CHAPTER

8 Hormones and the Kidney

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HORMONAL MODULATION OF NEPHRON FUNCTION: AN OVERVIEW

Modulation of Glomerular Filtration Rate

The major physiologic determinants of single nephron glomerular filtration rate (GFR) are glomerular plasma flow (Q_A), glomerular transcapillary hydraulic pressure (P_{GC}), and the ultrafiltration coefficient (K_f).[1] These variables are determined, in part, by the contractile state of the afferent arteriole, efferent arteriole, and mesangial cells. K_f also varies with alterations in the hydraulic permeability of the capillary filtration barrier, which consists of endothelial cells, visceral epithelial cells, and the glomerular basement membrane. By binding to specific receptors on cellular and structural components of the glomerulus, circulating and locally produced hormones influence one or more of the physiologic determinants of GFR. Figure 8.1 summarizes the effects of different hormones on pregomerular, glomerular, and postglomerular contractility. Because the same substance can act at different sites in the glomerular unit, the net effect on GFR will depend on whether its actions are antagonistic or complementary. For example, atrial natriuretic peptide (ANP) decreases afferent arteriolar resistance, whereas increasing efferent arteriolar resistance results in an augmented P_{GC} and a rise in GFR.[2] Under certain conditions, ANP also increases K_f, which, in turn, contributes to the enhancement of GFR.[3] On the other hand, angiotensin (Ang) II-mediated constriction of both afferent and efferent arterioles results in opposite effects on glomerular plasma flow and P_{GC} and, therefore, no change in single nephron GFR.[4] Regulation of glomerular hemodynamics is further complicated by multiple interactions between hormones in the kidney. For example, infusion of Ang II along with a cyclooxygenase inhibitor causes a significant decrease in single nephron GFR, suggesting that endogenous prostaglandin production antagonizes the glomerular effects of Ang II.[5] The net effects of renally relevant hormones on GFR are discussed in more detail later in this chapter.

Modulation of Tubule Water and Electrolyte Transport

Renal tubule cells express receptors for many circulating and locally synthesized hormones. The effects of a particular hormone on water or electrolyte transport are partly determined by the differential distribution of its receptor on functionally specialized segments of the renal tubule. For example, arginine vasopressin (AVP) binds almost exclusively to principal cells in the collecting tubule (CT), where it influences the physiologic functions of this segment, primarily water and urea absorption.[6] Parathyroid hormone (PTH), on the other hand, exerts its biologic actions on renal tubule segments proximal to the collecting duct, where it modulates calcium, phosphate, magnesium, sodium, and bicarbonate transport.[7] Table 8.1 summarizes the net effects of renally relevant hormones on water and solute handling in different tubule segments. Each hormone is discussed in detail in the sections that follow. As in the glomerulus, hormones may modulate their own actions by altering the production of counterregulatory hormones. For example, AVP induces local synthesis of prostaglandin E (PGE), which opposes the effect of AVP on water permeability in the CT.[8]

ARGININE VASOPRESSIN

In 1895, Oliver and Schafer were the first to describe a substance with potent vasopressor effects originating from the posterior pituitary, hence the name, vasopressin.[9] It was not until later in the 20th century that the effects of this hormone on modulation of water excretion by the kidney were discovered. In fact, vasopressin, also called AVP or antidiuretic hormone (ADH), is a key hormone for osmoregulation and maintenance of body homeostasis.[10] AVP was also found to exert effects on body temperature, glucose metabolism, memory, social behavior, and the hypothalamic-pituitary-adrenal axis.

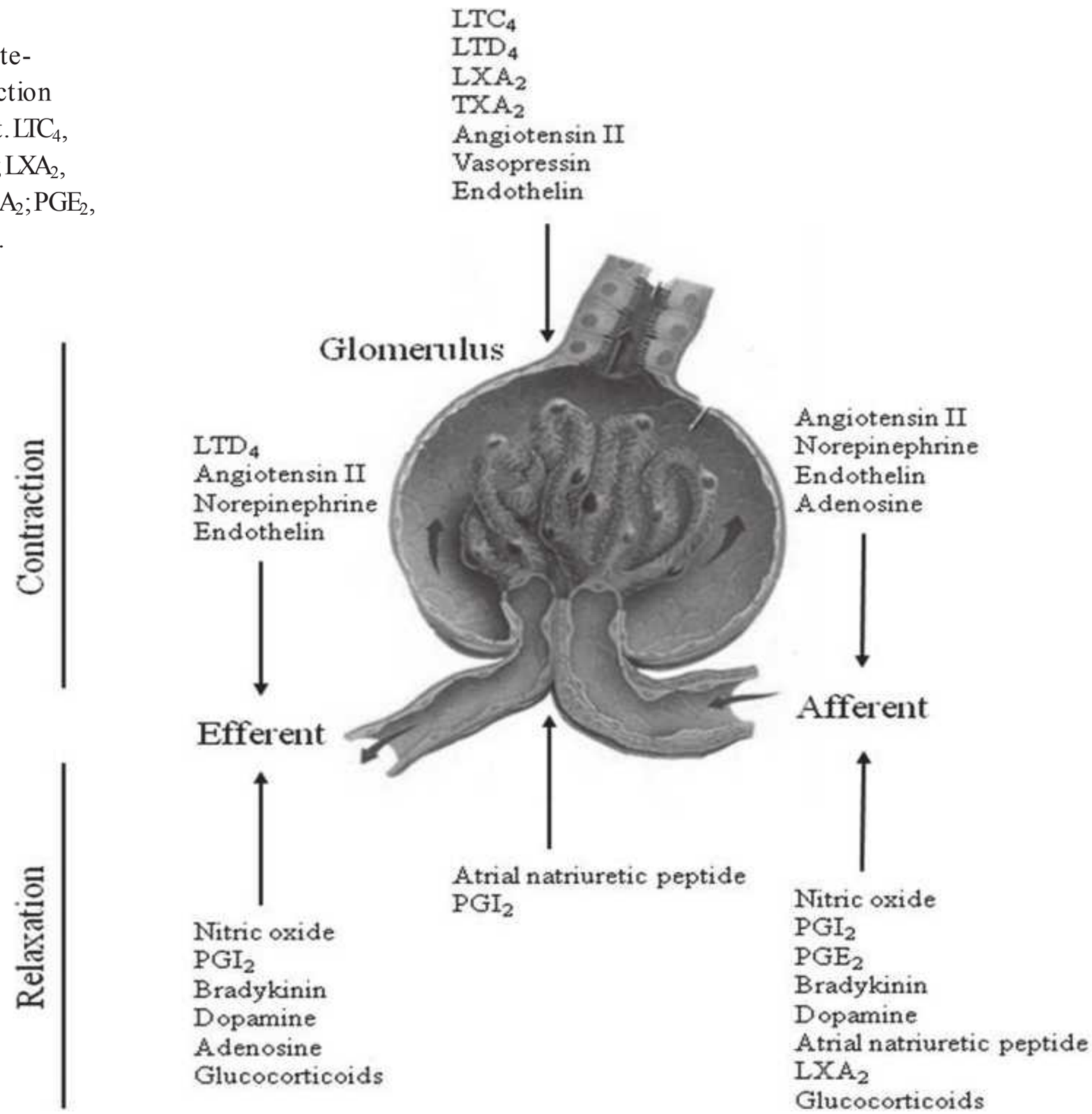

FIGURE 8.1 Hormones regulating glomerular, afferent, and efferent arteriolar contractility. Glucocorticoid action may be pharmacologic and indirect. LTC_4, leukotriene C_4; LTD_4, leukotriene D_4; LXA_2, leukotriene A_2; TXA_2, thromboxane A_2; PGE_2, prostaglandin E_2; PGI2, prostacyclin.

Structure and Synthesis of Arginine Vasopressin

AVP is a 9-amino acid neuropeptide synthesized by magnocellular neurons in the paraventricular and supraoptic nuclei of the hypothalamus.[11] The AVP gene, located on chromosome 20, consists of three exons that encode the signal peptide, AVP, neurophysin II (NPII), and a glycopeptide.[10] After cleavage of the signal peptide within the ER, the resulting prohormone is folded and packaged into secretory granules in neuronal bodies. These granules are then transported along the axons to nerve terminals in the posterior pituitary (neurohypophysis).[12] During axonal transport, further processing of the prohormone within secretory granules yields AVP, neurophysin II (NpII), and a glycopeptide. Interestingly, mutations of NpII impair AVP secretion, suggesting that NpII assists in the processing or secretion of AVP.[13] In addition to the posterior pituitary, AVP synthesis has been detected in the pancreas, adrenal gland, ovary, testis, and regions of the brain.[14] Its physiologic function in these sites, however, remains to be clarified.

Physiology of Arginine Vasopressin in the Kidneys

The most sensitive stimulus for AVP secretion into the bloodstream is increased plasma osmolality. Osmosensitive neurons that respond to changes in plasma osmotic pressure by varying their intracellular water content have been identified in the anterior hypothalamus, specifically in the organum vasculosum of the lamina terminalis (OVLT) and the subfornical organ (SFO).[15] When stimulated by osmosensitive neurons, the magnocellular neurons release the stored AVP into the posterior pituitary (an area that lacks a blood–brain barrier) and AVP enters the general circulation. As little as 1% change in plasma osmolality leads to a change in AVP concentration that is sufficient to modify renal water excretion.[16] AVP secretion is almost completely suppressed when plasma osmolality decreases below an average of 280 mOsm per kg of water in humans.[17]

Secretion of AVP is also influenced by alterations in intravascular volume and blood pressure, sensed by baroreceptors located in the heart, aortic arch, and carotid sinus.[18] These signals are transferred through the vagal nerves to the

8.1 Hormonal Modulation of Tubular Transport

	Hormones with Major Effects		
	Reabsorption	**Stimulatory**	**Inhibitory**
Proximal tubule	Na	Ang II, catecholamines, insulin	Dopamine, PTH
	P_i	IGF-1	PTH
	HCO_3	Ang II	PTH
	Ca		PTH
TALH	Na	AVP,[a] catecholamines	PGE
	Ca	PTH, calcitonin, glucagon	
	Mg		AVP, PTH, calcitonin, glucagon
DCT	P_i		PTH
	Ca	PTH	
CCD	H_2O	AVP	PGE, bradykinin, ANP, α-adrenergic agents
	Na	Aldosterone	ANP, PGE, EGF
IMCD	Urea	AVP	
SECRETION CCD	K	AVP, aldosterone	β_1 agonists
	H	Aldosterone	

[a]Unlikely in humans.
TALH, thick ascending limb of the loop of Henle; DCT, distal convoluted tubule; CCD, cortical collecting duct; IMCD, inner medullary collecting duct; Ang II, angiotensin II; IGF, insulinlike growth factor; AVP, arginine vasopressin; PTH, parathyroid hormone; PGE, prostaglandin E; EGF, epidermal growth factor.

nucleus solitarius in the brainstem, from which postsynaptic pathways project to the magnocellular neurons. Whereas a 5% to 8% decrease in blood volume or systemic arterial pressure has little effect, further hemodynamic compromise leads to a steep increase in circulating AVP levels. Significant reductions (10%–30%) in circulatory arterial volume or blood pressure can override osmoregulation and result in markedly increased AVP levels in the face of decreased plasma osmolality.[19] Other less potent stimuli for AVP secretion include fever, emesis,[20] and oropharyngeal osmoreceptors.[21]

AVP circulates in the plasma nearly in an unbound form. Levels of circulating AVP depend on both the rate of AVP release from the posterior pituitary and the rate of AVP degradation. As discussed, the major factor controlling AVP release is plasma osmolality. The liver and the kidney both contribute to the breakdown of AVP and the decline in AVP levels when secretion ceases. In fact, the half-life of AVP in the circulation is 18 minutes due to rapid clearance by hepatic and renal vasopressinases.[22] Under physiologic conditions, plasma vasopressin concentrations vary with serum osmolarity between 0 to 5 pg per mL.[22]

It is noteworthy that AVP levels are difficult to measure in plasma because of the instability of this peptide and the low sensitivity of available AVP antibodies. Copeptin (or C-terminal proarginine vasopressin, CT-proAVP) is the C-terminal part of AVP, which is secreted stoichiometrically with AVP in a manner similar to C-peptide and endogenous insulin.[23] CT-proAVP provides a reliable means for estimating prevailing AVP levels in the circulation, thus facilitating the study of AVP in human diseases. A recent cohort study in renal transplant patients suggests that high CT-proAVP strongly correlates with a negative renal prognosis. In fact, in this study, the plasma concentrations of CT-proAVP predicted renal function loss over a 3.2-year follow-up.[24]

AVP exerts its biologic actions through three specific cell-surface AVP receptors identified as V_1R (also called $V_{1a}R$), V_2R, and V_3R (also $V_{1b}R$).[25] These receptors belong to the G protein coupled receptor superfamily (Table 8.2). In the human kidney, mRNA for V_1Rs predominates in cortical collecting ducts (CCD), gradually decreasing as the collecting duct enters the medulla.[26] In addition, whereas V_1R mRNA is diffusely expressed in the CCD, it is restricted to the intercalated cells in OMCD. V_1Rs are responsible for mediating vascular smooth muscle cell vasoconstriction by activating G protein-dependent phospholipase C (PLC) and the downstream effectors, diacylglycerol (DAG), and inositol 1,4,5-triphosphate (IP_3). In turn, DAG stimulates protein kinase C (PKC), whereas IP_3 increases cytosolic Ca^{2+}, thus

8.2 Vasopressin Receptor Types, Genetics, Location, and Main Physiologic Effects

Receptor	Chromosome location	No. of amino acids	Site of action	Main second messenger	Main effects
V_1 (V_1a)	12 (q14–q15)	418	Vascular smooth muscle, platelets, liver, testes, brainstem, adrenal glands	PLC→IP3 + DAG/calcium and PKC	Vasoconstriction, platelet aggregation, glycogenolysis, stimulation of aldosterone and cortisol synthesis
V_2	X (q28)	371	Collecting duct cells of kidney, inner medulla, heart, pancreas	Adenylate cyclase/cAMP	Water retention, stimulation of atrial natriuretic peptide, stimulation of insulin synthesis, coronary and pulmonary artery vasodilation
V_3 (V_1b)	1 (q32)	553	Hypothalamus, anterior pituitary gland	PLC→IP3 + DAG/calcium and PKC	Modulation of ACTH synthesis; stimulation of ACTH, GH, and procaltin release
Oxytocin	3 (p25)	389	Uterus, breast, vascular endothelium	PLC→IP3 + DAG/calcium and PKC	Myometrial contraction, ductal myoepithelial contraction, vasodilation
P_2 Purinergic	11 (q13.5–14.1)		Cardiac endothelium	ATP	Vasoconstriction, reduced cardiac output

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initiating the second-messenger cascade responsible for the cellular actions of AVP.[25] Stimulation of V_1R, although not directly involved in control of tubular water and electrolyte transport, increases sodium excretion because of the influences on blood pressure, effective arterial circulating volume, glomerular filtration rate, and circulation in the vasa recta system.[27,28] Additional biologic effects of AVP mediated through V_1Rs include platelet aggregation[29] and increased glycogenolysis and gluconeogenesis in the liver.[30]

The V_3R ($V_{1b}R$), also coupled to PLC signaling, is present on neurons in the anterior pituitary (adenohypophysis) and is thought to mediate AVP-induced corticotropin secretion.[25,31,32] They are also found elsewhere in the brain, especially in the pyramidal neurons of the hippocampal CA2 field, in which they mediate fundamental physiologic actions such as memory and body temperature control as well as social behavior.[33] In addition, this receptor has been localized to pancreatic islet cells, modulating insulin secretion.[34] However, its presence and role at the level of the medulla in rat kidney remain unclear.

V_2Rs, on the other hand, are heavily expressed in the medullary TAL, macula densa (MD), connecting tubule, and cortical and medullary collecting duct, as well as weakly expressed in cortical thick ascending limb (TAL) and distal convoluted tubule.[35] These are the best characterized and studied vasopressin receptors. By binding to V_2R, AVP increases water reabsorption through multiple mechanisms.[31] Activation of V_2R results in increased cyclic adenosine monophosphate (cAMP) levels and activation of PKA, which promotes insertion of water channels into the luminal suface of the epithelial tubular cells.[36] This ultimately mediates the antidiuretic effect of AVP by allowing back diffusion of water down its concentration gradient.[37] In addition, V_2Rs modulate sodium reabsorption through the epithelial Na^+ channel (ENaC) across principal cells.[38–41] This facilitates free water reabsorption by supporting the axial corticomedullary hyperosmotic gradient. It was also recently shown in rats that AVP modulates sodium reabsorption even in the distal convoluted tubule by acting on the thiazide-sensitive Na^+-Cl^- cotransporter (NCC).[42] NCC is important in defining sodium delivery to the collecting duct,

which is necessary for ENaC activity. Finally, V_2Rs activate urea transporters, such as UTA1, in the distal nephron.[43–45] This increase in urea reabsorption and recycling maximizes sodium reabsorption in the TAL by supporting the axial hyperosmotic gradient drawing water from the distal nephron.[46] The clinical importance of the V_2R in water balance disorders is underlined by the current use of V_2R antagonists in a clinical setting (see later).

