaglandins are synthesized on demand and exert physiologic effects in discrete microenvironments along the nephron in close proximity to their points of synthesis (Table 32.1). Due to the virtual absence of distant effects, these compounds are best regarded as autacoids rather than hormones. Variations in the synthetic and degradative machinery along the length of the nephron account for the differing types and amounts of prostaglandins found in any given segment.[4] PGI_2 is the most abundant prostaglandin produced in the cortex and is primarily synthesized in cortical arterioles and glomeruli.[5] This location corresponds to the known effects of PGI_2 in regulating renal vascular tone, the glomerular filtration rate (GFR), and renin release. PGE_2 and thromboxane A_2 are also produced in the glomerulus and therefore may exert effects at this site.

The most abundant prostaglandin found in the tubules is PGE_2.[5] The cortical and especially the medullary portion of the collecting duct are the dominant sites of PGE_2 synthesis. Lesser amounts are found in the thin descending

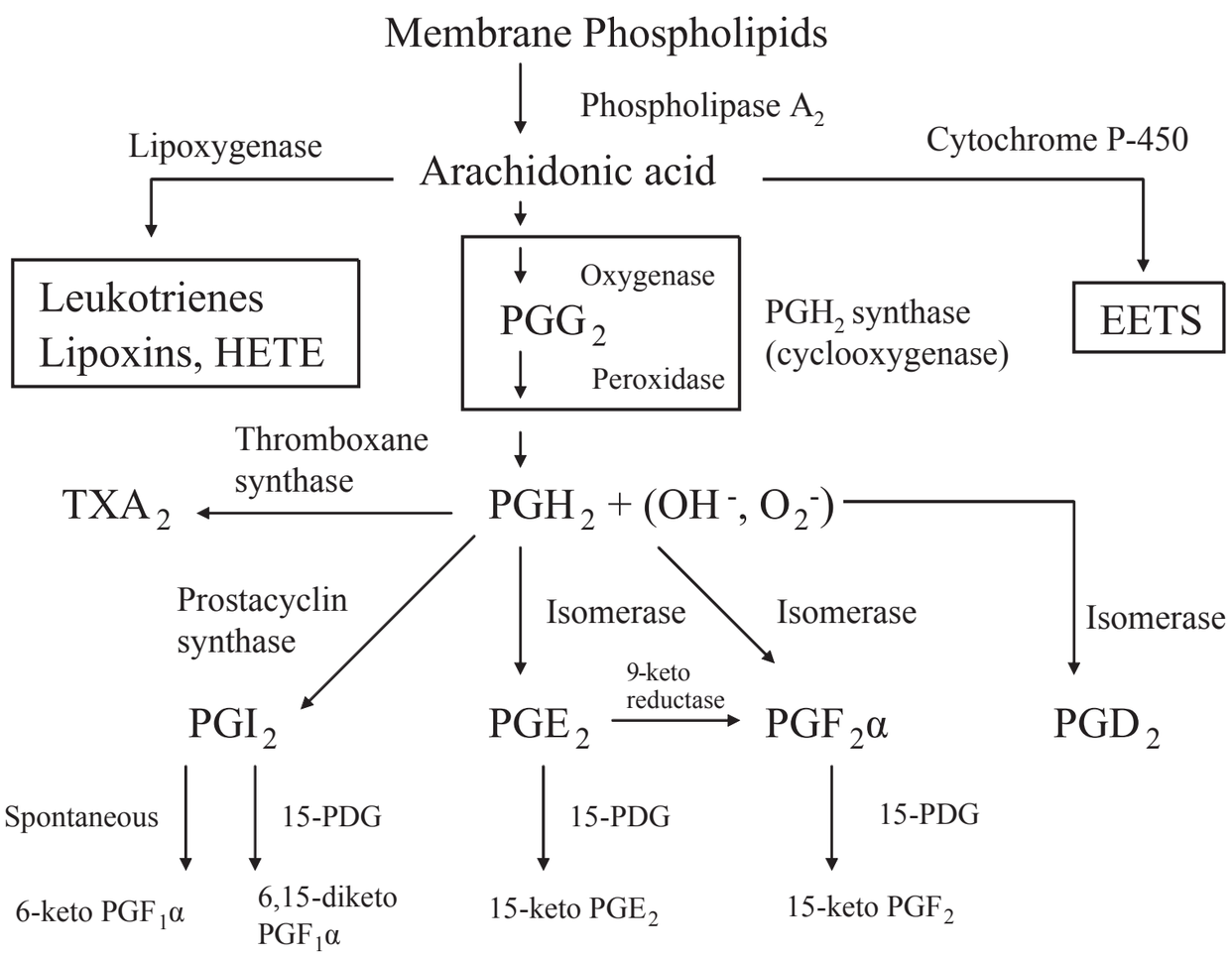

FIGURE 32.1 Synthetic and degradative pathways for the different types of eicosanoids. 15-*PDG*, 15 prostaglandin dehydrogenase; *EETs*, epoxyeicosatrienoic acids; *HETE*, hydroxyeicosatetraenoic acid; *TXA_2*, thromboxane A_2.

and thick ascending limb with the least amount of synthesis found in the proximal tubule. Medullary interstitial cells are also a rich source of PGE_2 production. This distribution provides the anatomic basis for PGE_2 to modulate sodium and chloride transport in the Henle loop, regulate arginine vasopressin-mediated water transport, and control vasa recta blood flow. $PGF_{2\alpha}$ is synthesized primarily by medullary interstitial cells and less by the papillary collecting tubule and glomeruli. Prostaglandin-degradative enzymes are found in both the cortex and medulla but are most abundant in the cortex. Except for PGI_2, which undergoes spontaneous hydrolysis to 6-keto-$PGF_{2\alpha}$, prostaglandins are rapidly metabolized into inactive products by a 15-prostaglandin dehydrogenase. An increased concentration of this enzyme in the proximal nephron may facilitate the degradation of prostaglandins delivered to the proximal tubule by glomerular filtration.[6]

32.1 Compartmentalization and Function of Renal Prostaglandins

Site	Eicosanoid	Action
Arterioles	PGI_2, PGE_2	Vasodilation
Glomeruli	$PGI_2 > PGE_2$ (human)	Maintain GFR
	$PGE_2 > PGI_2$ (rat)	Vasoconstriction
	TXA_2	
Tubules	PGE_2, $PGF_{2\alpha}$	Enhance NaCl and water excretion
Interstitial cells	PGE_2	Enhance NaCl and water excretion, influences regional blood flow
Juxtaglomerular apparatus	PGI_2, PGE_2	Stimulate renin release

PGI, prostaglandin I; PGE, prostaglandin E; PGF, prostaglandin F; TXA, thromboxane A; GFR, glomerular filtration rate.

BIOLOGIC ACTIONS OF PROSTAGLANDINS IN THE KIDNEY

Under baseline euvolemic conditions, prostaglandin synthesis is negligible, and as a result, these compounds play little to no role in the minute-to-minute maintenance of renal function. However, a major role occurs in the setting of a systemic or intrarenal circulatory disturbance. This interaction is best illustrated when examining the renal function under conditions of volume depletion (Fig. 32.2). In this setting, renal blood flow is decreased while sodium reabsorption, renin release, and urinary concentrating ability are increased. To a large extent, these findings are mediated by the effects of increased circulating levels of angiotensin II (AII), arginine vasopressin (AVP), and catecholamines. At the same time, these hormones stimulate the synthesis of renal prostaglandins, which in turn act to dilate the renal vasculature, inhibit salt and water reabsorption, and further stimulate renin release. Prostaglandin release under these conditions serves to dampen and counterbalance the physiologic effects of the hormones that elicit their production. As a result, renal function is maintained near normal levels despite the systemic circulation being clamped down. Predictably, the inhibition of prostaglandin synthesis will lead to unopposed activity