It is noteworthy that AVP also binds to two nonspecific receptors: oxytocin receptors and P2 purinoreceptors. Oxytocin receptors are found in the breast, ovary, uterus, and hypothalamus. Since the affinity of this receptor for vasopressin is relatively low, the clinical effects of this hormone are limited under physiologic conditions.[47] AVP may also act on P2 purinoreceptors in the heart, causing coronary vasoconstriction and contributing to the reduction in cardiac output.[48]

Water Channels

The discovery of the family of aquaporin water channels was crucial to the understanding of the mechanism by which AVP can increase water permeability in the kidney. The group of Peter Agre discovered the first aquaporin in human erythrocytes.[49] To date, seven different aquaporin (AQP) have been shown to be expressed in the human kidney and to be involved in renal water reabsorption.[50]

AQP2 is the vasopressin-sensitive water channel expressed in the principal cells of the collecting duct, where it shuttles between intracellular storage vesicles and the apical membrane.[51] Knocking out the AQP2 gene produces a severe concentration defect in these mice, resulting in postnatal death.[52] It has now been shown to be involved in many clinical disorders (see later). AQP1 is constitutively expressed on the basolateral and apical membrane of epithelial cells lining the proximal tubule and thin descending limb, as well as endothelial cells of the descending vasa recta. It not only plays a role in water reabsorption from urine in these segments but is also critical for a functional countercurrent multiplication system.[53] AQP3 and AQP4 are expressed on the basolateral membrane of the principal cells of the collecting duct, and they represent an exit pathway from these cells for water entering through AQP2.[54,55] Similar to AQP1, AQP7 is expressed at the apical membrane of proximal tubules (S3 segment) and has been shown to mediate glycerol reabsorption in addition to water.[56] AQP6 is found in intracellular vesicles of acid-secreting α-intercalated cells in the collecting duct.[57] It is thought to be involved in urinary acid secretion. AQP11 is localized to the endoplasmic reticulum (ER) in the proximal tubule. Interestingly, knocking out the AQP11 gene in mice is fatal because of the onset of polycystic kidney disease.[58]

Clinical Pathophysiologic Role of Arginine Vasopressin in the Kidneys

AVP is implicated in major clinical syndromes of alterations in water metabolism, namely nephrogenic diabetes insipidus (NDI) and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). In addition to water metabolism, it has been recently suggested that AVP may play a role in the initiation and the progression of chronic kidney disease (CKD) and in the most prevalent form of hereditary renal disease, namely the adult polycystic kidney disease (Fig. 8.2).[59]

NDI is characterized by impaired AVP-induced water reabsorption, resulting in polyuria and polydipsia.[60] If water intake is inappropriate, patients with NDI may fail to thrive, suffer from mental retardation, and die early. NDI can be acquired such as following lithium treatment, hypokalemia, hypercalcemia, or ureteral obstruction, all of which lead to downregulation of AQP2.[61–64] NDI can also be inherited (congenital).[65] In fact, two gene mutations have been linked to congenital NDI: one in the AVPR2 gene encoding V_2R (X-linked NDI) or mutations in the AQP2 gene (autosomal recessive or autosomal dominant NDI). More than 90% of patients with congenital NDI suffer from X-linked NDI. In both cases, patients cannot concentrate their urine despite normal or elevated plasma concentrations of vasopressin, leading to a massive loss of water through the kidney. So far, NDI is managed by salt restriction combined with hydrochlorothiazide diuretics to reduce urine output.[66] However, no cure is available so far.

Abnormal water handling of central origin includes SIADH in which AVP levels are abnormally elevated and not suppressed when plasma osmolality concentration falls below the osmotic threshold for physiologic AVP secretion.[67] SIADH is characterized by impaired water excretion in the absence of renal insufficiency, adrenal insufficiency, or any recognized stimulus for AVP secretion. Renal water retention and extracellular fluid expansion are compensated for by increased urinary Na^+ excretion leading to life-threatening hyponatremia. The most common causes of the syndrome of inappropriate AVP secretion are neoplasia, neurologic disorders, congestive heart failure, liver cirrhosis, preeclampsia, and drugs such as thiazide diuretics or selective serotonin reuptake inhibitor antidepressants.[67] Four patterns of AVP dysregulation in patients with SIADH have been observed.[68] The most common pattern (in ~40% of patients with SIADH) is the excessive and unregulated release of AVP, which is unrelated to plasma osmolality. In the second most common pattern (~30% of patients), referred to as "reset osmostat," AVP release continues to regulate water excretion at a lower plasma osmolality set-point. Although most tumors (e.g., lung carcinoma) manifest the first type of SIADH, some also present with the second type, thus the pattern of abnormal AVP secretion cannot be utilized to predict the cause of SIADH. A third rare pattern is characterized by an inability to stop AVP secretion at low plasma osmolalities, but the osmoregulation of AVP is otherwise normal. This pattern may be due to dysfunction of inhibitory hypothalamic neurons, leading to persistent low-grade basal AVP secretion. In the fourth pattern, a rare clinical picture of SIADH, the normal osmoregulation of AVP secretion is not altered (~10% of patients) but AVP levels are low or undetectable. It is thought that a nephrogenic SIADH

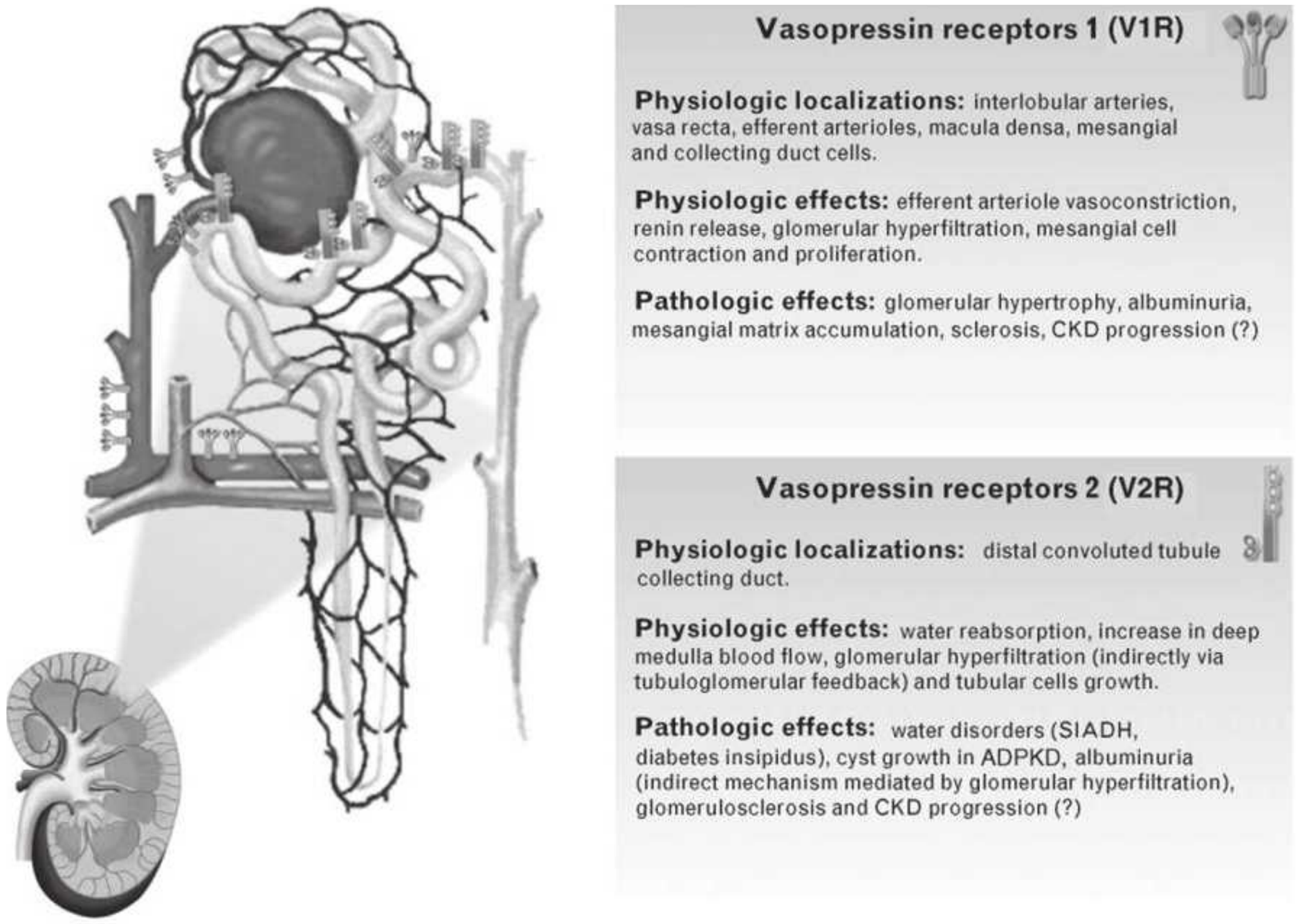

FIGURE 8.2 Vasopressin receptors: physiology and pathologic involvement in renal diseases. (Reproduced from Bolignano D, Zoccali C. Vasopressin beyond water: Implications for renal diseases. *Curr Opin Nephrol Hypertens*. 2010;19(5):499–504.)

(NSIADH) may be responsible for this picture. In fact, in some children, it appears to be due to an activating mutation of V_2R. In other patients, it may be due to abnormal control of aquaporin-2 water channels in renal collecting tubules or production of an antidiuretic principle other than AVP.[69] In a study with SIADH patients, treatment with V_2R antagonists, commonly referred to as vaptans, increased serum Na^+ concentration and decreased its excretion. Tolvaptan has been recently approved in the United States and Europe for the treatment of hyponatremia associated with SIADH, as well as cirrhosis and congestive heart failure. Recently, a dual vasopressin V_1R and V_2R antagonist, conivaptan, improves hyponatremia in rats with SIADH, suggesting a therapeutic potential for conivaptan in the treatment of SIADH.[70]

AVP has also been shown to modify vascular tone in renal microvessels. Short-term infusion of AVP does not alter either renal blood flow or the GFR.[71] Alternatively, chronic AVP administration increases the intraglomerular capillary pressure and GFR through tubuloglomerular feedback.[72] In addition, a sustained increase in water intake and the consequent AVP suppression reduce proteinuria and the severity of glomerular and tubular damage in 5/6 nephrectomized rats.[73,74] Thus, it seems likely that a chronic AVP-induced hyperfiltration may alter the glomerular barrier and start a series of events leading to enhanced protein loss and glomerulosclerosis. An increase in urinary albumin excretion represents an early predictor of glomerular damage in diabetes mellitus and a risk factor for cardiovascular complications in hypertension. Studies show that the Brattleboro rat, a model of central diabetes insipidus with complete lack of AVP, is protected from hyperfiltration, albuminuria, and renal hypertrophy after streptozotocin-induced diabetes mellitus.[75] This suggests that AVP plays a role in hyperfiltration and glomerular damage induced by diabetes. These observations are also of relevance to humans. A marked increase in AVP plasma levels is well documented in diabetes mellitus.[76] AVP through V_1R induces contraction of cortical efferent, but not afferent, arterioles. Administration of a V_1R selective antagonist to noninsulin-dependent diabetic patients modestly reduces albuminuria partly by decreasing intraglomerular capillary pressure.[77] Thus, although V_1Rs (but not V_2Rs) are downregulated in diabetes mellitus, they could mediate part of the increase in albumin excretion. Interestingly, administering desmopressin, a selective V_2R agonist, to healthy humans and patients with central diabetes insipidus significantly increases urinary albumin excretion, but this effect is absent in those with hereditary nephrogenic diabetes insipidus secondary to V_2R mutations.[78] These findings suggest that the AVP-induced rise in albuminuria depends on V_2Rs. This is further confirmed by the observation that plasma copeptin levels correlate with microalbuminuria

in the PREVEND study.[79] However, V_2 receptors have not been found in glomeruli or proximal tubules, suggesting indirect effects. Recent evidence suggests a strong interaction between AVP and the renin-angiotensin system (RAS).[80,81] In fact, chronic RAS blockade by angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) prevents the desmopressin-induced albuminuria, indicating that RAS mediates the effects of AVP on glomerular hemodynamics.[82] Recent studies using V_1R knockout mice show that AVP regulates body fluid homeostasis and the GFR by activating RAS through V_1Rs in MD cells, and subsequently the V_2R-aquaporin 2 system.[83] Simultaneous AVP and RAS blockade may represent a good therapeutic approach for delaying renal disease progression.

Another interesting observation is that mesangial cells express V_1Rs, which mediate AVP-induced cell contraction.[84] In addition, prolonged exposure to AVP promotes mitogenesis and proliferation of these cells, which ultimately leads to an increased accumulation of extracellular matrix, a pathologic feature found in various glomerular diseases.[85,86] In fact, addition of AVP to cultured mesangial cells increases in a dose-dependent manner the synthesis and release of matrix proteins, such as type I and IV collagen, fibronectin, and transforming growth factor β.[87] In addition, AVP inhibited the synthesis of matrix metalloproteinase (MMP)-2, which degrades matrix proteins including type IV collagen, and stimulated endothelin (ET)-1 secretion from mesangial cells, another mitogenic factor.[88]

In the remnant kidney model in rat, a model of progressive CKD in humans, V_1R antagonists (but not V_2R) prevent proteinuria and glomerulosclerosis in the initial phases of disease, but have limited effectiveness in established renal damage.[89,90] Similar observations were reported in 5/6 nephrectomized, salt-loaded spontaneously hypertensive rats (SHRs), in which the increase in urinary protein excretion and the progression of nephrosclerosis were attenuated with a V_1R antagonist but not with a V_2R antagonist.[91]

AVP has also been linked to autosomal dominant polycystic disease (ADPKD), an inherited disorder characterized by the development within renal tubules of innumerable cysts that progressively expand to cause renal insufficiency.[92] It has been shown that 3′-5′-cyclic adenosine monophosphate (cAMP) stimulates tubule cell proliferation and transepithelial fluid secretion, both of which contribute to enlarge renal cysts.[93] AVP operates continuously in ADPKD patients to promote cAMP production in the distal nephron and collecting ducts via V_2Rs, thereby contributing to cyst enlargement and renal dysfunction.[94] Studies in animal models of ADPKD provide compelling evidence that blocking AVP's actions dramatically improves disease progression.[95,96] This prompted the initiation of an international clinical trial[97] testing the efficacy of tolvaptan, a V_2R inhibitor, in the treatment of ADPKD.[98] Alternatively, a recent review discusses that the impact of simply increasing the amount of solute-free water drunk evenly throughout the day by patients with ADPKD on decreasing plasma AVP concentrations and mitigating the actions of cAMP on the renal cysts.[99]

In conclusion, in recent years, AVP has been implicated in the initiation and progression of many kidney diseases, playing a role beyond water metabolism. Further studies are required to determine whether AVP antagonists and/or AVP suppression by a high water intake can be useful for the treatment of nephropathies, from ADPKD to diabetic and nondiabetic CKD.

THE RENIN-ANGIOTENSIN SYSTEM

Historical Review

The discovery of renin goes back to 1898, when the Finnish physiologist Robert Tigerstedt and his student Per Gunnar Bergman found that extracts of rabbit renal cortex had a slowly developing and sustained pressor effect. Based on its origin, they named this substance renin.[100] This effect was not observed with extracts of renal medulla and persisted despite removal of sympathetic activation. Subsequently, efforts to verify these experiments were unsuccessful until the 1930s when Harry Goldblatt and his colleagues demonstrated that clamping the renal artery in dogs produced chronic hypertension.[101] This work converged with other subsequent experiments performed by leading scientists such as Juan Fasciolo and Bernardo Houssay to suggest the presence of a vasoactive substance produced by the kidney, other than renin.[102,103] This substance was later isolated from the blood and was named hypertensin. Based on their physiologic properties, renin and hypertensin were clearly two different compounds, but the relationship between them was not established. Renin was later identified by an Argentine group as a proteolytic enzyme that acts on a plasma constituent to produce hypertensin as the final product of the enzymatic reaction.[104] Subsequent research led to the characterization of the components of the renin–angiotensin system and Braun-Menéndez and Page gave the final nomenclature of the whole enzymatic system in 1958: the renin substrate was named angiotensinogen, hypertensin renamed angiotensin, and the enzymes that metabolize angiotensin were named angiotensinases.[105,106]

Components of the Renin-Angiotensin-Aldosterone System

Angiotensinogen

Angiotensinogen is a large molecular weight globulin primarily formed by hepatic cells. It is constitutively secreted into the circulation by the liver, therefore plasma levels are generally stable.[107] Other sources of angiotensinogen have been identified and mRNA expression detected in tissues such as the kidney, heart, brain, vessels, placenta, and adrenal glands.[108] It is currently accepted that intrarenal angiotensinogen is formed and secreted locally for several reasons: first, the molecular size of the molecule makes it unlikely for it to filter through the glomerular capillaries; second, intrarenal angiotensinogen mRNA and protein have been identified in proximal tubule cells[109]; third,

concentrations of angiotensinogen in the proximal tubule of anesthetized rats greatly exceeded the free angiotensin I and II concentrations[110]; and fourth, human angiotensinogen was not detected in urine of normotensive rats infused with the molecule.[111]

Renin and Prorenin

Renin is produced and stored in granular juxtaglomerular cells, which are modified smooth muscle cells found in the media of afferent arterioles.[112–114] Genomic analysis of the renin gene identified a single locus in humans and rats designated Ren-1, whereas mice have two renin genes, designated Ren-1 and Ren-2.[112] This duplicated renin gene in mice leads to production of substantial amounts of renin from submandibular and submaxillary glands.[115] Renin is synthesized in an inactive precursor form, preprorenin. Cleavage of the signal peptide from the carboxyl terminal of preprorenin results in prorenin, which is also biologically inactive. Subsequent glycosylation and proteolytic cleavage leads to formation of renin, a 37 to 40 kDa proteolytic enzyme. Both circulating active renin and prorenin are released mostly from the kidneys; however, other tissues also secrete these substances.[116,117] Because prorenin is the major circulating form, it is postulated that significant conversion of prorenin to renin follows secretion. Prorenin-activating enzymes have been localized to neutrophils, endothelial cells, and the kidney.[112] In addition to juxtaglomerular cells, renin production has also been detected in the submandibular gland, liver, brain, prostate, testis, ovary, spleen, pituitary, thymus, and lung.[112] Circulating renin, however, appears to be derived entirely from the kidney.