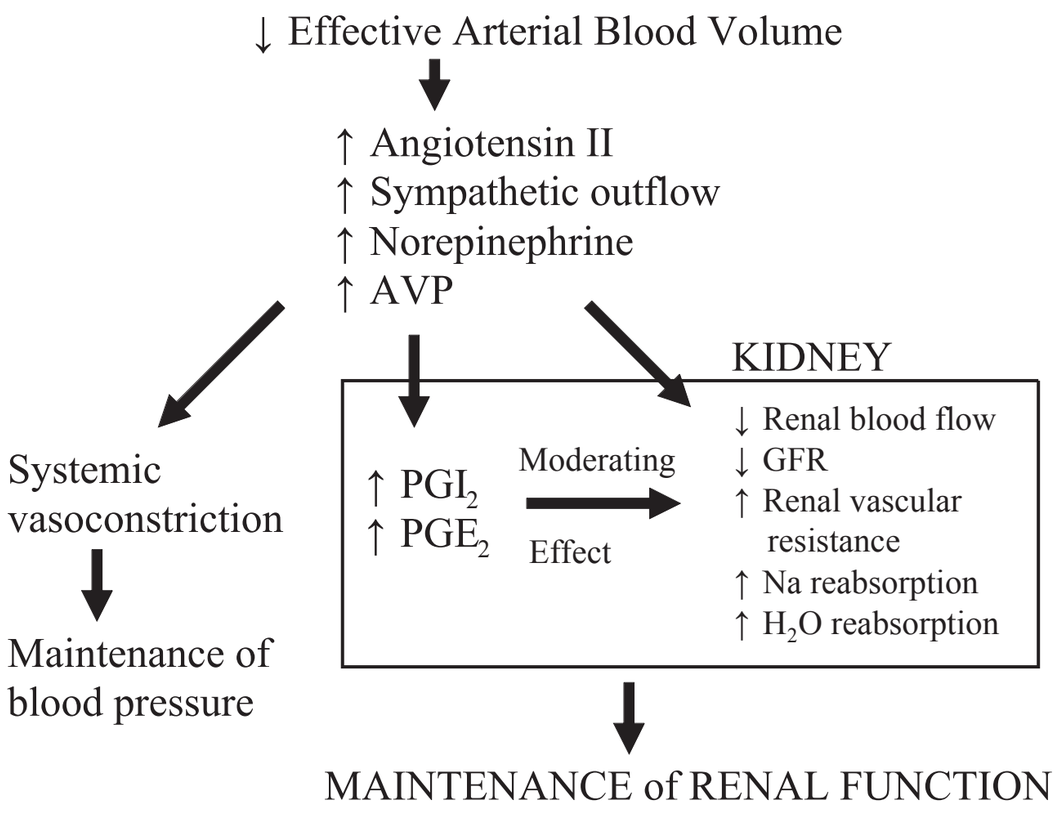

FIGURE 32.2 In the setting of absolute or effective volume depletion, a number of effectors are activated that serve to defend the circulation and, at the same time, stimulate the synthesis of renal prostaglandins. In turn, renal prostaglandins function to moderate the effects of these hormonal systems such that renal function is maintained in the setting of systemic vasoconstriction. *AVP*, arginine vasopressin; *GFR*, glomerular filtration rate.

of these hormonal systems, resulting in exaggerated renal vasoconstriction and magnified antinatriuretic and antidiuretic effects. In fact, many of the renal syndromes that are associated with the use of NSAIDs can be explained by the predictions of this model.

EEXPRESSION AND REGULATION OF CYCLOOXYGENASE-1 AND -2 IN THE KIDNEY

Aspirin and other NSAIDs exert their prostaglandin-inhibitory effects by inhibiting the COX enzyme. The COX enzyme exists as two isoforms termed COX-1 and COX-2. These enzymes are encoded by two different genes and differ significantly in their regulation. The COX-1 enzyme is constitutively expressed in most tissues and is responsible for producing prostaglandins involved in maintaining normal tissue homeostasis. The COX-2 enzyme is principally an inducible enzyme rapidly upregulated in response to a variety of stimuli such as growth factors and cytokines typically found in the setting of inflammation.[3] With the discovery of COX-2, a great deal of effort was put forth to develop compounds to selectively block the activity of this isoform without affecting the activity of COX-1. The availability of a COX-2–specific inhibitor would provide a therapeutic tool to inhibit the synthesis of arachidonic acid metabolites at sites of inflammation and yet leave unperturbed COX-1–derived prostanoids involved in normal homeostasis. In this manner the analgesic, anti-inflammatory, and antipyretic effects of an NSAID could be obtained with minimal to no side effects. Although the initial experience with specific COX-2 inhibitors has been associated with a reduction in gastrointestinal complications, this paradigm is not applicable to the kidney.

COX-1 and COX-2 are both constitutively expressed in the kidney. COX-1 is localized to mesangial cells, arteriolar endothelial cells, parietal epithelial cells of the Bowman capsule, and throughout the cortical and medullary collecting duct.[7] COX-2 is primarily expressed in the macula densa and the adjacent cells in the cortical thick ascending limb with lesser amounts in the podocytes and the arteriolar smooth muscle cells.[8–9] COX-2 is also abundantly expressed in interstitial cells in the inner medulla and the papilla.

The expression of COX-2 in different regions of the kidney varies in response to alterations in intravascular volume. This variation is particularly evident in the macula densa, where studies show COX-2 plays an important stimulatory role in the release of renin via the tubuloglomerular feedback mechanism. Under conditions of low renal perfusion when the chloride concentration at the level of the macula densa is low, renin release is inhibited by a COX-2 selective inhibitor but unaffected by a COX-1 inhibitor.[10] In genetically engineered mice lacking COX-2, there is a failure of renin release in response to a low salt diet, whereas renin release is intact in animals lacking COX-1.[11,12]

Stimulation of renin with the subsequent formation of angiotensin II is part of a feedback loop because angiotensin II exerts an inhibitory effect on COX-2 synthesis in the macula densa via the angiotensin type 1 (AT_1) receptor.[13] In contrast to effects at the macula densa angiotensin II upregulates COX-2 and prostaglandin synthesis in vascular smooth muscle cells and mesangial cells.[14] This latter effect provides a mechanism for COX-2 to both facilitate the tubuloglomerular feedback response to low salt delivery to the macula densa by increasing angiotensin II levels and preserve the glomerular filtration rate through the generation of vasodilatory prostaglandins to antagonize the vasoconstrictive effect of angiotensin II.[15]

The expression of COX-2 is also responsive to changes in volume. COX-2 expression decreases with salt depletion and increases with a high salt diet and dehydration.[9] COX-2–derived prostaglandins may play an important role in facilitating a natriuretic response to salt loading and may help protect against volume overload. The increase in COX-2 in response to dehydration is thought to provide a cytoprotective effect in the setting of hypertonic stress.[16,17] Treatment of water-deprived animals with a selective COX-2 inhibitor is associated with apoptotic patches of renal medullary interstitial cells. By contrast, no such changes are seen in animals treated with the inhibitor alone or in animals undergoing water deprivation without pharmacologic treatment.

In summary, COX-2 is constitutively expressed in the kidney and is highly regulated in response to physiologic perturbations in intravascular volume. The majority of experimental and clinical studies to date suggest that the specific COX-2 inhibitors may not offer any distinct advantage

over traditional NSAIDs with regard to renal toxicity. In fact, most of the renal syndromes that have been linked to nonselective COX inhibitors have now been described with the selective COX-2 inhibitors. The only exception is the development of chronic kidney disease and papillary necrosis. The failure to link COX-2 inhibitors use to these complications is not surprising because these agents have only been available for clinical use for a relatively short time. As with traditional NSAIDs, the COX-2 inhibitors need to be used cautiously and require close monitoring of renal function in patients at high risk for adverse renal outcomes.

EFFECTS OF PROSTAGLANDINS ON THE RENAL CIRCULATION

Prostaglandins primarily exert a vasodilatory effect on the renal vasculature. This vasodilatory effect alters the renal circulation in two major ways. First, these compounds influence the distribution of renal blood flow to different regions of the kidney. Prostaglandin stimulation results in a preferential increase in blood flow to the more juxtamedullary nephrons.[18,19] By contrast, the inhibition of prostaglandin synthesis results in a selective reduction of flow to the inner cortical nephrons while flow remains well preserved in the outer cortex.[20] Second, prostaglandins exert a vasoregulatory effect on the renal microcirculation to include the interlobular, afferent, and efferent arterioles as well as the glomerular mesangium. In isolated renal arterioles, both PGE_2 and PGI_2 attenuate AII-induced and norepinephrine-induced afferent arteriolar vasoconstriction. On the efferent side of the circulation, PGI_2 similarly antagonizes AII-induced and norepinephrine-induced vasoconstriction, but PGE_2 is without effect.[21] In addition to local production, vascular reactivity of the efferent arteriole appears to be influenced by prostaglandins produced in the upstream glomerulus. In this regard, Arima and associates[22] find that the orthograde infusion of AII (afferent arteriole-glomerulus-efferent arteriole) results in less vasoconstriction of the efferent arteriole as compared to when infused in a retrograde fashion (efferent arteriole-glomerulus-afferent arteriole). Pretreatment with indomethacin markedly increases the vasoconstrictive effect during an orthograde infusion but is without effect during the retrograde infusion.

Prostaglandins have also been shown to attenuate mesangial cell contraction induced by AII, endothelin, AVP, and platelet-activating factor.[23,24] Contraction of these cells will normally cause a decrease in the total glomerular capillary surface area and result in a fall in the GFR. Mesangial cell synthesis and the release of PGI_2 in humans and PGE_2 in rats dampen the constrictor effects of these hormones such that the glomerular capillary surface area is maintained, thereby minimizing any fall in GFR. Thus, in the setting of enhanced hormonal constrictor activity, prostaglandins play a major role in maintaining glomerular hemodynamics by exerting a vasodilatory effect at the level of the afferent and efferent arteriole as well as within the glomerular mesangium.

RENAL SYNDROMES ASSOCIATED WITH NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Vasomotor-Induced Acute Renal Failure

Prostaglandins appear to play a negligible role in the maintenance of renal function under normal circumstances. This conclusion is based on studies in both experimental animals as well as humans. In conscious, sodium-replete dogs and rats, the inhibition of renal prostaglandin synthesis with a variety of NSAIDs does not alter baseline renal blood flow or GFR.[25,26] Similarly, renal hemodynamics are unaffected in healthy humans after both the short-term[27,28] and the long-term administration of aspirin.[29] In related studies, the administration of indomethacin to healthy volunteers was also found to produce no change in renal hemodynamics.[30]

A sharply different effect of COX inhibition is observed when systemic hemodynamics are compromised. Under conditions of circulatory distress, renal blood flow represents a balance between vasoconstrictor influences on the one hand and vasodilatory prostaglandins on the other. Predictably, the administration of NSAIDs in this setting will shift this balance toward unopposed vasoconstriction and will potentially result in a precipitous decline in renal function.

This interplay between vasoconstrictive effectors and vasodilatory prostaglandins is particularly well illustrated in a series of studies using a model of hemorrhage in dogs.[31,32] In animals subjected to a hemorrhage, prostaglandin synthesis inhibition was associated with a marked reduction in renal blood flow as compared to prostaglandin-intact dogs. This renal ischemic response was found to be partly reversed after the infusion of an AII antagonist or after renal denervation. When renal denervation was combined with the AII antagonist, renal blood flow was restored to values comparable to that in the nonprostaglandin-inhibited animals. These findings illustrate the pivotal role that prostaglandins play in opposing the renal ischemic effects of AII and renal nerves.

The modulating effect of vasodilatory prostaglandins on renal hemodynamics can be expected to roughly parallel the extent to which vasoconstrictor effectors are activated. In turn, the activity of these effectors will reflect the degree of circulatory distress. With only mild perturbations in the circulation, one can begin to detect a discernible effect of prostaglandins on renal blood flow. For example, unlike subjects ingesting an ad lib sodium diet, normal subjects placed on a salt-restricted diet will demonstrate a modest fall in creatinine clearance and renal blood flow following the administration of aspirin or indomethacin.[33,34]

Diuretic therapy is a common clinical situation where NSAIDs may exert a deleterious effect on renal function in otherwise healthy subjects.[35] Like sodium restriction, diuretics

increase the dependence of renal blood flow and GFR on vasodilatory prostaglandins and potentiate the deleterious effects of prostaglandin inhibition with COX inhibitors. The degree to which renal function is disturbed, however, appears to vary depending on which diuretic–NSAID combination is used. In this regard, Favre and colleagues[35] found that the combination of triamterene and indomethacin given to healthy subjects results in a marked decline in creatinine clearance. By contrast, only a mild decrease in creatinine clearance is found when indomethacin is given in combination with furosemide, hydrochlorothiazide, or spironolactone. Interestingly, triamterene is the only diuretic associated with a marked increase in urinary prostaglandin secretion. Although there is little evidence to suggest that the renal failure patients in this study were volume-depleted, it appears that triamterene, by some unknown mechanism, renders the renal circulation critically dependent on vasodilatory prostaglandins. As a result, triamterene in combination with an NSAID should only be used with extreme caution.

As alterations in the circulation become more pronounced, rendering the renal circulation more dependent on vasodilatory prostaglandins, COX inhibition can be expected to result in more profound changes in renal hemodynamics. In congestive heart failure, a decrease in effective arterial circulatory volume is the proximate cause for activation of neurohumoral vasoconstrictor forces that participate in the maintenance of systemic arterial pressure and result in increased total peripheral vascular resistance. Important to note, the rise in renal vascular resistance is less than that seen in the periphery. Vasodilatory prostaglandins function in a counterregulatory role, attenuating the fall in renal blood flow and GFR that would otherwise occur if vasoconstrictor forces were left unopposed.[36]

Cirrhosis is another clinical condition in which the integrity of the renal circulation can become critically dependent on vasodilatory renal prostaglandins. Cirrhotic patients with a low urinary sodium concentration tend to be the most susceptible to develop acute decrements in renal function following the administration of NSAIDs.[37] These patients have a more marked decrease in effective arterial circulatory volume, primarily due to splanchnic vasodilation, which in turn leads to higher levels of circulating catechols, AII, and AVP.[38,39] As a result, the renal circulation in this subset of patients is more critically dependent on the effect of vasodilatory prostaglandins. As seen in patients with congestive heart failure, these patients have high urinary concentrations of PGE_2, which decline in parallel with the fall in GFR.[37]

Renal prostaglandins may play an important role in the maintenance of renal hemodynamics in nephrotic syndrome. GFR and filtration fraction are moderately decreased in most patients with the nephrotic syndrome.[40,41] Micropuncture studies in an experimental model of the nephrotic syndrome have indicated that the relative preservation of renal plasma flow may serve an important role in attenuating the fall in GFR that would otherwise occur due to a reduction in the ultrafiltration coefficient.[42] In this setting, locally produced vasodilatory prostaglandins may serve to reduce afferent arteriolar resistance, thereby increasing renal plasma flow and increasing filtration pressure.[43,44] The administration of NSAIDs in this setting would lead to increased afferent arteriolar tone. The resulting fall in renal plasma flow and filtration pressure combined with the already decreased ultrafiltration coefficient would result in a dramatic fall in GFR.[43] Indeed, the administration of prostaglandin synthesis inhibitors to nephrotic subjects is commonly associated with a fall in GFR and may precipitate acute renal failure in some patients.[45] Other settings in which there is an increased vasoconstrictive input focused on the kidney rendering it particularly vulnerable to the deleterious effects of NSAIDs include endotoxic shock[46] and anesthesia.[47]

Risk factors for the development of NSAID-induced acute kidney injury are not necessarily confined to conditions characterized by decreases in absolute or effective arterial circulatory volume (Table 32.2). One such example is the presence of underlying chronic kidney disease. In this setting, increased vasodilatory prostaglandins are thought to play an adaptive role in minimizing the decline in global renal function by increasing GFR in surviving nephrons through increased renal blood flow. The signal for increased prostaglandin production is generally not a disturbance in the systemic circulation leading to increased circulating levels of AII and catecholamines but rather intrarenal mechanisms leading to the generation of vasoactive compounds within the glomerular microcirculation.[48]

32.2 Risk Factors for NSAID-Induced Acute Vasomotor Renal Failure

Decreased EABV	Normal or ↑ EABV
Congestive heart failure	Chronic renal failure
Cirrhosis	Glomerulonephritis
Nephrotic syndrome	Elderly
Sepsis	Contrast-induced nephropathy
Hemorrhage	Obstructive uropathy
Diuretic therapy	Cyclosporin A
Postoperative patients with "third space" fluid	
Volume depletion/ hypotension	

EABV, effective arterial blood volume.

32.3 Predisposing Factors for NSAID-Induced Nephrotoxicity in the Elderly

Age-related changes in renal function
↓ in glomerular filtration rate ↓ in renal blood flow ↑ in renal vascular resistance
Age-related changes in pharmacokinetics
↑ free drug concentration - Hypoalbuminemia - Retained metabolites ↓ total body water ↓ hepatic metabolism resulting in longer drug half-life

Increasing age is a risk factor for the development of nephrotoxicity when using NSAIDs.[49,50] This susceptibility, in part, may be related to changes in kidney function that normally accompany the aging process (Table 32.3).[51] Aging is associated with a progressive decline in the GFR and total renal blood flow. In addition, there is an increase in renal vascular resistance. Important to note, the renal vasculature becomes less responsive to vasodilators, whereas the response to vasoconstrictors remains intact. In an analysis of 1,908 patients treated with ibuprofen, renal impairment was found to occur in 343 (18%) patients.[49] The two most important risk factors identified for the development of toxicity is an age greater than 65 years and preexisting renal insufficiency. In a prospective study of 114 older patients (mean age 87 years) started on NSAID therapy, a greater than 50% increase in the serum urea nitrogen concentration was found in 15 (13%) patients.[50] In this study, the concurrent use of a loop diuretic and large doses of NSAIDs were found to be predictive of those who developed significant azotemia.