Angiotensin I

Angiotensin I is an inactive decapeptide formed upon cleavage of angiotensinogen by active renin in the circulation. Its rate of formation is highly determined by renin activity. Angiotensin I is easily hydrolyzed to angiotensin II given the widespread availability of ACE on endothelial cells of many vascular beds, including the lungs; the octapeptide angiotensin II is therefore formed by cleavage of the C-terminal dipeptide of angiotensin I.[107]

Angiotensin-converting Enzyme

The ACE, also known as kininase II, is a membrane-bound peptidase that catalyzes the conversion of angiotensin I (Ang I) to angiotensin II (Ang II), the primary active product of the renin-angiotensin-aldosterone system (RAAS). This enzyme is localized on the membrane of various cell types, mostly the endothelial cells. Other cell types include the epithelial cells of the kidney (e.g., the brush border of the proximal tubule cells) and the neuroepithelial cells. The ACE exists also in the plasma as a soluble circulating enzyme, but it is thought that the membrane-bound form is the physiologically active one.[107] Other metabolic activities of ACE include the inactivation of the vasodilator peptides bradykinin and kallidin. Therefore, the functional activity of ACE results in enhanced vasoconstriction and reduced vasodilation. Differences between humans and various animal species regarding ACE localization in the kidney have been reported. Normal nonhypertensive human subjects show a widespread expression of ACE on the brush border of tubule epithelial cells and less expression on glomerular vascular endothelial cells, whereas the renal microvasculature of rats show more preponderant ACE expression compared to epithelial cells. These findings imply that the contribution of circulating angiotensin I to the local formation of angiotensin II in the kidney may be minimal.[118]

In the plasma, all conversion of Ang I to Ang II occurs by the activity of ACE with no species variation reported. However, non–ACE-dependent pathways exist at the tissue level and have species variation. In humans, tissue activity of chymase can allow for the local formation of Ang II in the heart, arteries, and kidney. In rats and rabbits, tissue activity of chymase is associated with the local degradation (instead of formation) of Ang II. Therefore, one must carefully evaluate experimental animal data when pharmacologic blockade of the renin-angiotensin system is used.[119]

Angiotensin Peptides

Ang II is the primary active product of the RAAS. It is an octapeptide derived from Ang I after cleavage of the C-terminal dipeptide by the ACE. Most of the physiologic actions of the RAAS on the vasculature and transport functions are mediated by Ang II action on angiotensin receptors, primarily type 1 (AT1) receptors. However, other angiotensin peptides with reported biologic activity have been identified, such as angiotensin III (Ang III) and IV (Ang IV), which are formed from Ang II by the sequential removal of amino acids from the N-terminus by aminopeptidases (Fig. 8.3). They are predominantly seen in the kidney and brain, where aminopeptidases A and N are prevalent.[107,117] Ang III, also known as angiotensin 2-8, is a heptapeptide with suggested role in blood pressure maintenance in the brain. Ang IV (angiotensin 3-8), on the other hand, is a hexapeptide that possibly enhances Ang II signaling. The heptapeptide Ang (1-7) is currently considered one of the biologically active end products of the RAAS. It is formed from Ang I or Ang II in the kidney and heart by the action of tissue peptidases at the C-terminus. Once formed, it is rapidly hydrolyzed by ACE; in conditions of ACE inhibition or AT_1 receptor antagonism, its concentration may increase severalfold. There are two major interactions between Ang (1-7) and bradykinin (BK): potentiation of BK by Ang (1-7) and mediation of vascular actions of Ang (1-7) by kinins. Both mechanisms are involved in the cardioprotective effects of ACE inhibitors. At the kidney level, the proposed role of Ang (1-7) is natriuresis and diuresis as opposed to Ang II, an effect blocked by AT_1 receptor antagonists like losartan. In the vascular bed, it antagonizes the vascular effect of Ang II by acting as a competitive antagonist to AT_1 receptors.[120]

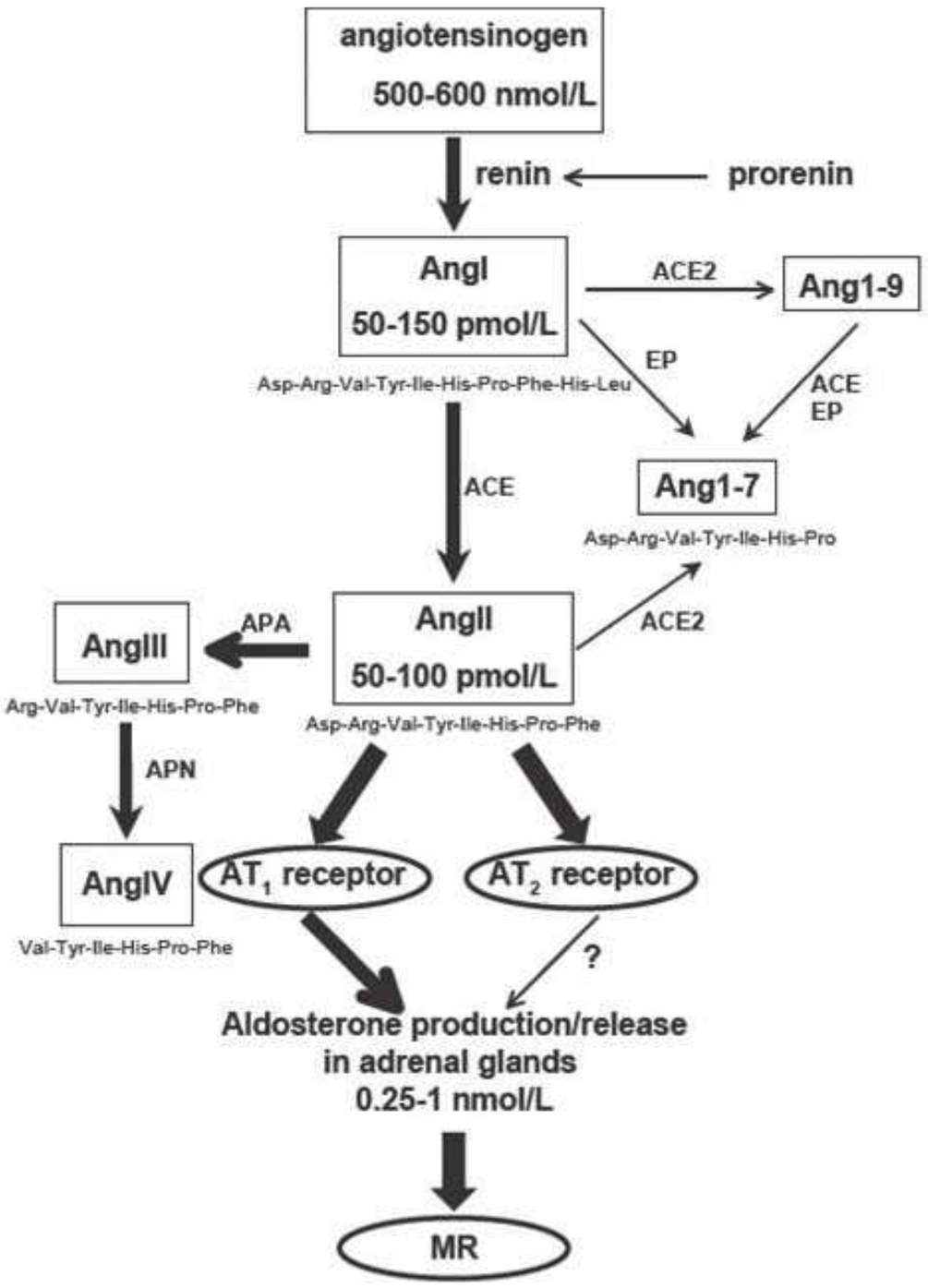

FIGURE 8.3 Schematic representation of the renin-angiotensin system showing plasma concentrations of some components as measured in anesthetized rats. *EP*, endopeptidase; *APA*, aminopeptidase A; *APN*, aminopeptidase N.

Angiotensin II Receptors

Circulating Ang II exerts its biologic effects by binding to specific receptors on the cell surface.[112,121] At least four angiotensin receptor subtypes have been identified. AT_1 receptors bind Ang II with higher affinity than Ang III and are selectively blocked by the biphenylimidazole compound losartan. AT_2 receptors bind Ang II and III with similar affinity and are selectively blocked by tetrahydroimidazopyridines, such as PD123177.[122] The type 3 angiotensin receptor AT_3 has no known function and the type 4 (AT_4) is thought to mediate the release of plasminogen activator inhibitor by Ang II, III, and IV.

Megalin is an abundant membrane protein heavily involved in receptor-mediated endocytosis. Megalin is a receptor for Ang II and Ang II internalization in some tissues is megalin-dependent. Megalin may play a role in regulating proximal tubule Ang II levels.[123] Ang (1-7) exert its vasodilator and natriuretic actions presumably through its binding to a unique receptor, the Mas receptor.[124]

In rodents, two isoforms of AT_1 receptors exist: AT_{1A} (nephron) and AT_{1B} (glomerulus), whereas in humans there is only one AT_1 isoform. The AT_1 receptor has widespread expression in the human adult and is found in the kidney, adrenal gland, heart, and brain. In the kidney, AT_1 receptors are found in the glomeruli, proximal tubule brush border and basolateral membranes, thick ascending loop, proximal convoluted tubule, renal vasculature, the proximal and distal nephron segments, and in both cortical and medullary regions.[125,126]

Aldosterone

Aldosterone was identified by Simpson SA in 1953 and named electrocortin.[127] Later studies characterized more the nature of this hormone and identified it as a mineralocorticoid synthesized and secreted by the zona glomerulosa of the adrenal cortex. The physiology of aldosterone action has been well established after several breakthroughs in research experiences, such as the identification of the mineralocorticoid receptor (MR) as the principal aldosterone receptor, the characterization of sites of aldosterone action in target tissues such as the ENaC, and the demonstration of post-receptor processes involved in physiologic responses to aldosterone.[128–130] Aldosterone secretion is determined by several stimuli, the most important being Ang II and plasma potassium concentration. The MR is the principal receptor for aldosterone, but other target proteins can also bind aldosterone, such as the glucocorticoid receptor. Aldosterone has been implicated in the pathophysiology of several cardiovascular and renal diseases and will be discussed in details in other sections.[129]

Physiologic Actions of Angiotensin II

Systemic Effects of Angiotensin II

AT_1 receptors have been shown to mediate many of the functions of Ang II in the regulation of blood volume, cell contraction, cell proliferation, aldosterone secretion, pressor and tachycardic responses, increased thirst, and hypertension secondary to renal artery stenosis. AT_1 receptors are positively coupled to phospholipase C and mitogen-activated protein kinases (PI3 and MAP) and negatively to adenylate cyclase.[122,125,131] The predominant function of the renin-angiotensin system is regulation of vascular tone and renal salt excretion in response to changes in the volume of extracellular fluid or blood pressure. Ang II represents the effector limb of this hormonal system, acting on several organs, including the vascular system, heart, adrenal glands, central nervous system, and kidneys. Through direct action on smooth muscle cells, Ang II significantly increases arteriolar resistance in renal, mesenteric, dermal, coronary, and cerebral vascular beds.[132] Skeletal muscle and pulmonary vessels, on the other hand, are not affected because of Ang II-stimulated production of vasodilatory prostaglandins by endothelial and smooth muscle cells in these vascular beds.[133,134] Ang II exerts indirect pressor effects via the central and peripheral nervous systems. Its effects on the central nervous system include increased sympathetic discharge and decreased vagal tone.[135] Peripherally, Ang II augments the vasoconstrictive response to renal nerve stimulation in

dogs[136] and its inhibition attenuates the pressor response to norepinephrine in humans.[137] Experimental data suggest the presence of a local renin–angiotensin system in the vasculature that contributes to the regulation of vascular tone.[112]

A more recently recognized function of Ang II is its growth-promoting effects in smooth muscles of the vasculature, heart, and the kidney. Ang II has been shown to induce hypertrophy and mitogenesis in cultured vascular smooth muscles.[138,139] This effect is at least, in part, mediated through autocrine production of growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β).[140] Some studies suggest that the renin–angiotensin system contributes to neointimal formation and restenosis after angioplasty.[112] Ang II has been shown to have direct inotropic, chronotropic, mitogenic, and hypertrophic effects on isolated atria and ventricles.[112] Amelioration of hypertensive cardiomyopathy by ACE inhibitors suggests that the renin-angiotensin system plays a role in cardiac hypertrophy.[112]

The predominant physiologic role of the AT_2 receptor is to initiate vasodilation and natriuresis as a counterregulatory response to the vasoconstriction caused by activation of the AT_1 receptor.[141] Other functions include inhibition of growth and hypertrophy, and stimulation of apoptosis.[142] This has been most clearly demonstrated in AT_2 receptor knockout mice that have slightly elevated blood pressure in the basal state, but have an exaggerated increase in blood pressure in response to Ang II infusion compared to wild type mice.[143,144] The intracellular signaling pathways coupled to the AT_2 receptor are unclear. However, there is evidence that the AT_2 receptor may be coupled to the production of a variety of renal vasodilator substances, counterregulating the pressor effects of Ang II via AT_1 receptors.[142] The most likely candidates are bradykinin and nitric oxide (NO)-stimulated cyclic guanosine monophosphate (cGMP),[145,146] but other candidates include products of cyclooxygenase, such as PGE_2 and PGI_2.[141]

Renal Effects of Angiotensin II

Ang II serves at least three important functions in the kidney: regulation of blood flow and GFR, reduction of salt excretion through direct and indirect actions on renal tubule cells, and growth modulation in renal cells expressing AT_1 receptors.

In conditions of decreased renal blood flow, GFR is preserved at nearly constant value over a wide range of perfusion pressures. This phenomenon is known as autoregulation of GFR. At low levels of renal perfusion pressures, Ang II contributes to this phenomenon.[147] Micropuncture studies have shown that Ang II exerts substantial effects on the renal microvasculature and hemodynamics; however, the individual contribution of the systemic and local renin-angiotensin systems to the overall regulation is still controversial. Ang II constricts both the afferent and efferent arterioles, reduces single nephron glomerular filtration rate and plasma flow, increases the filtration fraction, and decreases glomerular filtration coefficient. Other studies have shown that Ang II infusion preferentially vasoconstricts efferent arterioles counteracted by endothelial-derived NO[148] and constricts descending vasa recta (DVR) through Ca^{2+} signaling in pericytes.[149] The disproportionate increase in postglomerular resistance results in a marked increase in glomerular capillary hydrostatic pressure (P_{GC}), ultrafiltration pressure, and filtration fraction, thus preserving GFR in the face of declining renal plasma flow (RPF). The selectivity of the vasoconstrictive action of Ang II for the efferent arteriole results from stimulation of vasodilatory prostacyclin synthesis by the afferent arteriole and not a preferential action of Ang II on the efferent arteriole.[150] In fact, Ang II increases both afferent and efferent resistance in the presence of a cyclooxygenase inhibitor.[150] Under certain pathophysiologic conditions, afferent arteriolar constriction predominates, leading to a decrease in both RPF and GFR.[151] Deep nephrons have higher postglomerular Ang II tone and also higher Ang II sensitivity than superficial nephrons. The better preserved GFR in deep cortex during Ang II action may contribute to maintaining the renal-concentrating ability by providing NaCl for reabsorption by the ascending limb of the loop of Henle.[152]

In addition to its vascular effects, Ang II induces mesangial cell contraction, which leads to decreased K_f in vivo.[153,154] This effect, however, is attenuated by the concomitant production of prostaglandins by mesangial cells.[155]

Ang II is one of the most potent sodium-retaining hormones in the body. Increased tubular sodium reabsorption is enhanced by both direct and indirect tubular effects of Ang II. Physiologic concentrations of Ang II (10^{-12} to 10^{-10} M) stimulate proximal tubule NaCl and $NaHCO_3$ absorption at the proximal tubule.[156] Indirectly, Ang II stimulates ion transport in the proximal tubule by changing the peritubular milieu. Ang II can both decrease peritubular capillary hydrostatic pressure and increase peritubular oncotic pressure, resulting in an increased driving force for ion reabsorption. Directly, Ang II can stimulate transport in the proximal tubule through interaction with the AT_1 receptors found on both the apical and basolateral membranes of the tubule cells.[157,158] It also stimulates calcineurin phosphatase activity in proximal tubule epithelial cells through a mechanism involving AT_1 receptor-mediated tyrosine phosphorylation of the PLC isoform, both linked to sodium transport in the proximal tubule.[159] Specifically, Ang II stimulates the activity of apical membrane Na–H antiporters and basolateral membrane Na–HCO_3–CO_2 cotransporters[160] and the activity of Na–K-ATPase by changing phosphorylation and conformation of Na–K-ATPase.[161] The net effect is increased proximal tubule reclamation of Na and HCO_3. Denervation of the proximal tubule results in attenuation of the Ang II-stimulated NaCl, but not $NaHCO_3$ absorption, suggesting that Ang II enhances proximal Na transport indirectly by increasing presynaptic catecholamine release.[159] Of note is that supraphysiologic concentrations of Ang II (10^{-9} to 10^{-7} M) inhibit NaCl and water reabsorption in the proximal tubule and also inhibit Na–glucose cotransporter translocation by inactivation of PKA and decrease of PI3-kinase activity mediated through the AT_1 receptor.[162,163] Ang II increases proximal tubule phosphate absorption by

direct stimulation of Na/P_i cotransport activity as a result of increase in the expression of brush-border membrane NaPi-IIa protein level and that stimulation is most likely mediated by posttranscriptional mechanisms.[164]

Intraluminal conversion of Ang I to Ang II can occur in the cortical collecting duct, resulting in enhanced apical sodium entry.[165] The AT_2 receptor regulates epithelial sodium channel (ENaC) abundance, consistent with a role for Ang II in regulation of collecting duct function via AT_1 receptors.[166,167]

Ang II increases basolateral K-channel activity via the stimulation of AT_1 receptors and the stimulatory effect of Ang II is mediated by a NO-dependent cGMP pathway.[168]

Other effects of Ang II on proximal tubule cells include enhanced gluconeogenesis and ammonia production.[169] The effects of Ang II on distal tubule transport of Na and K are mediated through aldosterone release.[170] In addition to proximal tubule epithelial cells, vasa recta and outer medullary vascular bundles express high density of AT_1 receptors.[121] ACE inhibitors increase descending vasa recta blood flow, whereas Ang II infusion markedly decreases medullary blood flow in rats.[171] It is postulated that Ang II influences urinary dilution and concentration by modulating blood flow to the medulla.

Ang II induces hypertrophy of proximal tubule epithelial cells in vitro.[172] It also exerts similar growth-promoting effects on mesangial cells.[173] The signaling mechanism by which Ang II exerts this effect is not precisely known, but p27Kip1 is required for Ang II-induced hypertrophy.[174] Downstream potential targets of Ang II are the extracellular signal-regulated kinases 1 and 2 (ERK1/ERK2) and Ang II activates ERK1/ERK2 via the AT_1 receptor.[175] Studies have shown that connective tissue growth factor (CTGF) might be an important mediator of Ang II-induced renal hypertrophy, which suggests that inhibiting the production of CTGF might be the new strategy in early prevention of renal fibrosis.[176] Ang II can stimulate human kidney fibroblast (KFB) proliferation and enhance the expression of interleukin-6 in KFB. These findings suggest that Ang II might play a part in the mechanisms for modulating tubulointerstitial changes and inducing renal fibrosis.[177]

Previous in vivo studies in cardiomyopathic hamsters suggested that the expression of vasopressin (AVP) V_2 mRNA is upregulated by Ang II. Ang II caused a significant increase in the AVP V_2 mRNA in a dose-dependent manner mediated by PKA, whereas PKC suppresses the expression of V_2 mRNA in the inner medullary collecting duct (IMCD) of the rat kidney.[178]

The role of Ang II in the pathogenesis of hypertension is complex. Several studies have demonstrated a crucial role of the intrarenal renin-angiotensin system in the development of hypertension and kidney disease.[117] Animal studies have shown that blockade of the AT1 receptor resulted in increased plasma Ang II levels while it limited renal Ang II contents in response to Ang II infusion.[179] This dissociation between systemic and local Ang II regulation has been demonstrated in several animal hypertension models including renovascular hypertension.[180,181] Clinical studies have also shown that local intrarenal Ang II formation was central to the development of hypertension in humans.[182]

In addition to its effects on the maintenance of blood pressure, AT_1 receptors may play a role in embryonic nephrogenesis. Blockage of the renin-angiotensin system with ACE inhibitors or AT_1 inhibitors results in abnormal renal development that is characterized by both papillary and tubular atrophy and by interstitial fibrosis and infiltration. In addition, knockout mice lacking both the AT_{1A} and AT_{1B} receptor have similar renal abnormalities.[183] Ang II also modulates mesangial cell growth, and induces proximal tubular cell hypertrophy in humans, effectively inhibited by irbesartan, an Ang II receptor antagonist.[184]

The AT_2 receptor is expressed predominantly in fetal tissues, but in almost all tissues there is postnatal downregulation. AT_2 receptor mRNA is expressed in the fetal and neonatal rat kidney, but disappears after the neonatal period and is not expressed in the normal adult. Although the AT_2 receptor mRNA is not found in the adult kidney, both immunohistochemistry and Western blot analysis have detected AT_2 receptor protein in the glomeruli, cortical tubules, and interstitial cells of the adult kidney.[121,185] It was thought that AT_2 receptors might play a role in the development of the kidney and urinary tract given the high levels of expression in the fetus. However, although early studies of AT_2 receptor knockout mice showed no gross morphologic abnormalities of the kidney,[143,144] a more recent study has demonstrated the presence of increased numbers of congenital anomalies of the urinary tract.[186] The AT_2 receptor may be implicated in some congenital abnormalities of the urinary tract or may be involved in the pathophysiologic response to ureteral obstruction by protecting against the formation of interstitial fibrosis.[186,187] Ang II modulates the over-expression of AT_2 receptors in renal ablation experiments through its own AT_2 receptor and functional expression of this effect may represent a counterregulatory mechanism to modulate the renal damage induced by renal ablation.[188]

Ang II regulates renal parathyroid hormone-related protein (PTHrP), a vasodilator and mitogenic agent upregulated in kidney injury, and its type-I receptor (PTH1R) system via AT_1 receptors.[189]

Local Effects of Ang II in Nonrenal Organs

Ang II exerts its actions on other organs, such as the adrenals and the brain. At the level of the adrenals, it stimulates aldosterone synthesis and secretion.[170] Acute angiotensin administration stimulates the activity of 11β-hydroxysteroid dehydrogenase (HSD) type 2 in human kidneys and exerts a dual effect on the MR receptor (i.e., an indirect agonistic effect by increasing aldosterone availability and a direct or indirect antagonistic effect by stimulation of renal 11β HSD type 2 activity).[190]

At the central nervous system (CNS) level, it stimulates thirst and salt appetite[191,192] and may increase secretion of

vasopressin and oxytocin from the posterior pituitary, and adrenocorticotropic hormone (ACTH), prolactin, and luteinizing hormone from the anterior pituitary.[193]

Regulation of the Systemic Renin-Angiotensin-Aldosterone System

Ang II in the systemic circulation is produced primarily from circulating angiotensinogen through the proteolytic action of renin. Most of the circulating renin is derived from the kidney, although other organs can secrete prorenin in the circulation. Angiotensinogen is mostly formed and secreted in the circulation by liver cells, allowing for systemic formation of angiotensin peptides, principally Ang II. The circulating concentrations of angiotensinogen are more than 1,000 times greater than those of Ang I and Ang II, therefore changes in plasma renin activity is the major determinant of Ang I formation (Fig. 8.3). Renin secretion is stimulated by various dynamic parameters such as renal perfusion pressure, tubular fluid sodium chloride concentration at the MD, sympathetic discharge to the kidney, and endocrine and paracrine hormones and growth factors.[107]

Stimulation of renin release by juxtaglomerular cells is mediated by increased intracellular cAMP, whereas a rise in cytosolic free calcium is inhibitory.[194] Renin release responds inversely to changes in renal perfusion pressure.[114] Elevation of intrarenal arterial pressure inhibits renin release and induces a "pressure" natriuresis. At least two mechanisms have been postulated. Increased afferent arteriolar wall tension secondary to increased renal perfusion elevates intracellular calcium in juxtaglomerular cells and inhibits renin secretion.[114,194] Increased perfusion pressure also stimulates NO production and release by endothelial cells. NO, in turn, suppresses renin secretion.[195,196] Conversely, decreased renal perfusion results in increased production of prostacyclin (prostaglandin I_2), which enhances renin release.[197] Mechanical strain leads to upregulation of the AT1 receptor and increased Ang II production in conditionally immortalized podocytes. The resulting activation of a local tissue angiotensin system leads to an increase in podocyte apoptosis, mainly in an AT1 receptor-mediated fashion.[198]

Decreased NaCl delivery to MD cells stimulates renin secretion, whereas increased urinary NaCl exerts an opposite effect.[180] Schlatter and coworkers[199] demonstrate that changes in luminal Cl^- concentration alter the rate of Na^+-K^+-$2Cl^-$ transport in MD cells.[199] The precise mechanism by which variation in the activity of this transporter translates to a signal that regulates renin release by adjacent juxtaglomerular granular cells is not entirely clear. Postulated mediators include adenosine, which inhibits renin secretion via activation of A_1 receptors on juxtaglomerular cells, and alterations in interstitial osmolality, which may affect renin secretion directly.[96] Experimental evidence also suggests that NO produced by MD cells and endothelial cells regulates renin secretion.[195,200]

The importance of renal sympathetic innervation in controlling renin secretion is well recognized.[201] Stimulation of postjunctional β-adrenergic receptors increases renin release. The role of α-adrenergic receptors, on the other hand, is controversial.[201] Ample evidence suggests that dopamine stimulates renin secretion by direct activation of dopamine A1 (DA_1) receptors on juxtaglomerular cells.[201,202]

Several endocrine and paracrine hormones regulate renin secretion by the kidney. ANP has been shown to inhibit renin release from isolated juxtaglomerular cells.[203] Other inhibitory hormones include AVP, endothelin, and adenosine (A_1-receptor agonists).[114,195] Regulation of renin secretion by Ang II is probably the most physiologically relevant.[169] Ang II inhibits renin secretion and renin gene expression in a negative feedback loop. Treatment of transgenic mice bearing the human renin gene with an ACE inhibitor increases renin expression in the kidney by five- to tenfold.[204] Similarly, ACE inhibition in rats augments renal renin mRNA expression, an effect that is reversed by infusion of Ang II.[205] The effects of Ang II are believed to be direct and not dependent on changes in renal hemodynamics or tubular transport. Arachidonic acid metabolites produced in the kidney also play an important role in renin secretion.[195] Intrarenal infusion of arachidonic acid increases (and indomethacin decreases) plasma renin activity in rabbits.[206] Several studies have since confirmed that prostaglandins of the I series are potent stimulators of renin secretion.[195,197] On the other hand, lipoxygenase products of arachidonic acid metabolism (12-HPETE, 15-HPETE, and 12-HETE) and cytochrome P450-mediated epoxides (14,15-epoxyeicosatrienoic acid) have been shown to inhibit renin release in renal cortical slices.[207,208]

The Local Renin-Angiotensin System

The renin-angiotensin system has been characterized as an endocrine, paracrine, and autocrine system. Contribution of systemically formed mediators to local control of dynamics within tissues is difficult to delineate. Recent evidence suggests that local formation is a major determinant of Ang levels in organs and tissues. In the brain, for example, Ang peptide levels are regulated in an autonomous manner.[209] Local renin-angiotensin systems have been identified in several organs, including the kidney, heart, vasculature, brain, and adrenals.[210] Although most organs have elements of the renin-angiotensin system, the adult kidney is unique in expressing all the components of the system.[156,169]

Compared with plasma levels, the renal Ang II contents are much higher despite suppression of renin secretion and release.[126] Renin is principally produced by juxtaglomerular cells of the distal afferent arteriole, but has been shown to be expressed in the proximal tubule cells,[126] whereas its substrate, angiotensinogen, is expressed by proximal tubule cells. ACE activity in the kidney has also been localized to the proximal tubule, with the highest concentration present on the brush border. Several studies have provided evidence for production of Ang II by the kidney, mainly concentrated in the proximal tubules,[126] suggesting that the intrarenal renin-angiotensin

system is, indeed, functional.[156] Some investigators have proposed that this local system plays a role in proximal tubule NaCl and HCO_3 absorption, pathogenesis of essential hypertension, and expression of the phenotype of autosomal dominant polycystic kidney disease.[156] Independent regulation of renal Ang II production has not been definitively demonstrated. Circulating Ang II stimulates renal angiotensinogen mRNA production and intact urine angiotensinogen suggests its presence along the whole nephron and that renin and ACE activity are available all through the nephron.[126]

Endogenous Ang II in both peritubular blood and luminal fluid is important for maximal expression of the stimulatory influence of this peptide on proximal tubule fluid uptake.[211] Intraluminal conversion of Ang I to Ang II can occur in the cortical collecting duct, resulting in enhanced apical sodium entry.[165]

Renal degradation of Ang II is constitutively high, unaffected by chronic levels of arterial blood pressure, and is independent of long-term changes in levels.[212]

Low-density lipoproteins (LDLs) increase Ang II production by mesangial cells, which, in turn, results in increased O_2 production, cell proliferation, and hypertrophy—these effects of Ang II are mediated by the AT_1 receptor.[213]

Established Clinical Pathophysiologic Role of the Renin-Angiotensin-Aldosterone System in Humans

The RAAS has been implicated in the pathophysiology of several diseases of the cardiovascular system and the kidney, mostly hypertension and renal injury. The local renal renin-angiotensin system is activated in the renovascular type of hypertension in the stenotic kidney and accounts for most of the Ang II concentration in the renal tissue.[214] In addition, it plays a crucial role in other forms of hypertension. Administration of a renin inhibitor to normal subjects and hypertensive patients showed sustained local renal vascular responses but time-dependent decreased drug activity at the systemic level.[215] Several other studies demonstrated the importance of the intrarenal renin-angiotensin system in the pathophysiology of hypertension.[216,217]

Ang II promotes fibrogenesis and oxidative stress in the kidney by stimulating fibrogenic mediators, altering renal hemodynamics especially facilitating glomerular hypertension, inducing tubulointerstitial hypoxia, and enhancing free radical formation. Studies have shown that the degree of mesangial hypercellularity and expansion in IgA nephropathy correlated closely with glomerular expression of mRNAs for renin, ACE, chymase, and AT1 and AT2 receptors.[217,218] The role of the intrarenal renin angiotensin system has been also established in the pathogenesis of membranous nephropathy.[219] In diabetic nephropathy, the renin-angiotensin system plays a crucial role in disease progression: the intrarenal generation of Ang II is increased, despite suppression of the systemic RAAS. Details of the pathophysiologic mechanisms implicated in diabetic nephropathy are beyond the scope of this chapter.

The role of the RAAS in end-stage renal disease (ESRD) is even more complicated and implicates many parameters related to residual renal function, presence of renal replacement therapy and modality, and drug treatment of associated conditions. In addition, renal transplantation adds a new dimension to the complexity by introducing an immune component through graft rejection and immunosuppressive drugs. Despite the substantial decrease in renal blood flow and function in patients with ESRD on dialysis, studies have shown that those with remaining kidneys have an activated intrarenal renin-angiotensin system.[117] On the other hand, renal transplant diseases, especially rejection and cyclosporine-induced nephropathy, were associated with increased activity of systemic and local RAAS in several studies.[220,221]

In conclusion, the RAAS is one of the most powerful pressure and volume regulatory systems in the body, involved in physiologic responses and pathophysiologic processes at both the systemic and local levels. Autonomous and independent control of local renin-angiotensin systems in various organs and tissues may exist and contribute to disease progression. New areas of interest in the RAAS are continuously emerging, facilitating the understanding of mechanisms of diseases and development of specific drug targets.

ATRIAL NATRIURETIC PEPTIDE

Molecular and Biochemical Properties of Atrial Natriuretic Peptide

The cDNA for human ANP was isolated in 1984 and, shortly afterward, the gene was localized to the short arm of chromosome 1.[222,223] The chromosomal gene consists of three exons and two introns encoding for a mature mRNA transcript approximately 900 bases long.[223]

Translation of human ANP mRNA results in a 151-amino acid preprohormone.[224] Pro-ANP, a 126-residue molecule, is formed after cleavage of the signal peptide sequence of prepro-ANP and represents the major storage form of the hormone in atrial granules.[225] The circulating, biologically active form of ANP, often referred to as $AN_{99–126}$ or ANP_{1-28}, is a peptide comprising the 28 carboxy-terminal amino acids of the parent molecule.[224] The amino acid sequence of $ANP_{99–126}$ is highly conserved among mammalian species.[224] A disulfide bond between cysteine residues 105 and 121 gives $ANP_{99–126}$ its ring structure, which is essential for biologic activity.[226]

Pro-ANP (1–30), (31–67), and (68–98) are secreted from the heart and circulate in the plasma. Pro-ANP (1–30) and (31–67) increase sodium and water excretion and binding sites have been found in the proximal tubules and collecting ducts. Pro-ANP (31–67) inhibits the Na^+-K^+ pump at the medullary collecting duct through a prostaglandin-dependent mechanism and no effect on cGMP production. Pro-ANP (1–30) infusion in rats clearly increases urine output, sodium, and potassium excretion, the mechanism of which still needs to be elucidated.[227]

Secretion and Physiologic Regulation of Atrial Natriuretic Peptide$_{99–126}$

Cardiac atria contain the highest concentrations of ANP and serve as the major source of circulating hormone.[224] $ANP_{99–126}$ secretion from cardiomyocytes occurs largely in response to atrial stretch resulting from increased atrial transmural pressure.[228] Physiologic stimuli for the release of $ANP_{99–126,}$ include acute salt and volume loading, supine posture (head-down tilt), and head-out water immersion.[228–230] An increased rate of atrial contraction has also been shown to stimulate $ANP_{99–126}$ secretion.[231,232] Ang II, vasopressin, epinephrine, and phenylephrine stimulate $ANP_{99–126}$ secretion from the heart largely because of their systemic vasopressor effects.[233] On the other hand, glucocorticoids and endothelin raise $ANP_{99–126}$ levels possibly by acting directly on atrial myocytes.[234] Leptin decreases ANP secretion via an NO-mediated mechanism.[235] Physiologic and pathologic conditions in which elevated plasma levels of $ANP_{99–126}$ have been detected are summarized in Table 8.3.