In addition to age-related changes in kidney function, age-related changes in the pharmacokinetics of NSAIDs may also make this population more susceptible to renal toxicity.[52,53] Older patients, particularly those with chronic illness, often have lower albumin levels, which reduce the protein binding of the drugs and result in higher free-drug concentrations. This binding of the parent compound to circulating albumin is further impaired by retained metabolites, which accumulate as a result of the normal age-related impairment in renal function. Increased drug levels also occur as a result of the age-related decrease in total body water. Finally, decreased hepatic metabolism, which is often present in older adults, contributes to a longer half-life of the parent compound and can result in unexpectedly high drug levels.

Other conditions in which effective arterial circulatory volume is normal or increased and yet renal function is critically dependent on increased synthesis of prostaglandins include immune mediated glomerular injury, urinary obstruction,[54] radiocontrast-induced injury,[55] and the administration of calcineurin inhibitors.[56] In these conditions, the increased production of vasodilatory prostaglandins has been shown to counterbalance the effects of intrarenally generated vasoconstrictors such as thromboxane, leukotrienes, platelet-activating factor, and endothelin. The administration of NSAIDs in each of these settings can be expected to result in an exaggerated fall in renal function.

NSAID-induced acute kidney injury is most commonly an oliguric form of renal failure that begins within several days after the initiation of the drug (Table 32.4). The urinalysis is unremarkable in the majority of cases. Unlike other causes of acute kidney injury, the fractional excretion of sodium is often less than 1%. This low fractional excretion of sodium reflects the underlying hemodynamic nature of the renal failure. Hyperkalemia out of proportion to the decrement in renal function is also a typical feature of this lesion. If recognized early, the renal failure is reversible with the discontinuation of the NSAID. As a result, dialysis is usually not required.

Glomerular and Interstitial Disease

The use of NSAIDs can be associated with the development of a distinct syndrome characterized by the development of interstitial nephritis and nephrotic range proteinuria. The incidence of this lesion is unknown but is thought to be rare. One estimate for fenoprofen-induced interstitial nephritis was 1 case per 5,300 patient-years of treatment.[57] Although virtually all NSAIDs have been reported to cause this syndrome, the vast majority of cases have been reported in association with the use of propionic acid derivatives (fenoprofen, ibuprofen, and naproxen). Of these, fenoprofen has been implicated in greater than 60% of cases.[58] Interstitial nephritis with and without nephrotic syndrome has also been reported with the COX-2 inhibitors, rofecoxib and celecoxib.[59–63]

Unlike hemodynamically mediated ARF, there are no clear-cut risk factors that serve to identify those at risk for

32.4 Clinical Features of NSAID-Induced Vasomotor Renal Failure

• Oliguria
• Usually occurs within a few days of beginning medicine
• Hyperkalemia out of proportion to renal failure
• Low fractional excretion of Na
• Usually does not require dialysis
• Usually reversible

the development of this syndrome. The mean age of patients is 65 years.[58] The presence of an underlying renal disease prior to the exposure of the NSAID has been notably absent. This syndrome has generally been referred to as an example of acute interstitial nephritis. There are, however, a number of features that distinguish this form of interstitial renal disease from that observed with other pharmacologic agents (Table 32.5).[58] First, the average duration of exposure prior to the onset of the disease is typically measured in months and can be as long as a year. By contrast, allergic interstitial nephritis due to other drugs usually presents within several days to weeks after exposure to the drug. Second, nephrotic range proteinuria is found in >90% of cases of NSAID-induced interstitial disease, a degree of proteinuria that is distinctly uncommon in acute allergic interstitial nephritis due to other drugs. Third, symptoms of hypersensitivity that are commonly seen in acute allergic interstitial nephritis such as rash, fever, arthralgias, or peripheral eosinophilia are uncommon in NSAID-associated disease. Fourth, the vast majority of cases associated with NSAIDs have been reported in older patients. On the other hand, allergic interstitial nephritis is seen in all age groups.

Renal biopsy findings typically show a diffuse or focal lymphocytic infiltrate. The number of eosinophils in the infiltrate is variable but generally is not marked. The glomerular changes are most commonly those seen in minimal change disease. In particular, the glomeruli are normal by light microscopy, whereas fusion of the podocytes is seen with electron microscopy. In some cases there is evidence of glomerulosclerosis. Because most patients who develop this syndrome are older, this latter finding may simply represent the normal age-related increase in glomerulosclerosis. Immunofluorescent studies are typically nonspecific. There has been an occasional report of weak and variable staining for immunoglobulin G and C_3 along the tubular basement membrane. Electron microscopy typically shows a diffuse fusion of the podocytes in cases with heavy proteinuria. Mesangial, electron-dense deposits have been observed only rarely, suggesting that this is not an immune-mediated disease.

32.5 Clinical Characteristics of NSAID-Induced Tubulointerstitial Nephritis (TIN) Versus Typical Drug-Induced TIN

Characteristic	NSAID-Induced TIN	Typical Drug-Induced TIN
Duration of exposure	5 days to >1 year	5–26 days
Hypersensitivity symptoms	7%–8%	80%
Eosinophilia	17%–18%	75%–80%
Proteinuria >3.5 gms/24 hours	>90%	<10%
Eosinophiluria	0%–5%	80%–85%
Peak serum creatinine	1.5– >10 mg%	1.5– >10 mg%

Although the combination of interstitial nephritis and nephrotic syndrome is the most common clinical manifestation, a second presentation is the development of nephrotic syndrome without evidence of interstitial renal disease.[64] Once again, the glomerular histology is typical of minimal change disease, although a few patients have been described with changes typical of membranous glomerulopathy.[59,65] It is likely that the pathophysiologic mechanism that underlies the development of glomerular disease in the absence of interstitial disease is similar, if not identical, to the more common finding of combined nephrotic proteinuria and interstitial nephritis.

A third presentation that has uncommonly been reported is the development of interstitial nephritis without nephrotic proteinuria.[66,67] The onset of disease following the initiation of drug therapy tends to be much shorter and, in this respect, resembles the more common form of drug-induced allergic interstitial nephritis. In addition, these patients are more likely to exhibit a systemic hypersensitivity reaction. Given the closer temporal relationship between the administration of the offending NSAID and the development of renal insufficiency, one may confuse this latter presentation with that of NSAID-induced vasomotor ARF. Symptoms of hypersensitivity as well as histopathologic changes typical of interstitial renal disease should allow one to distinguish this lesion from hemodynamically mediated ARF.

Finally, NSAID toxicity may present as an exacerbation of an underlying disease. In a case report of a patient with systemic lupus erythematosus, the development of interstitial nephritis and nephrotic syndrome after the administration of naproxen clinically appeared as a rapidly progressive lupus glomerulonephritis.[68]

The clinical course of patients who present in any one of these manners is to develop a spontaneous remission after the removal of the offending NSAID. The time until resolution is variable but can range from a few days to several weeks. In some patients, the degree of renal insufficiency can be severe enough that dialytic support is required. Steroid therapy has been used in many of the reported cases; however, the efficacy and necessity of this therapy are unknown. It should be noted that relapses have been reported after inadvertent exposure to the same NSAID or after exposure to a different NSAID.[69]

Renal Sodium Retention

Sodium retention is a characteristic feature of virtually all NSAIDs, occurring in as many as 25% of patients who use them. The physiologic basis of this effect is directly related to

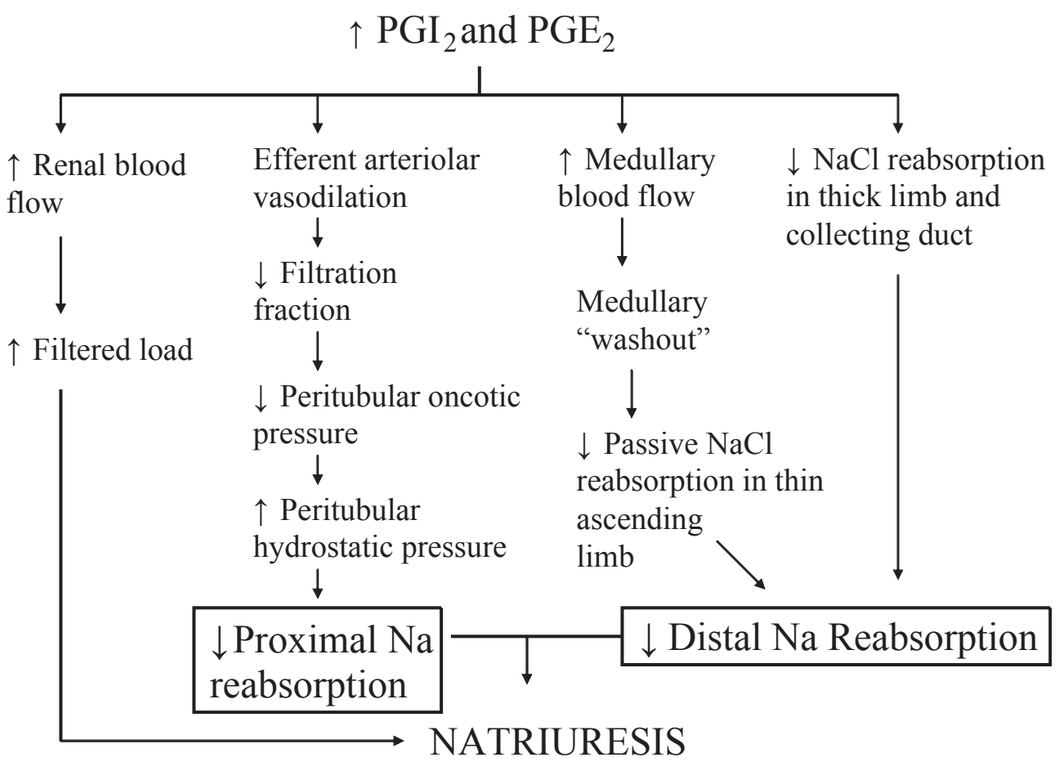

FIGURE 32.3 The direct and indirect mechanisms by which renal prostaglandins exert a natriuretic effect.

the natriuretic properties of prostaglandins. Prostaglandins increase urinary sodium excretion by both indirect and direct mechanisms (Fig. 32.3). Through their activity as renal vasodilators, prostaglandins may cause an increase in the filtered load of sodium. In addition, these compounds preferentially shunt blood flow to the inner cortical and medullary regions of the kidney.[19–21] As a result of increased medullary blood flow, there is a fall in the medullary interstitial solute concentration. Processes that reduce the degree of medullary hypertonicity lead to a concomitant reduction in the osmotic withdrawal of water from the normally sodium-impermeable thin descending limb of Henle. This in turn decreases the sodium concentration of fluid at the hairpin turn. The net effect is less passive reabsorption of sodium across the normally water-impermeable thin ascending limb of Henle. Consistent with this mechanism, the infusion of PGE_1 lowers and the prostaglandin synthesis inhibition raises sodium chloride and total solute concentration in the medulla.[70]

Finally, prostaglandins can affect sodium reabsorption in the proximal tubule by virtue of their ability to influence the tone of the efferent arteriole. Changes in the tone of this vessel play a central role in determining the Starling forces that govern fluid reabsorption in this nephron segment. Increased resistance of this vessel, as that which occurs in the setting of high concentrations of AII, leads to a decrease in the downstream peritubular hydrostatic pressure. In addition, efferent constriction increases the filtration fraction by reducing glomerular plasma flow and increasing the upstream glomerular pressure. The increased filtration fraction leads to an increase in the peritubular oncotic pressure. A decrease in hydrostatic pressure and the increase in oncotic pressure in the peritubular vessel favor fluid reabsorption in the proximal tubule. By modulating the degree to which the efferent arteriole is constricted and thus altering peritubular Starling forces acting on the proximal tubule, prostaglandins can decrease proximal tubular sodium reabsorption. Predictably, in a model of high circulating levels of AII induced by suprarenal aortic constriction, the inhibition of prostaglandin synthesis was found to increase efferent arteriole oncotic pressure and decrease peritubular hydrostatic pressure, resulting in a significant increase in proximal fluid reabsorption.[71]

In addition to these hemodynamically mediated changes in renal sodium handling, prostaglandins have direct effects on tubular sodium transport. In the isolated perfused tubule, PGE_2 has been shown to inhibit sodium transport in the cortical and outer medullary collecting duct.[72,73] Using the same technique, PGE_2 has also been shown to decrease chloride transport in the thick ascending limb of Henle.[74] In vivo studies also support a direct inhibitory effect of prostaglandins on the sodium transport in the loop of Henle, the distal nephron, and the collecting duct.[75,76] The mechanism of this direct inhibitory effect is unclear but may involve decreased activity of the Na^+-K^+-ATPase pump.[77] Prostaglandins have also been shown to mediate the natriuretic response to increased renal interstitial hydrostatic pressure that occurs during renal interstitial volume expansion.[78,79] In addition, these compounds play a permissive role in the sodium excretion that follows volume expansion and an increase in renal perfusion pressure.[80]

It would at first seem paradoxical that under conditions of volume depletion the kidney would elaborate a compound that would have further natriuretic properties. The role of prostaglandins in this setting, however, is to moderate the avid salt retention that would otherwise occur in the setting of unopposed activation of the renin–angiotensin–aldosterone and adrenergic systems. By virtue of their natriuretic properties, prostaglandins play a role in ensuring adequate delivery of filtrate to more distal nephron segments under conditions in which distal delivery is threatened (e.g., renal ischemia, hypovolemia). In addition, diminished NaCl reabsorption in the thick ascending limb of Henle reduces the energy requirements of this segment. This reduction in thick ascending limb workload in conjunction with a prostaglandin-mediated reallocation in renal blood flow helps to maintain an adequate oxygen tension in the medulla under conditions that would otherwise have resulted in substantial hypoxic injury.[81,82]

NSAIDs are thought to cause salt retention primarily by inhibiting prostaglandin synthesis and therefore disrupting the foregoing mechanisms. The extent to which salt retention becomes clinically manifest depends on the degree of baseline prostaglandin production. In normal healthy humans, baseline prostaglandin production is minimal. As a result, NSAID-induced positive sodium balance is transient and usually of no clinical importance. By contrast, NSAID administration in clinical conditions such as congestive heart failure, cirrhosis, or nephrotic syndrome can result in marked sodium retention and potentially adverse clinical consequences.

In addition to causing sodium retention, NSAIDs have been shown to attenuate the natriuretic effect of diuretics.[83] The mechanism of this resistance is multifactorial. The natriuretic effects of loop diuretics have, in part, been linked to

the ability of these drugs to increase renal blood flow, an effect mediated by the stimulation of vasodilatory prostaglandins.[84,85] By inhibiting prostaglandin synthesis, NSAIDs limit sodium excretion by preventing the increase in renal blood flow normally seen after the administration of the diuretic.[85] In addition to this hemodynamic effect, micropuncture and microperfusion studies have shown that prostaglandin inhibition also blunts the effect of furosemide at the level of the thick ascending limb of Henle.[86,87] This latter effect may be related to the inhibition of furosemide-induced stimulation of natriuretic prostaglandins that act within this tubular segment. Finally, NSAIDs may limit the diuretic response to loop diuretics by competing for tubular secretion, thereby limiting the delivery of the drug to the luminal surface of the thick ascending limb.

Indomethacin has also been shown to attenuate the diuretic response to hydrochlorothiazide.[88] The mechanism of this interaction may result from enhanced salt absorption in the loop of Henle, which would then limit the delivery of chloride to the site of the thiazide action in the distal nephron. A similar explanation may underlie the resistance that has been described with NSAIDs and spironolactone.[89]

Sodium Balance and Hypertension

In considering the natriuretic and vasodilatory properties of prostaglandins, it is not surprising that the administration of NSAIDs has been shown to interfere with blood pressure control. In pooled studies, the administration of NSAIDs has been associated with an average increase in blood pressure of between 5 and 10 mm Hg.[90,91] Of the various subgroups examined, this effect is most pronounced in patients who are already hypertensive and much less so in those who are normotensive. Of the hypertensive patients, those treated with β-blockers seem to be the most vulnerable to the hypertensive effect of NSAIDs.[91] In this regard, it is particularly interesting to note that propranolol has been shown to increase prostacyclin formation.[92] There is less of an interaction with diuretics and angiotensin-converting enzyme inhibitors, whereas no effect is seen with calcium channel blockers.

Subgroup analysis shows that patients with low renin hypertension (older adults and blacks) are at higher risk for worsening hypertension in association with NSAID use. Older hypertensive patients have reduced urinary PGE_2 excretion when compared to younger hypertensive patients.[93] The pathogenesis of NSAID-induced hypertension is not known with certainty. In a recent meta-analysis, NSAIDs were found to not alter body weight or urinary sodium excretion significantly, implying that mechanisms other than salt retention were responsible for the increased blood pressure.[91] In this regard, elimination of the vasodilator prostacyclin from the resistance blood vessels is believed to play some role in the development of hypertension in individuals at risk.[93,94]

The use of COX-2 inhibitors is complicated by the development of peripheral edema with a frequency similar to that seen with traditional NSAIDs. In addition, the majority of data suggest no difference between the various COX-2 inhibitors and the tendency to develop increased blood pressure.[95]

Potassium Metabolism

The use of NSAIDs has been associated with the development of hyperkalemia in the setting of chronic kidney disease as well as with normal renal function.[96,97] The physiologic basis for this effect is inhibition of prostaglandin-mediated renin release with the subsequent development of hypoaldosteronism. Both in vivo and in vitro studies have shown a direct stimulatory effect of prostaglandins (primarily PGI_2 and PGE_2) on renin release from the juxtaglomerular cells.[98,99] Clinical studies in salt-restricted subjects have shown the COX-2 selective inhibitors reduced urinary potassium excretion to a similar extent as traditional NSAIDs. Both celecoxib and rofecoxib have been reported to cause significant hyperkalemia in case reports. These findings are consistent with COX-2 in the macula densa playing an important role in stimulating renin release.