The local synthesis of natriuretic peptides is increased in the kidney and in the vasculature in obstructive uropathy.[236] The activation of the renin-angiotensin system during low sodium intake antagonizes the biologic effect of ANP by interfering in the intracellular metabolism of cGMP.[237]

8.3 Conditions Associated with Increased Levels of Circulating Atrial Natriuretic Peptide

Physiologic	Pathologic
Acute volume expansion	Congestive heart failure
Supine posture	Atrial tachycardias
Head-out water immersion	Myocardial ischemia
Mineralocorticoid escape	Acute and chronic renal failure
Exercise	Postobstructive diuresis
Neonatal period	Nephrotic syndrome (subset) Cirrhosis with ascites Severe hypertension Primary hyperaldosteronism Hypoxia Other (SIADH myxedema)

SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Physiologic Actions of Atrial Natriuretic Peptide$_{99–126}$

Three subtypes of ANP receptors (NPRs) have been identified.[238–240] NPR-A and -B have intrinsic guanylate cyclase activity that catalyzes production of cGMP after ligand binding. cGMP then serves as an intracellular second messenger that mediates the biologic activities of $ANP_{99–126}$.[241] NPR-B appears to have 50-fold higher affinity for a related natriuretic factor originally purified from porcine brain, known as C-type natriuretic peptide (CNP).[242] NPR-C, previously known as the (clearance) receptor, is devoid of guanylate cyclase activity and, therefore, does not confer biologic activity and is thought to mediate clearance of circulating ANP along with metalloendoprotease (E.C.3.4.24.11)[242] and of other related hormones, such as brain natriuretic peptide (BNP).[243] Selective downregulation of NPR-C in the kidney in response to dietary salt supplementation may contribute to local elevation in ANP levels and may be functionally significant in attenuating the development of salt-sensitive hypertension.[244] NPR density is decreased in diabetic rats with significant increase in plasma ANP levels.[245] ANP also antagonizes AVP-mediated increases in water permeability in IMCD cells.[246]

The major sites of action of $ANP_{99–126}$ are the kidneys, adrenal glands, and vascular smooth muscle.[247] Short-term administration of $ANP_{99–126}$ in laboratory animals and in humans induces pronounced natriuresis, diuresis, alteration in renal hemodynamics and tubular function, suppression of renin release, inhibition of aldosterone secretion by the adrenal glands, and decreased vasomotor tone, resulting in transient drop in systemic blood pressure. From these actions it has been postulated that ANP plays an important physiologic role in protecting against extracellular volume overload.[248]

Renal Actions of Atrial Natriuretic Peptide$_{99–126}$

ANP-induced increase in the GFR is well established.[249–251] $ANP_{99–126}$ increases efferent arteriolar resistance, resulting in increased P_{GC} and filtration fraction.[249] In addition, $ANP_{99–126}$ relaxes mesangial cells in vitro, suggesting that it can increase filtration area by cGMP generation in podocytes[252] and K_f in vivo.[253] Indeed, when baseline K_f is low, as in water-deprived animals, $ANP_{99–126}$ enhances GFR mainly by increasing K_f.[253] If preexisting vascular constriction is present in isolated perfused kidney, ANP tends to vasodilate renal vessels and increase renal blood flow (RBF).[254] In whole animals, however, $ANP_{99–126}$ infusion causes either a decline or no change in RBF.[254] The effects of $ANP_{99–126}$ on RBF are influenced by its systemic actions on blood pressure and the renin-angiotensin system. ANP seems to increase NO production at both renal and cardiac levels, further explaining its natriuretic and diuretic effects.[255] Finally, ANP has been reported to induce redistribution of blood flow from the cortex to the medulla and to increase vasa recta flow, leading to dissipation of the medullary solute gradient.[256,257]

$ANP_{99–126}$ has both direct and indirect effects on tubular transport of Na, chloride, and water.[258] In the proximal tubule, $ANP_{99–126}$ antagonizes Ang II-induced Na reabsorption[259] and, along with endothelin-3, inhibits the sodium-glucose transporter[260] and, like urodilatin, inhibits Na^+-ATPase activity.[261] In the IMCD, it directly inhibits Na transport by binding to ANP-R1 receptors and influencing amiloride-sensitive Na channels and the activity of apical Na-K-2Cl cotransporters.[262] Other mechanisms by which $ANP_{99–126}$ induces natriuresis and diuresis include suppression of renin and aldosterone release,[263] inhibition of the tubular actions of AVP,[246] and dissipation of the medullary solute gradient by impairing the increase in intracellular Ca^{2+} concentration. ANP blocks both the stimulatory and inhibitory effects of AVP on Na^+-dependent pHi recovery.[264]

Atrial Natriuretic Peptide Transgenic Mice

Transgenic mice over-express pro-ANP in hepatocytes. These transgenic animals have a hypotensive phenotype (20 to 30 mm Hg lower than control littermates) without compensatory tachycardia. GFR remained normal despite hypotension. Moreover, significant diuresis or natriuresis during steady state was not detected. Contrary to observations made after short-term infusion of $ANP_{99–126}$, plasma renin activity also did not change while aldosterone levels were elevated.[265–267]

Physiologic Consequences of Interrupting the Atrial Natriuretic Peptide Pathway

Disruption of the gene that encodes pro-ANP results in knockout mice that lack expression of ANP. Homozygous ANP knockout mice fed a standard diet have both mildly elevated blood pressure (average increase of 8 mm Hg) and cardiac hypertrophy compared to wild type mice, suggesting that ANP has a physiologic role in maintaining the normotensive state. This hypertension appears to be sensitive to dietary salt intake as feeding the homozygous ANP knockout mice a diet with an intermediate salt content (2%) would further increase blood pressure by an average of 20 mm Hg compared to wild type mice.[268] Knockout mice lacking ANP-R1 activity (known as GC-A null mice) have both elevated blood pressure and cardiac hypertrophy, similar to pro-ANP knockout mice, but the GC-A null mice have a salt-insensitive form of hypertension.[267] It is unclear why there should be a difference in the phenotype of these two types of knockout mice. It is possible that other guanylyl cyclase receptors, such as guanylyl cyclase C, can help regulate blood pressure in the face of changes in dietary salt intake and compensate for the lack of GC-A receptors.[268] ANP (−/−) mice have a blunted pressure-natriuresis response and suppressed expression of local renal renin-angiotensin system.[269]

Atrial Natriuretic Peptide-Related Peptides[149,212]

BNP is a 32-amino acid peptide with structural homology to $ANP_{99–126}$. Although originally isolated from porcine brain,[270] it is also secreted by cardiac ventricles and, to a lesser extent, from atria. The biologic effects of BNP infusion are similar to those of $ANP_{99–126}$. Unlike ANP, BNP secretion seems to be constitutive and unrelated to myocyte stretch. The kidney-specific degradation of ANP provides a mechanism for preferential regulation of kidney function by BNP, independent of peripheral ANP concentration.[270] In 1990, another homologous peptide, CNP, was isolated from porcine brain.[271] CNP is produced in the brain, where it achieves concentrations much higher than those of ANP and BNP. In contrast, circulating levels of CNP are lower. CNP lacks natriuretic, diuretic, and hypotensive effects and probably acts in a paracrine fashion in the CNS. The physiologic significance of BNP and CNP remains unclear.

Clinical Use of Atrial Natriuretic Peptide and Atrial Natriuretic Peptide Analogs in the Diagnosis and Treatment of Kidney Injury and Congestive Heart Failure

Measurement of circulating ANP and ANP analogs is now a well established marker in assessment of volume overload and left ventricular dysfunction and for predicting mortality, in the presence or absence of renal dysfunction.[272–276] A number of studies, reviewed recently,[277] provide support for the use of ANP/ANP analogs in protection against and treatment of acute kidney injury (AKI).[278–281] In these studies, low (but not high)-dose ANP infusions reduced the need for renal replacement therapy and hospital and intensive care unit length of stay, but did not appear to improve mortality in the management of cardiac surgery–associated AKI. Hyporesponsiveness to ANP in congestive heart failure may be due to reduced NPR-A expression.[282] In dogs, maximizing cGMP action with type V phosphodiesterase inhibitors augments the natriuretic responses to exogenous ANP.[283] Animal studies have shown the usefulness of encapsulated ANP gene transfected cells as a new tool for ANP gene delivery with possible implication for future therapy.[284]

URODILATIN OR RENAL NATRIURETIC PEPTIDE

Urodilatin is best described as a paracrine renal natriuretic peptide (RNP).[285] It was first isolated from human urine in 1988.[286] Its amino acid sequence is identical to $ANP_{99–126,}$ except for an additional four amino acids at the amino terminal. Despite its high degree of homology to $ANP_{99–126,}$ specific antihuman RNP polyclonal antibody has been generated and RNP levels can be measured by radioimmunoassay.[287] To date, RNP has not been detected in the circulation and the kidney is presumed to be its site of synthesis and action.[285]

RNP binds to ANP receptors in the kidney and stimulates cGMP production.[288] Its renal actions parallel those of $ANP_{99–126}$ and include more potent hyperfiltration, diuresis, and natriuresis.[288] RNP, like $ANP_{99–126}$, inhibits sodium uptake by inner medullary duct cells by inhibiting entry of Na

through apical sodium channels.[289] It appears that the natriuretic effect of RNP is more potent than that of ANP, possibly because it is resistant to degradation by renal cortical metalloendopeptidase.[290] Systemic infusion of RNP results in effects similar to those of $ANP_{99–126}$.

Several physiologic studies suggest that RNP functions as a paracrine hormone that regulates renal Na excretion. Drummer and coworkers[291] demonstrated in the human that urinary excretion of RNP, but not plasma ANP concentration, correlates with circadian variation in sodium excretion over a 9-day period. Moreover, acute infusion of normal saline in healthy subjects, balloon dilatation of left atrium, and water immersion induce a significant increase in urinary RNP.[292,293]

GUANYLIN AND UROGUANYLIN

Guanylin and uroguanylin are cGMP-regulating agonists isolated in 1994, respectively, from rat intestine and human/opossum urine that appear to have natriuretic properties.[294,295] In humans and mice, earlier studies reported that both genes for guanylin and uroguanylin are located close to each other on chromosomes 1 and 4, respectively, near the ANP A and B genes and probably arising from an ancestral uroguanylin/guanylinlike gene.[296] Preproguanylin and preprouroguanylin probably derived from a common precursor gene, as they share approximately 35% homology.[297] Bioactive uroguanylin can be found in the urine at higher concentrations than guanylin, suggesting that uroguanylin may be a hormonal link between the intestine and the kidney.[298] Uroguanylin, prouroguanylin, and proguanylin peptides have been shown to circulate in the plasma of humans and other animals.[299]

CORTICOSTEROIDS

Corticosteroids are steroid hormones synthesized by the adrenal cortex. On the basis of their physiologic functions, corticosteroids are traditionally divided into two groups—glucocorticoids (cortisone and cortisol) and mineralocorticoids (aldosterone)[300]—based on their potency in electrolyte and metabolism regulation.

Corticosteroids bind to intracellular receptors: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). They are both part of the nuclear receptor family that also includes receptors for steroid and thyroid hormones, vitamin D_3, and retinoic acids. These receptors translocate to the nucleus after ligand binding[301] and regulate nuclear gene transcription at specific DNA response elements located in the five regulatory regions near the promoters of specific target genes (Fig. 8.4).[302] Both glucocorticoids and mineralocorticoids modulate renal function. Aldosterone-sensitive tissues include the distal parts of the nephron (distal tubule, connecting tubule, and all along the collecting duct), the surface epithelium of the distal colon (where it increases sodium absorption and potassium excretion), and other specific nuclear-binding sites for aldosterone in the thick ascending limb of Henle's loop and salivary and sweat glands. All MR-expressing tissues also express GR. In the kidney, evidence exists for distribution of the GR receptors along the whole parts of the nephron, except for the proximal tubule. No evidence exists for a glucocorticoid role in the colon.[303–305]

MR has the same affinity for both aldosterone and glucocorticoids. Glucocorticoids concentration in plasma is 100- to 1,000-fold higher than aldosterone and only 10% of it circulates as free, whereas all circulating aldosterone is free. MR selectivity exists to prevent complete occupancy of the MR receptor by glucocorticoids at physiologic concentrations. This is mainly mediated by the colocalization of the 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) enzyme in the distal nephron, along with MR. This enzyme transforms glucocorticoids (cortisol in humans) into metabolites (cortisone) that have weak affinity to MR.[301,305–307] 11β-HSD has two main isoforms. 11β-HSD1 acts predominantly as a reductase in vivo in many tissues, regenerating biologically active glucocorticoids (mainly cortisol in human and corticosterone in rodents) from their inactive forms (cortisone in human and 11-dehydrocorticosterone in rodents). 11β-HSD2, on the contrary, is a dehydrogenase that inactivates glucocorticoids.[308] The major role of 11β-HSD2 is highlighted in clinical situations, such as the syndrome of apparent mineralocorticoid excess where it is inactivated or after ingestion of excessive amounts of licorice where glycyrrhetinic acid, a derivative of licorice, has been described to inhibit 11β-HSD2.[309,310] Both of these conditions lead to hypokalemic hypertension with low renin and aldosterone levels. In cirrhosis also, there is MR activation by cortisol explained by a reduced activity of 11β-HSD2, which allows promiscuous activation of MR by the glucocorticoid cortisol as suggested by Frey.[311]

GRs have approximately equal affinities for aldosterone and endogenous glucocorticoids, but have the highest affinity for dexamethasone, a synthetic glucocorticoid.[301] Because mineralocorticoids circulate at much lower concentrations than glucocorticoids, significant binding of mineralocorticoids to GR does not occur under physiologic conditions.

Nongenomic Actions of Aldosterone

The effects of aldosterone on its target cells have long been considered to be mediated exclusively through the genomic pathway and were characterized by a 45-minute lag period; however, evidence has been provided for rapid effects of the hormone that may involve nongenomic mechanisms.[5–7,19,32] On the other hand, in a series of in vitro studies, aldosterone was shown to have a half maximal effect on both rapid (15 minutes) and delayed (120 minutes) Na flux.[4,32] The Na/H exchanger has been identified as a target for nongenomic regulation. Aldosterone rapidly increases Na/H exchanger activity in a variety of cells, including distal colon and renal epithelial cell lines,[3] but rapidly inhibits apical NHE_3 and HCO_3^- reabsorption in medullary thick ascending limb (MTAL) and has a dose-dependent biphasic effect on the Na/H exchanger (low doses stimulate and high doses inhibit it).[312]

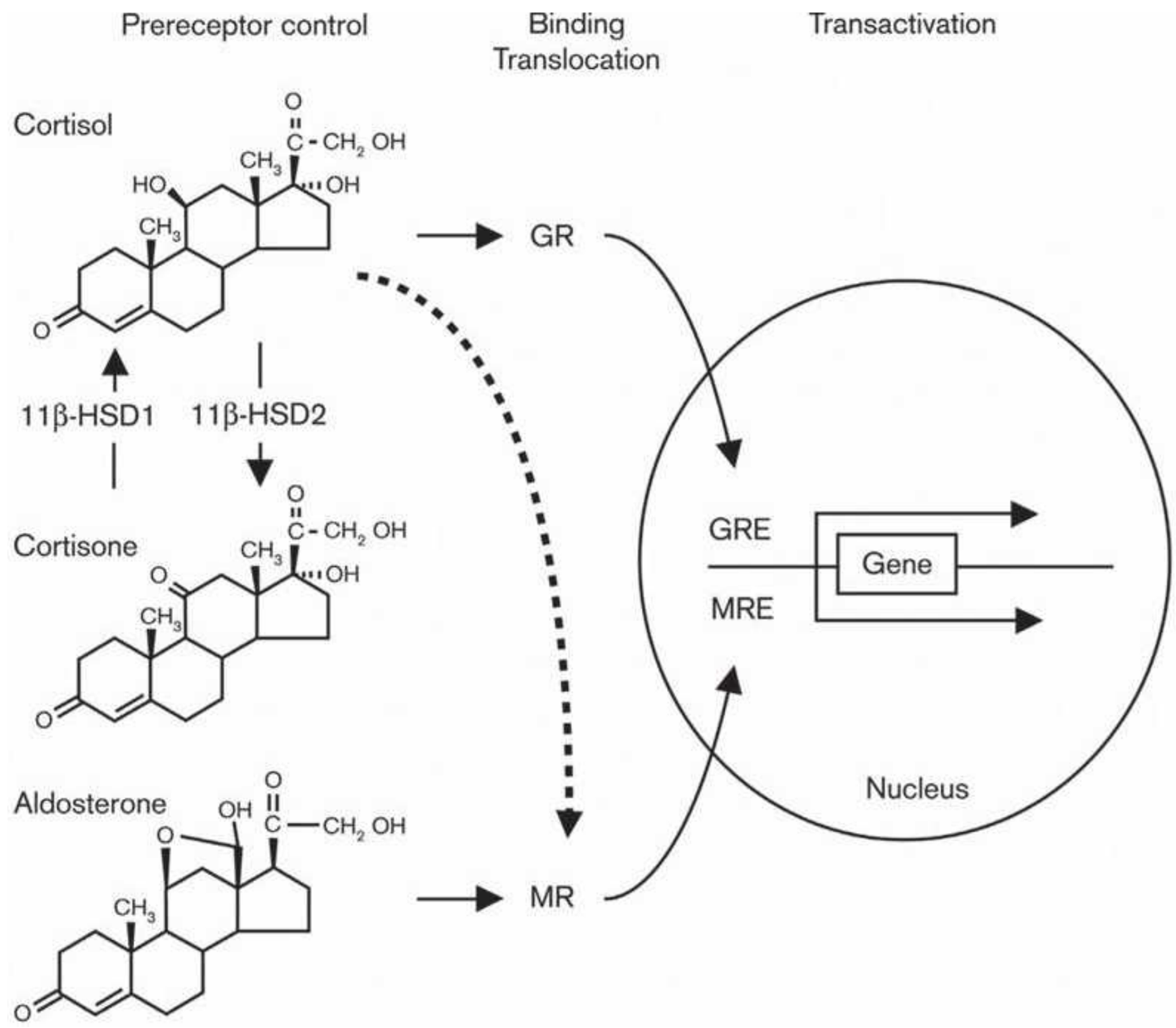

FIGURE 8.4 The intracellular concentrations of steroid molecules available for binding to glucocorticoid receptor (GR) or mineralocorticoid receptor (MR) depend on the free extracellular concentrations available for diffusion into the cytoplasm and the intracellular prereceptor control mechanism constituted by the 11β-hydroxysteroid dehydrogenase type 1 and 2 (11β-HSD1, 11β-HSD2) enzymes. Whereas 11β- HSD1 acts predominantly as a reductase and converts the 11-ketosteroid cortisone with virtually no affinity for MR and GR into the 11β-hydroxyglucocorticoid cortisol with a high affinity for both GR29,58 and MR, 11β-HSD220 is exclusively an oxidase and inactivates cortisol into cortisone, which allows protection of MR-expressing cells from promiscuous activation of MR by the glucocorticoid hormone cortisol. *GRE*, glucocorticoid-response element; *MRE*, mineralocorticoid-response element. (Frey FJ, Odermatt A, Frey BM. Glucocorticoid-mediated mineralocorticoid receptor activation and hypertension. *Curr Opin Nephrol Hypertens*. 2004;13:451–458.)

Aldosterone acts through nongenomic pathways to regulate many different ion transport proteins and signaling pathways in a variety of renal epithelial cells, such as proximal tubule cells derived from human renal cortex, MDCK-C11 cells (a cell line that exhibits properties of collecting duct intercalated cells), and principal cells isolated from rabbit cortical collecting duct and both M-1 and RCCD2 cortical collecting duct cell lines.[6] Studies using isolated perfused tubules also demonstrate that aldosterone, via nongenomic mechanisms, regulates the transepithelial transport function of different nephron segments, such as proximal S3 segment,[21] renal MTAL, type A intercalated cells of outer medullary collecting ducts, and principal cells in the connecting tubule and inner medullary collecting ducts.[6,313] In renal epithelial cells, an elevation in cytosolic Ca_2 serves as a second messenger for the nongenomic Na^-/H exchanger activation initiated by aldosterone.[2] The existence of a nongenomic action of aldosterone is in general attributed to conditions where this action is observed over a short period of time (minutes) against the much longer time (hours, days) needed for a genomic action.[313]

Rapid nongenomic aldosterone effects are characterized by their rapid onset of action (within minutes) and an insensitivity to inhibitors of transcription (e.g., actinomycin D) and of protein synthesis. Aldosterone also acts via rapid nongenomic effects in vivo in humans at the renal vasculature. Antagonizing the endothelial NO synthase unmasks these effects. Therefore, rapid nongenomic aldosterone effects increase renal vascular resistance and thereby mediate arterial hypertension if endothelial dysfunction is present.[314] Evidence suggests that there is a nonclassical membrane-bound aldosterone receptor.[315] These data come from kinetic studies that demonstrate saturable, radiolabeled binding of aldosterone to cell surface membranes that have kinetics compatible with physiologic activity.[316,317] In some cell lines, aldosterone can have very rapid physiologic effects that are not blocked by inhibitors of cell transcription and translation. For instance, in human mononuclear leukocytes, aldosterone can stimulate release of IP_3 or calcium within 30 seconds of exposure.[318,319] These membrane-bound receptors may explain some of the effects of aldosterone that occur prior to gene transcription, such as early stimulation of

sodium reabsorption[320] or early stimulation of salt intake,[321] possibly via phospholipase C/PKC signaling pathways.

Mineralocorticoid Actions in the Kidney

Aldosterone originates primarily from the zona glomerulosa of the adrenal glands. Some recent studies have suggested that the heart, vasculature, and brain can also synthesize aldosterone in response to local tissue injury, although extraadrenal synthesis in humans is still debated.[6–8,11,17,322] It is the chief mineralocorticoid of the body. Its physiologic role as a regulator of sodium and volume balance also allows aldosterone the potential to play a pathologic role in the development of hypertension in patients with renal disease.[322] It is also implicated in the pathophysiology of cardiac fibrosis and cardiac hypertrophy in end-stage heart failure.[3,4,323]

The major action of aldosterone in the kidney is regulation of Na, K, and H handling by the distal part of the nephron. Mineralocorticoid deficiency is associated with volume depletion, hyperkalemia, and mild metabolic acidosis. Conversely, mineralocorticoid excess leads to Na retention, hypokalemia, and metabolic alkalosis.

Ang II, high serum K^+ levels, and ACTH stimulate aldosterone secretion from the adrenal gland.[324] ANP and dopamine, on the other hand, suppress aldosterone secretion. Dietary sodium also modulates aldosterone release through its effects on the renin-angiotensin system. In addition to sodium and volume homeostasis, other triggers for aldosterone release have been cited, including hyperglycemia, adrenocorticotropic hormone (ACTH), and, more importantly in patients with CKD, angiotensin II and potassium.[49]

Sodium Reabsorption

One of the best-documented functions of aldosterone is its ability to increase Na reabsorption in the distal tubule and collecting duct.[325–327] The rate-limiting step to sodium reabsorption across tight epithelia is the permeability of the apical membrane of the transporting cell. Aldosterone increases apical Na permeability of tight epithelia, such as those found in the mammalian distal tubule and descending colon, by increasing the activity of the amiloride-sensitive epithelial sodium channel (ENaC). ENaC is formed by three subunits (alpha, beta, and gamma) and, based on coexpression studies in Xenopus oocytes, these subunits assemble into a complex heterooligomer forming the amiloride-sensitive pore.[328–330]

Other characterized aldosterone-induced targets include the serum and glucocorticoid-regulated kinase-1 (SGK-1), an important mediator of renal sodium homeostasis; corticosteroid hormone-induced factor (CHIF), which regulates the activity of the sodium and potassium-dependent adenosine triphosphatase pump (Na-KATPase); the glucocorticoid-induced leucine zipper protein; a transcription factor; and the G protein K-Ras2.[10–12] SGK-1 is thought to regulate Na^+ flux by increasing ENaC activity at the apical surface of epithelial cells. Aldosterone treatment of a rat collecting duct cell line as well as an adrenalectomized rat model demonstrated a rapid induction of SGK-1 mRNA within 30 minutes of treatment.[13,14] However, SGK-1 null mice only show mild abnormalities in sodium homeostasis, suggesting that other genomic targets are important for overall regulation of sodium transport.[15] Wong et al. demonstrated that ET-1 is a direct aldosterone gene target in the kidney and colon in Sprague dawly rats and may play an important role in aldosterone-regulated ion homeostasis.[323]

Aldosterone also enhances Na reabsorption by increasing Na–K-ATPase activity in basolateral membranes of principal cells in mammalian collecting duct and distal tubule.[327] Studies in toad bladder and mammalian nephron suggest that aldosterone upregulates Na–K-ATPase activity by at least three mechanisms: increased Na influx due to opening of amiloride-sensitive Na channels, induction of Na–K-ATPase subunit expression at the gene level, and induction of intracellular alkalosis, which occurs in tissues that contain aldosterone-sensitive Na/H exchangers.[331] Other hormones also modulate aldosterone's action on Na transport; for example, ANP is inhibitory and vasopressin is stimulatory (Table 8.3).[332]

Hypersecretion of endogenous mineralocorticoids or the administration of mineralocorticoids lead to transient sodium retention followed by a return to Na balance within a few days.[333] The return to Na balance despite elevation of circulating mineralocorticoid levels is referred to as aldosterone or mineralocorticoid "escape." During mineralocorticoid escape, increased Na reabsorption by the distal tubule and collecting duct remains unchanged, but is offset by decreased Na reabsorption in other nephron segments.[332,334] The latter results from increased renal arterial pressure and elevated plasma ANP levels, both of which suppress proximal tubule transport of Na. Mineralocorticoid escape is also, in part, mediated by decreased Na and water reabsorption in the loop of Henle.[334] Other factors, such as TGF-β and interleukin-1 (IL-1), may play a role in regulation of mineralocorticoid escape. These factors have been recently found to inhibit the action of aldosterone on the cells of the IMCD.[335]

Ang II binds to Ang II type 1 (AT-1) receptors in the kidney, which leads to glomerular hypertension, sclerosis, renal fibrosis, and cardiac remodeling, possibly through a TGF-β-mediated pathway.[30–32] ACE inhibitors provide renoprotection by inhibiting the conversion of Ang I to Ang II and precluding the negative effects of AT-1 receptor activation. Studies have shown that Ang II can be generated by ACE-independent pathways such as chymase in the heart,[33] which leads to "angiotensin escape." Angiotensin escape is one of the factors frequently cited to explain aldosterone breakthrough, which may be secondary to the generation of non-ACE mediated angiotensin II.[34] Potassium and adipocyte-released factors may also contribute to the phenomenon of aldosterone breakthrough. Continual dietary intake of potassium in the setting of reduced GFR may promote elevated potassium levels that subsequently trigger aldosterone secretion, as seen in the rat remnant kidney model.[28] ACE inhibitors and ARBs are also known to reduce

potassium excretion, so prolonged use of such agents may enhance potassium retention and predispose a patient to aldosterone breakthrough. Recent studies in rat models of metabolic syndrome with early nephropathy have shown enhanced aldosterone secretion due to adipocyte activity that was not abolished by candesartan administration.[35] These results suggest that adipocyte-released factors outside of Ang II may enhance aldosterone secretion and lead to increased proteinuria and podocyte injury in rats.[35] Thus, potassium, angiotensin II, and adipocyte-released factors may all contribute to the increase in aldosterone secretion in patients on prolonged ACE inhibitors or ARB therapy. The exact definition of aldosterone breakthrough has been a subject of controversy, as there is no current consensus on its precise definition. One of the common definitions is a rise in plasma aldosterone concentration, often past baseline values, following an initial decrease after the initiation of ACE inhibitor or ARB therapy.[322]

Potassium Secretion

Mineralocorticoids are the predominant hormonal influence on K secretion by principal cells of the collecting duct and connecting segment of the distal tubule.[335,336] Although mineralocorticoids always increase K secretion by these nephron segments, this does not necessarily translate into a kaliuresis because of the strong dependence of K excretion on distal Na delivery and urinary flow rate.[337] For example, in conditions of decreased Na delivery and urinary flow to the distal nephron, the kaliuretic effect of aldosterone is either diminished or abolished. The mechanisms by which aldosterone stimulates K secretion by principal cells overlap with those responsible for its Na-retaining action. The late distal convoluted and connecting tubules (CNTs) and cortical collecting duct (CCD) of the distal nephron mediate, in large part, the final regulation of urinary K^+ excretion.[19] The traditional model by which K^+ secretion is accomplished in these segments can be summarized as follows. Na^+ enters the CNT and principal cell from the urinary fluid through the apical amiloride-sensitive ENaC and is then transported out of the cell at the basolateral membrane in exchange for uptake of K^+ via the basolateral Na^+-K^+-ATPase. The high K^+ concentration within the cell and lumen-negative voltage, established by electrogenic Na^+ reabsorption, create a favorable electrochemical gradient for K^+ to diffuse into the urinary space through apical K^+-selective channels. Thus vectorial K^+ secretion in these segments requires a favorable electrochemical gradient and an apical permeability to K^+ increases in extracellular K^+ concentration directly stimulate aldosterone production in zona glomerulosa cells of adrenal glands.[6,59,338]

Aldosterone-induced Na influx through the apical membrane leads to the generation of a lumen-negative potential difference that favors K secretion.[326,327] In addition, although mineralocorticoids do not increase the density of active K channels in the apical membrane, they increase the conductance of apical and basolateral K channels independent of Na flux.[327,339] Physiologically, it is difficult to understand how one hormone can regulate the concentration of two different solutes that have varying levels of dietary intake. Patch-clamp experiments have demonstrated that other nonaldosterone circulating factors exist that can regulate K channel activity. Infusion of aldosterone by osmotic minipump will increase the density of EnaC, but not of K channels.[339] However, an increase in dietary K does increase the K-channel density.[340] Currently, it is unknown what other circulating factor controls K secretion.

A large body of evidence suggests that SGK1 mediates, at least in part, the effect of aldosterone on renal K secretion.[41,88,113,116] This notion is supported by studies performed in SGK1 knockout mice demonstrating that the phenotype of SGK1 deletion is similar to MR knockout mice and displays impaired renal K secretion in response to high dietary K intake.[41,341]

Renal Acidification

The role of mineralocorticoids in regulation of renal acidification is supported by several clinical observations. Syndromes of aldosterone deficiency are associated with metabolic acidosis because of reduced urinary acid excretion, whereas mineralocorticoid excess results in metabolic alkalosis. Aldosterone enhances urinary acidification through direct actions on epithelial cells in the collecting duct and indirectly by influencing various intrarenal and extrarenal factors.[342] Aldosterone increases H secretion by type A intercalated cells in the collecting duct via two mechanisms: direct stimulation of the proton pump (H-translocating ATPase), and indirectly by stimulating Na influx, which creates a lumen-negative potential difference.[342] As with K, the overall effect of aldosterone on renal acid excretion depends on Na delivery to the distal part of the nephron. Reduction of Na transport in the collecting duct, because of either decreased Na delivery or inhibition of distal Na reabsorption by amiloride, significantly attenuates the effect of aldosterone on net H excretion.[343] Aldosterone regulates the expression of aquaporin, AQP3, with no effect on AQP1 and AQP2, in the collecting duct, independently of Na intake.[344]

Effect on Inflammation

Besides its classical effects on salt homeostasis in renal epithelial cells, aldosterone promotes inflammation and fibrosis and modulates cell proliferation. As outlined by recent reports, mineralocorticoid also mediates inflammation and fibrosis through NF-κB activation in liver, heart, and glomerular mesangial cells[9–13] via a pathway involving the aldosterone early-induced gene, serum, and glucocorticoid-induced kinase 1 (SGK1).[11,12,345]

Studies in vitro revealed that aldosterone could induce proliferation of rat glomerular mesangial cells and promote collagen gene expression and synthesis via activation of extracellular signal-regulated kinase 1 and 2 (ERK1/2) mitogen-activated protein (MAP) kinase in renal fibroblast. Aldosterone

treatment of renal tubular epithelial cells increases calcium inflow and intracellular cyclic adenosine monophosphate levels. The results suggest that aldosterone plays a pivotal role in tubulointerstitial fibrosis by promoting tubular epithelial–mesenchymal transition and collagen synthesis in proximal tubular cells. The process is MR-dependent, and mediated by ERK1/2 mitogen-activated protein kinase pathway.[346]

Clinical trials have shown a potential role for MR blockers to further delay the development of end-stage renal disease by completing renin–angiotensin blockade. MR blockade produces a significant antiproteinuric effect and has minimal risk of causing hyperkalemia if the condition of the patient is closely monitored. As well as in the collecting ducts, mineralocorticoid receptors are distributed throughout the body, including the proximal tubule, thick ascending segment of the nephron, the heart, and the brain.[14,20,21,31] Aldosterone is thought to mediate fibrosis by activating factors such as reactive oxygen species; TGF-β; and increasing collagen synthesis, the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and plasminogen activating factor I (PAI-1).[7,20,22,23] The fibrotic effect of aldosterone is often enhanced by high dietary salt intake.[24] Fibrosis and kidney damage induced in uninephrectomized rats placed on a high-salt diet and treated with angiotensin II were reduced by treatment with spironolactone and an aldosterone synthase inhibitor, FAD286.[32,322]

Quan et al. studied chronic kidney disease in rats subjected to subtotal nephrectomy.[37] Rats with intact adrenal glands were found to have increased proteinuria, renal histopathologic changes, and decreased inulin clearance when compared with rats subjected to adrenalectomy. Furthermore, the difference in the severity of kidney disease between rats that had undergone adrenalectomy and those that had not was not abolished with corticosteroid administration, which suggested that some other factor from the adrenal gland was responsible for the renal defects.[322]