In addition to direct effects, these compounds play an essential intermediary role in those pathways that are of primary importance in the regulation of renin release. In particular, renin release stimulated by both decreased perfusion pressure and decreased delivery of filtrate to the macula densa is dependent on an intact cyclooxygenase system.[100] By contrast, β-adrenergic stimulation of renin release can occur independently of prostaglandin synthesis.[101]

NSAID-induced suppression of renin release with the subsequent development of a hyporenin–hypoaldosterone state is thought to be the primary mechanism of hyperkalemia. Decreased renin release leads to decreased circulating levels of angiotensin I, which in turn results in low levels of AII. Because AII normally stimulates aldosterone release from the zona glomerulosa cells in the adrenal gland, serum aldosterone levels fall. In addition to low circulating levels, the effect of any given level of AII on aldosterone release is impaired because prostaglandins have been shown to play an intermediary role in this stimulatory effect.[102] Low circulating levels of AII further contribute to the development of hypoaldosteronism because adequate levels of AII are required for the stimulatory effect of hyperkalemia on aldosterone release at the level of the adrenal gland.[103] In addition to interfering with the renin–angiotensin–aldosterone cascade, NSAIDs favor positive potassium balance in other ways. As discussed earlier, the inhibition of prostaglandin synthesis is associated with increased sodium reabsorption in the loop of Henle and thus decreased distal delivery. A reduction in sodium delivery to the aldosterone-sensitive cortical collecting tubule is a known factor impairing potassium excretion. In addition, tubular flow rates are an important determinant of potassium excretion. Because NSAIDs increase the hydroosmotic effect of AVP, flow rates can fall, further impairing potassium excretion. Finally, decreased synthesis of prostaglandins may have effects of decreasing potassium secretion at the level of the potassium channel.[104]

The development of hyperkalemia in patients receiving an NSAID is most likely to occur in the setting of renal insufficiency or those with baseline abnormalities in the renin–angiotensin–aldosterone system.[98] Diabetic patients are at risk due to the increased incidence of hyporeninemic hypoaldosteronism that occurs in this patient population.[105,106] Similarly, older adults are at higher risk by virtue of the normal age-related decrease in circulating renin and aldosterone levels. Particular caution should be used when NSAIDs are combined with other pharmacologic agents known to interfere with the renin–angiotensin–aldosterone cascade.[107] Examples would include β-blockers, calcineurin inhibitors, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, heparin, ketoconazole, high-dose trimethoprim, and potassium-sparing diuretics.

Water Metabolism

Prostaglandins have important modulatory effects on renal water metabolism. Their primary effect is to impair the ability to maximally concentrate the urine. In doing so, two processes that are central in the elaboration of concentrated urine are interfered with; namely, the generation of a hypertonic interstitium and maximal collecting duct water permeability. The decrease in interstitial hypertonicity is due to a washout effect that results from the ability of prostaglandins to shunt blood flow to the inner cortical and medullary regions of the kidney. In addition, prostaglandins decrease sodium absorption in the thick ascending limb and decrease AVP-induced urea permeability in the medullary collecting duct. The decreased accumulation of sodium and urea in the interstitium further reduces the interstitial osmolality. The impairment in the collecting duct water permeability is the result of prostaglandins opposing the hydro-osmotic effect of AVP.[108] Interesting to note, AVP is known to stimulate PGE_2 synthesis in collecting duct cells; by doing so, AVP induces its own antagonist. This interaction is another example in which prostaglandins exert a moderating effect on an effector mechanism that elicited their synthesis. In this case, prostaglandins play an important role in minimizing the water retention that would otherwise occur if the activity of AVP was unopposed. By opposing the vasoconstrictive action of AVP, prostaglandins also contribute to the maintenance of glomerular perfusion and filtration.

Based on the foregoing discussion, the administration of NSAIDs would predictably impair solute-free water excretion by increasing the hydro-osmotic effect of any given level of circulating AVP and increasing the degree of interstitial hypertonicity (Fig. 32.4). In most circumstances, however, hyponatremia is not associated with the use of NSAIDs. Under normal conditions, any decrease in serum osmolality would be sensed in the hypothalamus and result in the inhibition of AVP release. As a consequence, excess solute-free water would be promptly excreted, restoring the serum osmolality back to normal. On the other hand, the administration of NSAIDs in the setting of nonsuppressible AVP release may result in dramatic falls in the serum sodium concentration. Patients at risk for this complication would include those with high circulating levels of AVP driven by a decreased effective arterial circulatory volume such as congestive heart failure or cirrhosis.[109] Patients with syndrome of inappropriate antidiuretic hormone secretion (SIADH) or those taking medications capable of stimulating AVP secretion or impairing urinary dilution by other mechanisms are also at risk for the development of hyponatremia.[47]

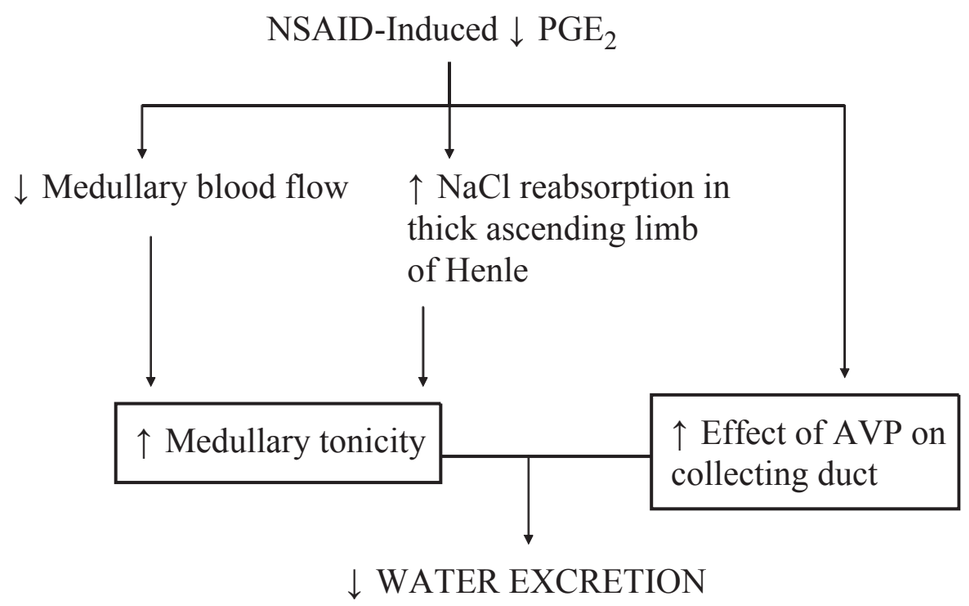

FIGURE 32.4 The mechanisms by which nonsteroidal anti-inflammatory drugs lead to decreased renal water excretion. *AVP*, arginine vasopressin.

In this regard, a recent study examined the effects of ibuprofen and a thiazide diuretic on renal water handling in otherwise healthy young and older volunteers subjected to a water load.[110] Three days of hydrochlorothiazide (100 mg per day) was found to impair both solute-free water clearance and the ability to elaborate a maximally dilute urine. A delay in the recovery of serum osmolality was noted in both the young and older subjects but to a significantly greater extent in the older subjects. When the young subjects were then given a water load after treatment with ibuprofen together with the thiazide, solute-free water clearance and serum osmolality were reduced further and to a degree similar to that seen in the older subjects on the thiazide regimen alone. It was postulated that the susceptibility to thiazide-induced hyponatremia known to occur in some elderly patients may, in part, be related to lower renal prostaglandin production. It can be expected that a greater number of older patients will be taking a combination of NSAIDs and hydrochlorothiazide given the efficacy of thiazide diuretics in the treatment of systolic hypertension.

NONSTEROIDAL ANTI-INFLAMMATORY DRUG-INDUCED CHRONIC KIDNEY DISEASE AND ANALGESIC NEPHROPATHY

The most common form of drug-induced chronic kidney disease is analgesic nephropathy. This lesion has most commonly been linked to the chronic ingestion of compound analgesics containing aspirin, phenacetin, and caffeine.[111]

A still unresolved question is whether long-term use of NSAIDs alone can similarly result in a progressive and irreversible form of chronic kidney disease. In this regard, a number of observations have emerged that would appear to substantiate the belief that long-term use of NSAIDs can lead to a chronic form of renal injury. Furthermore, the clinical characteristics of NSAID-induced chronic kidney disease are sufficiently different from those in analgesic nephropathy to suggest that this is a distinct clinical entity. Before reviewing the data linking chronic NSAID use and renal insufficiency, a brief description of analgesic nephropathy will be provided.

Analgesic nephropathy is a chronic kidney disease characterized by renal papillary necrosis and chronic interstitial nephritis.[111–113] The early reports linking analgesics and renal disease were generally found in patients who consumed combination products containing phenacetin. This fact focused attention on phenacetin as the primary cause of the syndrome and prompted many countries to officially remove the drug from nonprescription analgesics. Significantly, the removal of phenacetin has not been uniformly followed by the expected reduction in the incidence of the syndrome.[114] Given that other agents such as acetaminophen or salicylamide have been substituted for phenacetin in many combination products, the lack of decline in incidence of analgesic nephropathy suggests that the use of combination products is as important as whether the compound contains phenacetin.[114,115] This conclusion is further supported by the experience in Belgium where a strong geographic correlation exists between the prevalence of analgesic nephropathy and sales of analgesic mixtures containing a minimum of two analgesic components.[116,117]

Numerous epidemiologic studies performed in the past demonstrated a wide variation in the geographic incidence of analgesic nephropathy.[114,115,118–121] Much of this variability could be explained by differences in the annual per capita consumption of phenacetin.[113,114] In those countries with the highest consumption such as Australia and Sweden, analgesic nephropathy was found responsible for up to 20% of cases of end-stage renal disease. In Canada, which had the lowest per capita consumption, analgesic nephropathy accounted for only 2% to 5% of end-stage renal disease patients. It has been estimated that between 2% and 4% of all end-stage renal disease cases in the United States can be attributable to habitual analgesic consumption. Within the United States, there are also regional differences in the reported incidence of analgesic nephropathy, which are thought to be reflective of differences in analgesic consumption.[114,115,118,119] For example, the use of combination analgesics is more common in the southeastern United States, and the incidence of analgesic nephropathy is three to five times as common a cause of end-stage renal disease in North Carolina compared to Pennsylvania.[114,115,118,119]

The development of analgesic nephropathy is associated with a number of well-defined clinical characteristics.[122] The disease is more common in women by a factor of 2 to 6 and has a peak incidence at age 53 years. Patients typically consume compound analgesics on a daily basis, often for chronic complaints such as headache, dyspepsia, or to improve work productivity. It has been estimated that nephropathy occurs after the cumulative ingestion of 2 to 3 kg of the index drug. Often, patients will exhibit a typical psychiatric profile characterized by addictive behavior. Gastrointestinal complications, such as peptic ulcer disease, are common. The patients are frequently anemic as a result of gastrointestinal blood loss as well as renal insufficiency. Ischemic heart disease and renal artery stenosis have both been reported to occur with higher frequency in these patients.[113] In fact, regular use of analgesic drugs containing phenacetin is associated with an increased risk of hypertension and mortality and morbidity due to cardiovascular disease.[121,123] Finally, long-term use of analgesics is known to be a risk factor for the subsequent generation of uroepithelial tumors.[124]

Patients with analgesic nephropathy predominantly have tubulomedullary dysfunction characterized by an impaired concentrating ability, acidification defects, and occasionally a salt-losing state. Proteinuria tends to be low to moderate in quantity. Interesting to note, the pattern of proteinuria is typically a mixture of glomerular and tubular origin. Pyuria is common and is often sterile. Occasionally, hematuria is noted, but if persistent should raise the possibility of an uroepithelial tumor.

There are several features of analgesic nephropathy that make it difficult to diagnose. The disease is slowly progressive and the symptoms and signs are nonspecific. Patients are often reluctant to admit to a heavy usage of analgesics and therefore are either misdiagnosed or not diagnosed at all until the renal failure is far advanced. In addition, the lack of a simple and noninvasive test that reliably implicates analgesics as the cause of the renal injury has been an important limiting factor. Noncontrast abdominal computed tomography (CT) may emerge as a useful diagnostic tool in this setting given its usefulness in the diagnosis of papillary necrosis.[125] Characteristic findings by CT suggesting the diagnosis include small kidneys with an irregular contour and intrarenal calcifications, particularly in the medulla.

As mentioned earlier, there are a number of reports that suggest that chronic use of NSAIDs alone may also lead to renal injury. In this regard, several NSAIDs have been associated with the development of papillary necrosis either when administered alone or in combination with aspirin.[126] In addition to inhibiting prostaglandin synthesis, the ability of these agents to redistribute blood flow to the cortex, thus rendering the renal medulla ischemic, may underlie this association. Although the reports linking papillary necrosis and NSAIDs are predominantly anecdotal in nature, more recent observations would suggest that chronic renal failure resulting from long-term use of NSAIDs may be more prevalent than once thought.[127,128] In a multicenter case-control study, Sandler and associates[127] reported a twofold increase in the risk for chronic kidney disease associated with the previous daily use of NSAIDs. Chronic kidney disease in these patients was newly diagnosed and was defined as a serum creatinine concentration of 1.5 mg per deciliter or greater. This increased risk was primarily limited to older men. An

additional report linking the chronic use of NSAIDs with the development of chronic kidney disease described 56 patients from Australia.[113] These patients had taken only NSAIDs over a period of 10 to 20 years for treatment of varying rheumatic diseases. In 19 patients (34%), radiographic evidence of papillary necrosis was found. In 37 patients, renal biopsy material was available that disclosed evidence of chronic interstitial nephritis. The clinical characteristics of these patients were quite different from those with analgesic nephropathy, suggesting that NSAID-induced chronic kidney disease is indeed a distinct entity. In particular, patients with NSAID-associated renal disease were older, had an equal female-to-male ratio, a lower incidence of papillary necrosis, less severe renal insufficiency, and a lower incidence of urinary tract infections.[113] In addition, an increased risk of uroepithelial tumors has not been described in these patients.

Further evidence of chronic toxicity has been reported in a preliminary communication in which patients treated with NSAIDs for rheumatoid arthritis and osteoarthritis were compared to a matched control arthritis population.[129] In this study, the NSAID-treated patients had a rise in the serum creatinine concentration from 1.28 to 2.58 mg per deciliter over a mean period of 47.5 months. The control group not taking NSAIDs had stable renal function. Finally, Segasothy and colleagues[128] report on the risk of chronic renal disease in a prospective study of 259 heavy analgesic abusers. In this study, 69 patients developed radiographic evidence of papillary necrosis. Of these, 29 used NSAIDs either singularly (17 patients) or in combination with another NSAID (12 patients). Another 9 patients used NSAIDs in combination with paracetamol, aspirin, caffeine, or a traditional herbal medicine. Renal insufficiency (serum creatinine concentration 1.4 to 8.8 mg per deciliter) was noted in 26 of the 38 patients who had used an NSAID chronically. Similar to the patients from Australia,[113] this disorder was more common in males (1.9:1.0), distinguishing this disorder from classic analgesic nephropathy, which typically occurs in females. Similarly, these patients did not exhibit the usual psychological profile associated with analgesic abuse.

Thus, although further studies are needed to definitely assess the question of cumulative toxicity, it appears that some chronically treated patients may develop a change in renal function over a long-term period. Given the abuse potential of powerful NSAIDs and the fact that ibuprofen, naproxen, and ketoprofen are now available on an over-the-counter basis, it is possible that chronic NSAID abuse may become a more common cause of chronic kidney disease in the future.

In considering the definite association of compound analgesic abuse and the possible linkage of chronic NSAID use to the development of chronic kidney disease, it has become common clinical practice to recommend acetaminophen whenever possible for analgesia. In this regard, a recent case-control study examining the use of over-the-counter analgesics as a risk factor for end-stage renal disease found that acetaminophen may also cause chronic kidney disease when used on a continual basis.[130] In this study, heavy average use of acetaminophen (>1 pill per day) and medium- to high-cumulative intake (1,000 or more pills in a lifetime) each doubled the odds of end-stage renal disease. These authors conclude that a reduced consumption of acetaminophen could decrease the overall incidence of end-stage renal disease approximately 8% to 10%. The findings in this study confirmed an earlier report that also concluded that long-term daily use of acetaminophen is associated with an increased risk of chronic kidney disease.[118] Although these studies do not establish a cause-and-effect relationship between acetaminophen ingestion and chronic kidney disease, the data do suggest that the ingestion of acetaminophen on a continual and chronic basis should be discouraged.

An organized review was conducted by a consensus panel of the National Kidney Foundation (NKF) in which over 600 articles were surveyed. This review studied the implications of several different kinds of analgesic ingestion and renal failure risks.[131,132] The highlights of the recommendations from the NKF consensus panel based on this review are that:

1. The ingestion of aspirin and nonsteroidal combinations are not encouraged because of an increased risk of renal failure when those combinations are ingested together.
2. The habitual consumption of analgesics is discouraged, and monitoring is recommended when such use is mandatory.
3. Combination analgesics are recommended to be available by prescription only with an explicit warning to physicians that the habitual consumption of these combination products could lead to the insidious development of chronic kidney disease.
4. There should be an explicit warning to consumers regarding NSAID ingestion.