Experiments conducted on saline drinking, stroke prone, spontaneously hypertensive (SHRSP) rats have shown that inhibition of mineralocorticoid receptor activation may delay renal disease. Spironolactone, a mineralocorticoid receptor blocker, implanted into SHRSP rats results in a reduction in proteinuria. The expression of TGF-β, NADPH oxidase, and collagen I/IV was increased in the untreated diabetic rats, but was reduced in spironolactone-treated rats. Aldosterone was found to increase collagen expression in rat renal fibroblasts, which may contribute to fibrosis.[20] Studies of humans have also shown that the deleterious effects of aldosterone are enhanced by high dietary salt intake, which is typical of the Western diet. A study involving 2,700 participants in the Framingham Offspring Study has shown that greater excretion of urinary sodium (a marker for dietary salt intake) correlates strongly with elevated urinary albuminuria and weakly (albeit nonlinearly) with serum aldosterone levels.[52] In a subsequent study conducted on patients with resistant hypertension despite the use of three antihypertensive medications, elevated dietary salt intake correlated with higher levels of proteinuria in patients with elevated urinary aldosterone levels.[53] This suggests that aldosterone may work in concert with dietary salt to accelerate kidney injury.[322] Studies designed to delineate the factors responsible for the renal injury associated with aldosterone have also been performed in humans. Sato and Saruta measured the urinary excretion of collagen type IV (a turnover product of fibrosis) by patients with diabetes and found that those on spironolactone showed a significant decrease in urinary collagen excretion, which suggests that collagen may be one factor associated with aldosterone-mediated fibrosis.[57] Because aldosterone is a major regulator of sodium and volume balance, it could also, theoretically, mediate its negative effects by increasing blood pressure.[322]

Glucocorticoid Actions in the Kidney

Glucocorticoids appear to be important for the normal maintenance of GFR.[347] In both adrenalectomized animals and in humans with adrenal insufficiency, GFR is reduced compared to controls. Adrenalectomized rats given physiologic doses of glucocorticoids regain a normal GFR.[348] Furthermore, short-term administration of pharmacologic doses of glucocorticoids has been reported to increase inulin clearance in both normal animals and humans.[349,350] Micropuncture studies in normal rats indicate that glucocorticoids enhance GFR by increasing glomerular plasma flow.[347,351] The latter results from selective vasodilation of both afferent and efferent renal arterioles.[351] The mechanisms by which glucocorticoids alter the glomerular microcirculation remain obscure. Because amino acid infusion causes similar glomerular hemodynamic changes, Baylis and colleagues suggest that glucocorticoids may increase GFR through their effects on catabolism of proteins to free amino acids.[347]

Glucocorticoid actions on the proximal tubule include enhancement of gluconeogenesis, ammoniagenesis, and Na reabsorption.[352] Lag in ammonium excretion resulting in acid retention is well described in subjects in a glucocorticoid-depleted state.[353] In adrenalectomized animals, glucocorticoid replacement restores proximal tubule ammoniagenesis and the ability of the kidney to respond to the chronic phase of acidosis.[354] Furthermore, in whole animals, glucocorticoid excess accelerates renal base generation, resulting in metabolic alkalosis.[355] Glucocorticoids regulate ammoniagenesis possibly through altering glutamine uptake and metabolism by proximal tubule cells.[355] Glucocorticoids increase proximal tubule Na reabsorption by at least two mechanisms: enhanced Na–K-ATPase activity and Na–H exchange.[356,357] Several experiments suggest that glucocorticoids inhibit Na-dependent phosphate and sulfate reabsorption in the proximal tubule.[352] These observations are supported by clinical reports of phosphaturia and lower serum phosphate levels in patients with Cushing disease and subjects given high doses of glucocorticoids.[358]

Both patients with Addison disease and adrenalectomized animals have decreased urinary concentrating ability,[359] due in part to reduction in RBF, GFR, and hydroosmotic

permeability of the collecting tubule.[360] In addition, adrenal corticosteroids contribute to urinary concentration by stimulating Na, K, and HCO_3 transport in the thick ascending limb of Henle's loop.[361] It is not entirely clear whether glucocorticoids, mineralocorticoids, or both mediate the effects of corticosteroids on renal-concentrating mechanisms.

Systemic excess of glucocorticoids is known to cause hypertension. The effect of glucocorticoids may be in part mediated by the suppression of endothelial nitric oxide synthase (eNOS).[2] Acute administration of glucocorticoids, however, may have beneficial effects on the cardiovascular system in part through nontranscriptional activation of eNOS.[308]

CATECHOLAMINES

Structure and Biosynthesis of Catecholamines

Norepinephrine (noradrenaline), epinephrine (adrenaline), and dopamine are collectively called catecholamines. These endogenous amines are derived from the amino acid tyrosine and the enzymes involved in their biosynthesis have been identified, cloned, and characterized[362] and include: tyrosine hydroxylase, dopa decarboxylase, dopamine β-hydroxylase, and phenylethanolamine-N-methyltransferase. The first step in catecholamine synthesis involves the hydroxylation of tyrosine by tyrosine hydroxylase, which is regarded as a rate-limiting step. This enzyme is activated by stimulation of sympathetic nerves or the adrenal medulla and is subject to feedback inhibition by catechol compounds. Catecholamines are synthesized in nerve terminals of the postsynaptic neurons of the sympathetic nervous system and in the adrenal medulla. Most of the steps occur in the cytoplasm whereas some take place in storage vesicles.[363] Storage of catecholamines in vesicles ensures their regulated release, protects them from enzymatic degradation, and prevents their leakage outside the cell. Termination of action of norepinephrine and epinephrine includes reuptake by nerve terminals, reuptake by nonneuronal cells, and metabolic transformation. Major enzymes involved in catecholamine metabolism include monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT). The main source of epinephrine in the body derives from the adrenal medulla whereas noepinephrine originates mostly from nerve terminals.[363] At the renal level, catecholamines derive from renal efferent nerves (norepinephrine and, to a lesser extent, dopamine), from the circulation (epinephrine and norepinephrine), from the adrenal medulla (epinephrine), and from renal proximal tubule cells (dopamine) via α_1, α_2, β_1, and β_2 receptors for epinephrine and norepinephrine and D_1- and D_2-like receptors for dopamine.[364–367]

Physiology of Catecholamine Action in the Kidney

Catecholamines play an important role in the regulation of RBF, GFR, renin secretion, and tubular transport. Their effects depend on site of action and receptor type. The kidney is one of the major long-term regulators of blood pressure (BP). This is achieved by the interplay of several hormonal, neural, and humoral factors that would regulate principally two parameters: sodium homeostasis and peripheral vascular resistance.[368] In the following section, we discuss the renal functions of catecholamines separately on their receptors.

Alpha-adrenergic Stimulation in the Kidney

Both α_1- and α_2-adrenergic receptors have been localized to vascular smooth muscle and tubule cells of the nephron. Norepinephrine is the major agonist at these levels and adrenergic stimulation causes renal arteriolar vasoconstriction (increased afferent and efferent arteriolar resistance) by activating mainly α_1 receptors on vascular smooth muscle cells.[369] This α_1-mediated renal vasoconstriction results in decreased RBF and GFR. Recent evidence suggested that norepinephrine increases afferent arteriolar sensitivity to angiotensin II through activation of α receptors and secondary increase in calcium sensitivity of mouse afferent arteriole.[370]

In the proximal convoluted tubule, where α_1- and α_2-adrenergic receptors are expressed in high density, norepinephrine increases Na and water reabsorption, in part, by stimulation of Na^+-K^+-ATPase activity.[371–373] This activity is partially dependent on the cosecretion of neuropeptide Y that acts to synergize the stimulatory α-adrenergic effects of norepinephrine and to antagonize the inhibitory β-adrenergic effects. This is demonstrated by the fact that norepinephrine alone does not affect Na^+-K^+-ATPase activity in the proximal convoluted tubule unless neuropeptide Y or other β-adrenergic inhibitors are present.[374] In isolated rat and rabbit proximal convoluted tubule cells, α_1 and α_2 agonists stimulate Na^+–H^+ exchange, the overall effect of which is enhanced Na^+ and fluid absorption.[375,376]

In the loop of Henle, experimental evidence showed that α-adrenergic stimulation increases sodium and water reabsorption at the thick ascending limb level through α_1- and α_2-mediated activation.[377,378] In the collecting duct, Krothapalli and Suki[379] report that α_2 agonists inhibit vasopressin-stimulated water reabsorption by inhibiting adenylate cyclase activity.[379] Other investigators, however, challenge this observation.[380]

Beta-adrenergic Stimulation in the Kidney

β-adrenergic receptors have been identified in the glomerulus, juxtaglomerular apparatus, thick ascending limb of loop of Henle, distal convoluted tubule, and collecting duct.[380,381] β_1 stimulation enhances renin release from the juxtaglomerular cells of the afferent arterioles. Otherwise, there are few β receptors in renal vessels. Although β receptors have not been localized to the proximal tubule, physiologic studies suggest that β-adrenergic stimulation increases Na^+ and fluid transport in this nephron segment independently of enhanced renin secretion and angiotensin II production.[380] In the thick ascending limb, β-adrenergic receptor activation stimulates cAMP production and NaCl reabsorption.[380] β agonists also

increase Cl^-–HCO_3^- exchange and H^+-K^+-ATPase activity in the collecting duct.[371] The latter effect results in enhanced K^+ reabsorption by type A intercalated cells (and an apparent decrease in K^+ secretion).[371] A potential mechanism of action involves β-adrenergic stimulation of cAMP production and subsequent conversion to adenosine.[381]

Dopamine and the Kidney

Dopamine is the immediate metabolic precursor of norepinephrine and epinephrine. Locally, dopamine is synthesized by proximal tubule cells via enzymatic decarboxylation of L-dopa by aromatic amino acid decarboxylase (AADC). L-dopa reaches the tubule cell after filtration and Na^+-coupled reabsorption because renal proximal tubule cells lack tyrosine hydroxylase. The contribution of presynthesized and stored dopamine to local renal physiology is not yet clearly established.[368,382] High salt intake increases AADC activity and dopamine synthesis in proximal tubule possibly by enhancing Na^+-coupled uptake of L-dopa.[383,384] Regulation of intrarenal dopamine concentrations can occur at several levels: synthesis, storage, or degradation. Dopamine is a substrate for both MAO and COMT. Synthesis and metabolism of dopamine differs between neural and nonneural cells. Dopamine synthesized in the proximal tubule does not undergo further metabolism to norepinephrine and epinephrine because of the lack of dopamine β-hydroxylase[385]; instead, it diffuses to peritubular space and tubular lumen where it acts locally on its receptors.

Dopamine receptors are members of the G protein-coupled superfamily of heptahelical receptors. At least five receptors have been identified, subclassified into D_1- and D_2-like subfamilies based on their molecular structure and pharmacology. Both of the cloned members of the D_1-like receptor group (D_1 and D_5, also known as D_{1A} and D_{1B} in rodents) are coupled with the stimulating G protein, $G_s\alpha$, and stimulate adenylyl cyclase. All three of the cloned D_2-like receptors (D_2, D_3, and D_4) are associated with the inhibitory G protein, G_i/G_0, and inhibit adenylyl cyclase. Both families of receptors are expressed in the kidney. D_1 and probably D_5 are localized in the smooth muscle layer of renal arterioles, juxtaglomerular cells, proximal tubules, and cortical collecting duct. The D_3 receptor is present in arterioles, glomeruli, proximal tubules, MTAL of loop of Henle, and the collecting duct. The D_4 receptor is localized in the cortical collecting duct.[386,387]

Locally produced dopamine plays a central role in the regulation of sodium excretion. Circulating dopamine concentrations are in the picomolar range, hence not sufficiently high to activate dopamine receptors. The major signaling mechanism by which dopamine induces natriuresis is by inhibiting Na^+-K^+-ATPase in all the segments of the nephron via D_1-like receptors, whereas D_2-like receptors stimulate this enzyme. The end result of Na^+-K^+-ATPase inhibition is a dopamine-induced natriuresis. Several investigators suggest that the role of dopamine is to counterbalance the effects of antinatriuretic factors in the kidney.[383] Interestingly, Kuchel and Kuchel[388] point out that dopamine is the predominant catecholamine in fish, in which salt excretion is a priority. On the other hand, norepinephrine predominates in terrestrial animals, in which salt retention is essential for survival. In addition to inhibition of Na^+-K^+-ATPase activity, other studies suggest that dopamine suppresses Na^+–phosphate cotransporter, antagonizes the stimulatory effect of Ang II on Na^+–H^+ exchange in cortical brush-border membranes mediated by cAMP and PKA,[389,390] and stimulates renin synthesis in cultured rat juxtaglomerular cells.[391] Studies in humans have shown that dopamine does not induce natriuresis in Na^+-depleted subjects and that its natriuretic effect is more pronounced during conditions of volume expansion.[368,392] This demonstrates again that the natriuretic and diuretic effects of D_1-like receptors are dependent on sodium balance.

In the whole kidney, dopamine increases RBF and GFR through its D_1 receptor-mediated vasodilatory effects.[383,392] Supraphysiologic concentrations of dopamine, however, stimulate α-adrenergic receptors, which lead to vasoconstriction and decreased RBF. The natriuretic and vasodilating effects of dopamine have suggested a therapeutic role in patients with volume expansion, particularly when administered in low doses that do not activate adrenergic receptors. However, several studies have shown that dopamine has no major role as a therapeutic strategy in the prevention of further renal damage in acute kidney injury.[393,394] Moreover, dysfunction of the renal dopamine system has been postulated to contribute to the pathogenesis of systemic hypertension.[368,383] Results from at least two studies suggest that defects in renal generation of dopamine are common in patients with essential hypertension.[395,396]

The ability of the D_1 receptor to induce both natriuresis and vasodilation makes D_1 agonists, such as fenoldopam, potential therapeutic agents for the treatment of both hypertensive urgencies and acute renal failure. In healthy normotensive volunteers, fenoldopam has been shown to significantly increase renal plasma flow while only minimally reducing systemic blood pressure.[397] In people with hypertensive urgencies, fenoldopam has been shown to reduce systemic blood pressure by 23% while increasing natriuresis by 200%, diuresis by 46%, and renal blood flow by 42%.[398] Although the selective increase in renal plasma flow could be advantageous in the treatment of certain forms of acute renal failure, further studies must be done to define the specific utility of fenoldopam in this setting.

THE RENAL KALLIKREIN-KININ SYSTEM

In 1909, Abelous and Bardier reported for the first time the hypotensive effect of human urine when injected into the bloodstream of dogs.[399] Further studies by Werle and colleagues from 1926 to 1939 attributed these effects to the kallikrein-kinin system (KKS) and described its basic components: kallikreins, kinins, kininogens, and kininases. The

major actions of this system are mediated by bradykinin, a peptide hormone that exerts potent proinflammatory and vasodilatory effects. Interestingly, all components of the KKS are also expressed in the kidney, especially in the distal convoluted and connecting tubule as well as in the collecting duct, and have been shown to regulate renal hemodynamic and tubular function. In addition, in the last few years, studies have linked the KKS to different pathologic states including the diabetic nephropathy as reviewed here.

Structure and Synthesis of Kinins

The KKS is a complex multienzyme system that can be divided into two types: (1) a circulating KKS that belongs to the coagulation system and (2) a tissue KKS that acts in a paracrine or autocrine fashion. The KKS leads to the production of kinins, namely bradykinin and lys-bradykinin (kallidin), from kininogens through the action of kininogenase, namely kallikrein (Fig. 8.5).[399] Two types of kallikreins have been identified—a plasma and a tissue kallikrein—both of which are serine proteases that are encoded by different genes and differ in their distribution and regulation.[399] Mice lacking tissue kallikrein show dramatically reduced levels of renal kinin, suggesting that tissue kallikrein is the main system involved in the kidney,[400] although little is known regarding the putative role of plasma kallikrein under pathologic conditions. Renal tissue kallikrein is synthesized in large amounts by connecting tubule cells and is mainly secreted into the urinary fluid and to a lesser extent to the peritubular interstitium.[399]

In humans, two types of kininogens have so far been described: a high molecular weight (HK) form present in blood and a low molecular weight (LK) form present in various tissues. It is generally accepted that tissue kallikrein prefers LK but is capable of cleaving HK, whereas plasma kallikrein cleaves HK exclusively.[399] Kininogens are synthesized in the liver and circulate in blood plasma at concentrations of 45 to 120 μg per mL for LK and of 65 to 115 μg per mL for HK, but are also found in other body fluids and organs such as kidney.[401]

Novel functions of kininogens have been recently discovered. Derivatives of HK have been shown to be involved in the regulation of endothelial cell proliferation, angiogenesis, and apoptosis.[402] In addition, some seem to possess potent and broad-spectrum microbicidal properties against both gram-positive and gram-negative bacteria, and thus may represent an alternative to conventional antibiotic therapy.[402]

Physiology of Kallikrein-Kinin System in the Kidneys

Tissue kallikrein is secreted by many cells throughout the body but some tissues produce particularly large quantities such as the kidney, lung, intestine, brain, and glandular tissues (salivary and sweat glands and pancreatic exocrine gland). This enzyme is activated intracellularly from a precursor, prokallikrein, to produce tissue kallikrein.[403] The enzyme responsible for this conversion has not yet been identified.