The panel concluded that there is negligible clinical evidence that suggests the habitual use of acetaminophen alone causes the clinical entity of analgesic nephropathy and that there is no evidence that the occasional use of acetaminophen causes renal injury. Finally, the panel points out that there is no risk from the regular use of aspirin in the relatively small doses recommended for the prevention of cardiovascular events.

NEPHROTOXICITY OF INHIBITORS OF THE RENIN-ANGIOTENSIN SYSTEM: ANGIOTENSIN CONVERTING ENZYME INHIBITORS, ANGIOTENSIN RECEPTOR BLOCKERS, AND DIRECT RENIN INHIBITORS

The most common form of nephrotoxicity associated with inhibitors of the renin-angiotensin system is an increase in the serum creatinine concentration occurring in the setting

of antihypertensive therapy.[133] This complication is becoming more common in clinical practice because guidelines governing adequate blood pressure control have been made more stringent. This decline in renal function is hemodynamic in origin and not secondary to structural injury to the kidney and can be traced to changes in renal autoregulation that accompany chronic kidney disease.

Normal renal autoregulation enables the kidney to maintain fairly constant renal blood flow and glomerular filtration rates in the setting of varying systemic blood pressure. One component of this process is an intrinsic property of the afferent arteriole called the myogenic reflex. The myogenic reflex causes this vessel to either constrict or dilate in response to changes in intraluminal pressure. An increase in arterial pressure elicits a vasoconstrictive response, whereas decreased arterial pressure results in vasodilation. These changes in afferent tone provide an immediate response to maintain intraglomerular pressure and glomerular filtration rate relatively constant in the face of everyday fluctuations in systemic blood pressure.[134]

In the setting of chronic hypertension, the small arteries of the kidney, including the afferent arteriole, undergo a number of pathologic changes that give rise to alterations in the way the kidney autoregulates.[135] As with vessels elsewhere, the afferent arteriole initially demonstrates evidence of endothelial dysfunction leading to impaired vasodilation. Over time, this impairment is exaggerated by histologic changes of hyaline arteriosclerosis and myointimal hyperplasia. These changes lead to a blunted ability of the preglomerular circulation to either constrict or dilate in response to changes in renal perfusion pressure. In essence, these vessels take on the characteristics of a pressure-passive vasculature where changes in mean arterial pressure are matched by proportional change in GFR (Fig. 32.5).[135,136]

A blunted ability of the preglomerular circulation to dilate in response to a drop in the mean arterial pressure will cause an exaggerated decrease in the intraglomerular pressure and GFR. This impairment in autoregulation explains why patients with hypertension and chronic kidney disease are more likely to have an increase in the serum creatinine concentration when blood pressure is lowered. Any drug that lowers blood pressure can cause an increase in the serum creatinine concentration through this mechanism but inhibitors of the renin-angiotensin system are more commonly associated with this complication. Angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and the direct renin inhibitor will exaggerate the decline in intraglomerular pressure due to blood pressure reduction by concomitant vasodilation of the efferent side of the glomerular circulation.

As long as the increase in serum creatinine concentration is not excessive (>30% above the baseline value) or progressive, discontinuation of these drugs is not necessarily warranted particularly considering the potential benefit these agents have in slowing the progression of chronic kidney disease. Long-term trials in both diabetic and nondiabetic patients have shown that the initial decline in renal function reaches a plateau within several weeks and is reversible with discontinuation of the blocker even after several years of therapy.[138,139] Thus a small, stable increase in the serum creatinine concentration after the start of an ACE inhibitor, ARB, or the direct renin inhibitor is hemodynamic in nature and reflects a fall in intraglomerular pressure.

If the rise in serum creatinine is >30% or the repeat value shows a progressive rise, then the appropriate response is to discontinue the drug and initiate a search for other causes of renal dysfunction. There are several conditions in which use of renin-angiotensin blockers may cause exaggerated or progressive declines in renal function. The first setting involves significant (usually >70%) bilateral renal artery obstruction or unilateral renal artery obstruction to a solitary functioning kidney. Under these conditions, increased tone of the efferent arteriole acts to attenuate the decline in intraglomerular pressure that results from the arterial obstruction. The trade-off is that renal function and glomerular filtration rate become dependent upon sustained constriction of the efferent vessel by AII. A similar physiology can develop in patients with polycystic kidney disease where the renal arteries become extrinsically compressed by large cysts.[140] Unless the underlying obstruction can be treated, other classes of antihypertensive agents will have to be used.

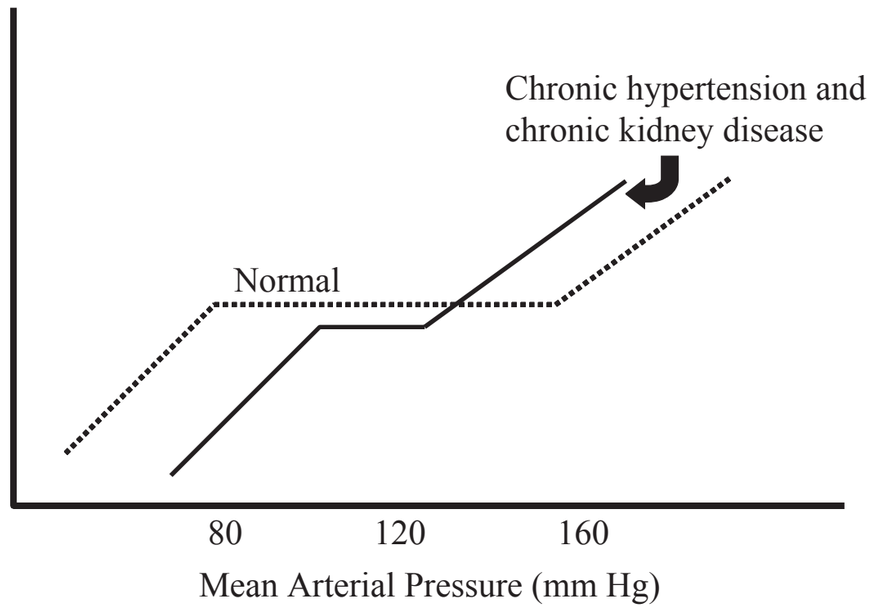

FIGURE 32.5 Renal autoregulation normally maintains relatively constant intraglomerular pressure despite variations in renal perfusion pressure. In patients with chronic hypertension or mild chronic kidney disease renal autoregulation changes in such a way that intraglomerular pressure begins to vary more directly with changes in mean arterial blood pressure. One can conceptualize this change as if the normal sigmoidal relationship between systemic blood pressure and intraglomerular pressure becomes progressively more linear. As a result, increases in mean pressure cause exaggerated rises in intraglomerular pressure, whereas declines in mean pressure will cause exaggerated falls in intraglomerular pressure. The decline in intraglomerular pressure accompanying more stringent levels of blood pressure control will manifest itself by an increase in the serum creatinine concentration. Renal dysfunction that occurs in this setting is hemodynamic in origin and is reflective of a lower intraglomerular pressure.

Blockade of the renin-angiotensin system can also cause an azotemic response under conditions of an absolute (gastroenteritis, aggressive diuresis, poor oral intake) or effective reduction in arterial circulatory volume (moderate to severe congestive heart failure). In these settings, AII–mediated constriction of the efferent arteriole serves to minimize the decline in glomerular filtration rate that would otherwise occur as a result of the fall in renal perfusion pressure. In the volume-contracted patient, the appropriate response is to hold the drug and then restart the medication once the extracellular fluid volume has been replenished. In a patient with congestive heart failure, renin-angiotensin blockade will increase the serum creatinine when the decrease in intraglomerular pressure resulting from efferent vasodilation is not offset by an increase in renal perfusion. This can occur in patients with severely depressed cardiac function in which afterload reduction can no longer increase cardiac output or in the setting of aggressive diuresis.

A similar mechanism is responsible for renal dysfunction that occurs in patients given renin-angiotensin system blockers in the setting of NSAIDs, cyclosporin A, or early sepsis.[141–143] In these settings, there is increased vasoconstriction of the renal vasculature. Inhibiting AII-mediated efferent vasoconstriction in the face of decreased renal perfusion pressure accounts for the fall in GFR.

A few cases of membranous nephropathy have been attributed to the use of ACE inhibitors,[144,145] but the overall incidence of this complication and that of tubulointerstitial nephritis are believed to be low. To date, there are no such reports linking ARBs or the direct renin inhibitor to the development of glomerular or interstitial renal disease.

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