Regulatory mechanisms of tissue kallikrein remain partly unknown. Aprotinin, a polypeptide purified from the lung, and kallistatin have been shown to inhibit the activity of renal and other tissue kallikreins.[404] In addition, it has been shown that salt restriction stimulates the synthesis of renal kallikrein through an unclear mechanism, possibly implicating aldosterone.[405] Interestingly, it was also recently shown that potassium intake triggers an increase in renal kallikrein secretion through an aldosterone-independent mechanism

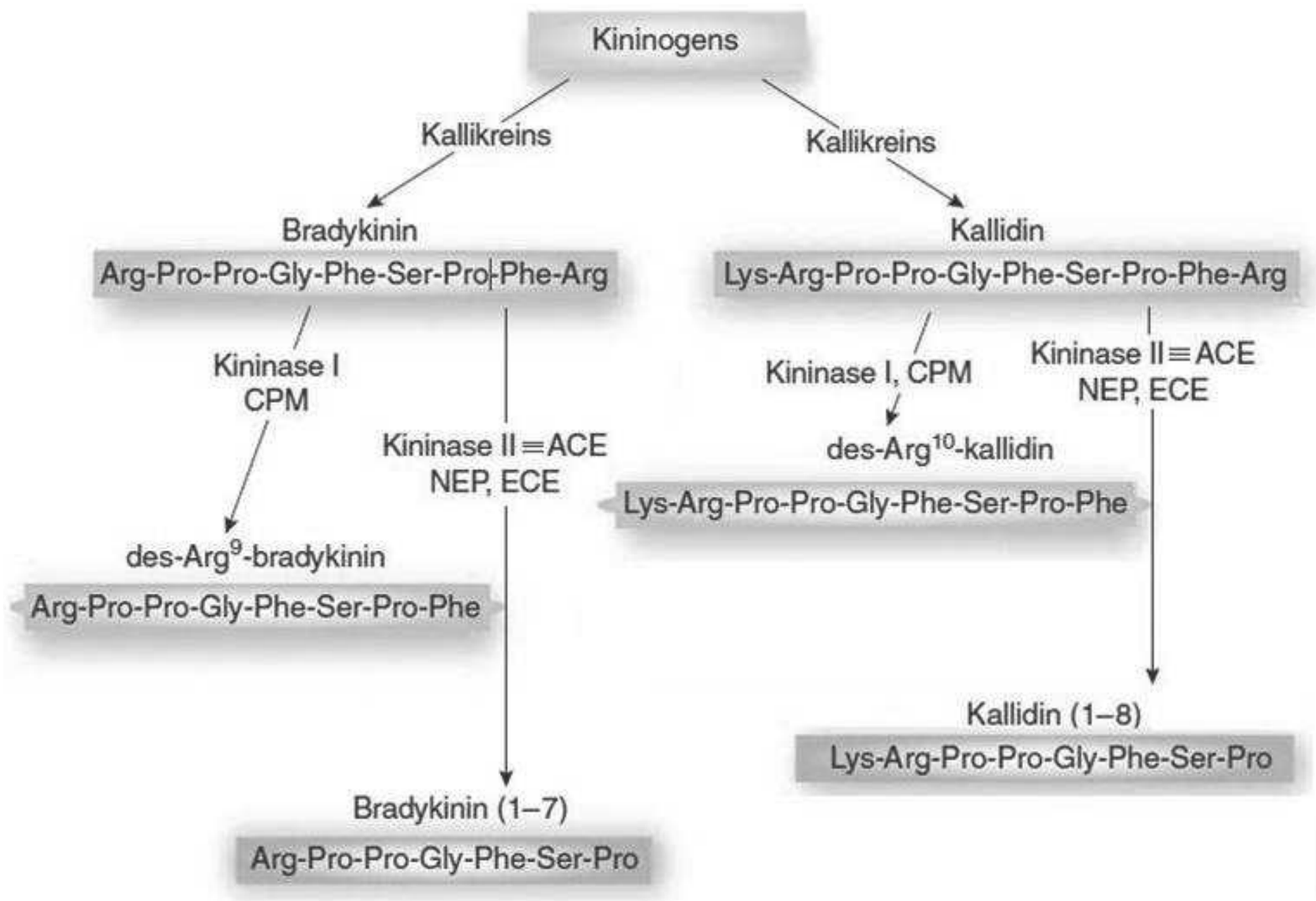

FIGURE 8.5 Biosynthesis and metabolism of kinins. *CPM*, carboxypeptidase-M; *ACE*, angiotensin I-converting enzyme; *NEP*, neprilysin (endopeptidase 24.11); *ECE*, endothelin-converting enzyme; *red*, active peptides; *blue*, inactive peptides. (Adapted from Kakoki M, Smithies O. The kallikrein-kinin system in health and in diseases of the kidney. *Kidney Int.* 2009;75(10):1019–1030.) (See Color Plate.)

involving membrane depolarization of kallikrein-secreting cells in the renal connecting tubules, followed by enhanced calcium influx.[406,407] In addition to dietary sodium and potassium intake, hereditary factors may determine tissue kallikrein activity. In fact, a loss of function polymorphism in the human tissue kallikrein gene (R53H) has been identified with a frequency of 0.03 in Caucasians.[408] Interestingly, these partially tissue kallikrein-deficient subjects develop a form of arterial dysfunction characterized by remodeling of the brachial artery, which is not adapted to a chronic increase in wall shear stress.[408]

Although of little relevance for the kidney, it is noteworthy that plasma kallikrein is regulated through a different, more complex, mechanism. Plasma kallikrein is synthesized and secreted by the liver as an inactive zymogen. It is activated by the intrinsic coagulation cascade whereby contact of plasma with negatively charged macromolecular surfaces initiates a proteolytic cascade that ultimately converts prekallikrein to plasma kallikrein.[409]

The half-life of bradykinin in plasma is short (~30 seconds), suggesting that its actions are regulated locally through its production and degradation within tissues. In fact, both bradykinin and kallidin can be metabolized through two pathways.[410] Kininase I (also called carboxypeptidase-N), as well as carboxypeptidase-M, remove the C-terminal arginine from the kinins to generate their des-Arg derivatives, which are agonists of B1R (see later). Kininase II (also known as ACE), neprilysin (endopeptidase 24.11), and endothelin-converting enzyme cleave off the two C-terminal amino acids (Phe and Arg) of the kinins, thereby inactivating them.[411,412] It is noteworthy that kallidin can be converted into bradykinin by a plasma aminopeptidase.

Kinins exert their biologic effects by acting on two types of G protein-coupled receptors called bradykinin B1 receptor (B1R) and B2 receptor (B2R) (Fig. 8.6). Although B2R is ubiquitous and expressed throughout the kidney, B1R is mainly expressed after induction by endotoxin, cytokines, ischemia, and other noxious stimuli.[411] Interestingly, treatment with an inflammatory signal (lipopolysaccharide) induces the expression of B1R mRNA in all renal segments except the outer medullary collecting ducts. B1R, once induced by inflammatory mediators and tissue damage, assumes some of the physiologic roles of B2Rs.[413] Bradykinin and kallidin are equipotent and both have higher affinity for B2R. Interestingly, metabolites (des-Arg9-BK [DABK] and Lys-DABK) of bradykinin and kallidin, which result from the action of carboxypeptidases, have higher affinity for B1R.

Both receptors activate similar intracellular signaling cascades involving phospholipase C activation and intracellular calcium mobilization. In addition, through calcium-dependent and -independent mechanisms, KKS increases NO and prostaglandin synthesis, both of which seem to mediate some of the effects of kinins.[410] Alternative mediators of kinins also include endothelium-derived hyperpolarizing factor (EDHF), norepinephrine, substance P, cytokines, and tissue plasminogen activator.[410]

Experimental evidence suggests that kinins regulate renal blood flow and renal excretion of sodium and water.[414,415] Studies on the role of the renal KKS, using congenitally kininogen-deficient Brown-Norway Katholiek rats and B2R knockout mice, amongst other models, revealed that this system starts to induce natriuresis and diuresis when sodium accumulates in the body as a result of excess sodium intake or aldosterone release, for example, by angiotensin II. Thus, it is hypothesized that the system works as a safety valve for sodium accumulation. In fact, mice lacking B2R and/or B1R develop salt-sensitive hypertension.[416] Interestingly, humans with essential hypertension have low levels of urinary

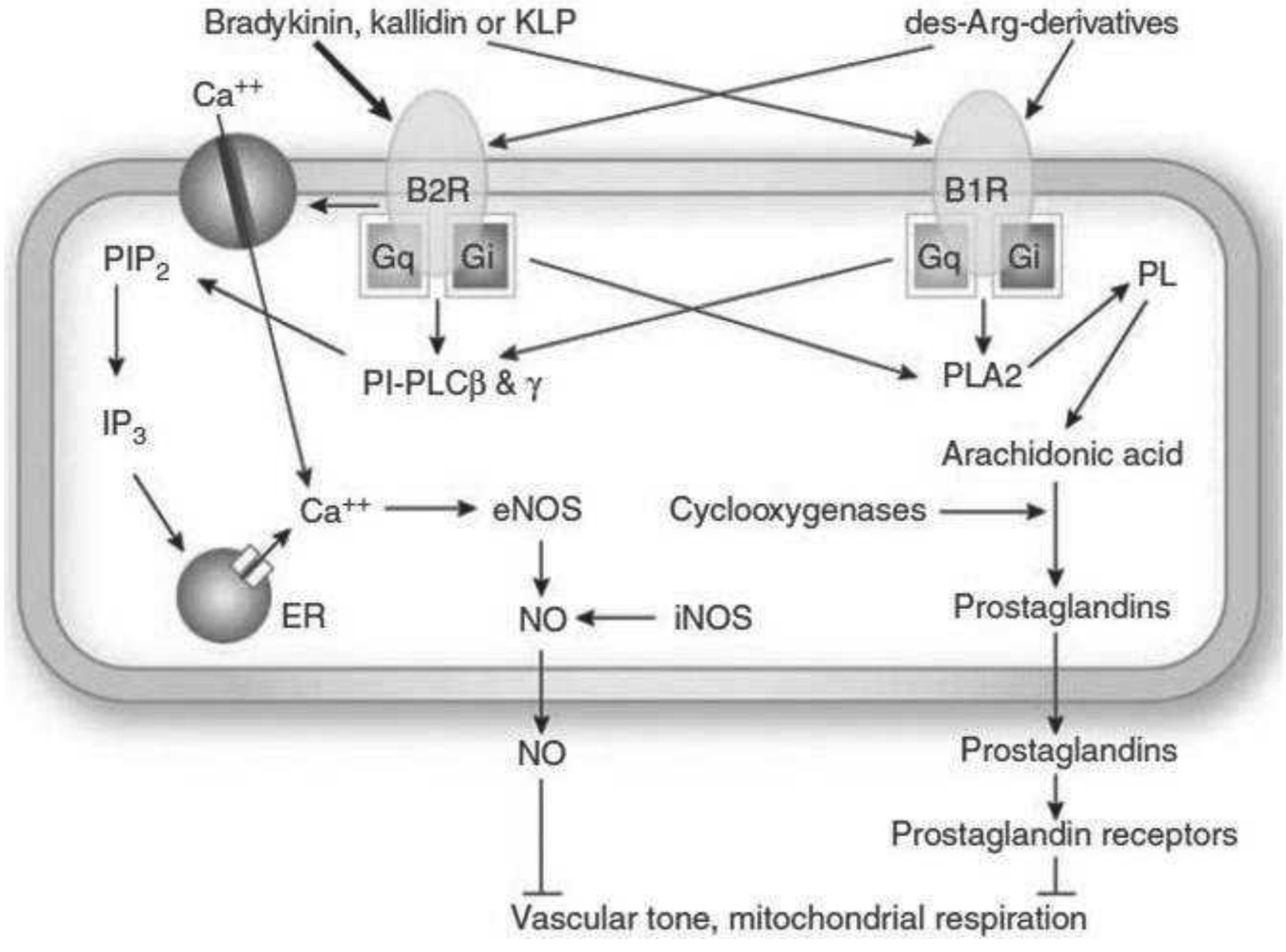

FIGURE 8.6 Bradykinin intracellular signaling cascade. The thickness of arrows arising from the kinins indicates the relative potency of each peptide to elevate intracellular calcium concentrations. *PIP_2*, phosphatidylinositol-4,5-bisphosphate; *PI-PLC*, phosphatidylinositol-specific phospholipase C; *IP_3*, 1,4,5-inositol triphosphate; *ER*, endoplasmic reticulum; *PL*, phospholipids; *PLA2*, phospholipase A2. (Reproduced from Kakoki M, Smithies O. The kallikrein-kinin system in health and in diseases of the kidney. *Kidney Int.* 2009;75(10):1019–1030.)

kallikrein.[405] Conversely, hypertensive mice and rats over-expressing the human kallikrein develop hypotension.[417] However, the renal KKS seems to be involved only in the long-term regulation of blood pressure under conditions of hypertensive insult such as high salt intake.[418] Evidence suggests that bradykinin promotes natriuresis, in part, by decreasing sodium reabsorption in the distal part of the renal nephron. Bradykinin has been shown to inhibit the amiloride-sensitive component of conductive sodium uptake in inner medullary collecting duct cells[419] and to cause a reversible inhibition of sodium reabsorption ex vivo in rat cortical collecting ducts.[420] Furthermore, inhibition of B2Rs in rats fed a normal salt diet decreases fractional sodium excretion with little effect on medullary and cortical perfusions or on GFR.[421] Recently, Zaika et al. confirmed that bradykinin inhibits ENaC in the aldosterone-sensitive distal nephron.[422] It is noteworthy that during volume expansion, a condition that requires further sodium reabsorption, at least one additional mechanism is activated: kinins mediate the increase in papillary blood flow, thereby indirectly inhibiting further tubular electrolyte reabsorption.[421]

The renal KKS is believed to operate in concert with the renin-angiotensin system to physiologically regulate the distribution of RBF and the excretion of water and electrolytes. It has been confirmed that the effects of kinins antagonize the effects of RAAS on blood pressure and sodium handling. In fact, reduced KKS activity may contribute to the establishment of a pathophysiologic state characterized by unopposed hyperactivity of the renin-angiotensin system, resulting in salt retention.[423] It has been shown that this reduced activity of the KKS predominates over renin-angiotensin system overactivity in all conditions of sodium balance in essential and family-related hypertension.[424] KKS and the renin-angiotensin system are functionally coupled at the level of ACE. Inhibition of this enzyme not only blocks angiotensin II production but also increases bradykinin production. It was shown that the beneficial effects of ACE inhibitors were mainly due to NO production following B2R activation.[425] Interestingly, chronic treatment with ACE inhibitors induces B1R expression in vasculature and in the kidney, which could mediate the renoprotective effects of ACE inhibition.[426]

Interestingly, the contribution of the KKS to renal handling of potassium has been recently addressed by Chambrey's group.[407] Usually, potassium is almost completely reabsorbed by the end of the loop of Henle and active secretion in the late distal nephron determines the fraction that needs to be excreted in the urine. Thus, except in a situation of potassium depletion, in which net potassium absorption also occurs in the collecting system, the latter is generally a site of net potassium secretion. It was recently shown that cortical collecting ducts isolated from mice with tissue kallikrein gene disruption do not secrete potassium but instead exhibit net transepithelial potassium absorption due to abnormal activation of H^+-K^+-ATPase.[407] This suggests that potassium absorption is constantly under the negative control of tissue kallikrein. However, the mechanism or signaling pathway by which tissue kallikrein controls H^+-K^+-ATPase remains to be determined.

In addition to sodium and potassium, the KKS seems to regulate the metabolism of calcium, through a B2R/B1R-independent mechanism. Picard et al. showed that knocking out tissue kallikrein in mice leads to hypercalciuria of renal origin.[427] In fact, the distribution of tissue kallikrein overlaps that of the epithelial calcium channel (TRPV5) in the distal nephron. Furthermore, kallikrein gene expression was increased by a low-calcium diet.[427] Interestingly, no such abnormalities were observed in B2R knockout mice with or without treatment with B1R antagonist. This suggests that the effect of kallikrein on calcium excretion is independent of kinin production.

Furthermore, products of the KKS may modulate cell growth. Experimental evidence suggests that while under certain conditions, in vitro bradykinin may inhibit growth of normal renal fibroblasts.[428,429] It can also stimulate the growth of fibroblasts, mesangial cells, and arterial smooth muscle cells in other conditions.[430] Over-expression in hypertensive Dahl salt-sensitive (DSS) rats of the human kallikrein gene by adenoviral delivery results in reversal of the changes associated with hypertensive nephrosclerosis.[430] Chao et al. further confirmed that kinin exerts its renoprotective effects against salt-induced renal injury in the DSS rat model by inhibiting cellular apoptosis, inflammatory cell recruitment, and fibrosis through suppression of oxidative stress, TGF-β expression, and MAPK activation, with no effect on blood pressure.[431] To a large degree, the benefits of kinins in that study were dependent on the elevated levels of renal NO.[431] NO has been shown to play an important role in protection against hypertension and glomerulosclerosis in DSS rats.[432] These renoprotective effects of NO may be attributed to a decrease in oxidative stress. In fact, NO can scavenge superoxide anions. It can also inhibit the assembly of a functional NADH/NADPH oxidase, thereby attenuating the production of superoxide.[433] In addition, given that oxidative stress can stimulate the expression of proinflammatory and profibrotic molecules, the increase in NO production triggered by kinins could not only decrease oxidative stress but consequently attenuate the inflammatory and fibrotic responses.[434] Tissue kallikrein has also been reported to attenuate salt-induced renal damage by activation of B2R.[435,436] The protective effect of the KKS against renal injury was also confirmed in B2R knockout mice.[437] In addition, a human B2R gene polymorphism has been demonstrated in patients with chronic renal failure, suggesting a role of this receptor in the early development of this pathology.[438]

Furthermore, as mentioned previously, bradykinin, through its receptors, increases prostaglandin production in at least three ways. First, it promotes translocation into the cell membrane and phosphorylation of cytosolic phospholipase A2 through a Ca^{2+}-dependent phosphorylation. Second, it activates membrane-associated phospholipase A2 through a Ca^{2+}-independent mechanism. Phospholipase A2 frees arachidonic acid from membrane phospholipids.

This arachidonic acid gets converted to prostaglandins by cyclooxygenase. The third mechanism by which bradykinin increases the production of prostaglandins is by inducing cyclooxygenase-2.[403,433] It has been shown that the prostaglandins formed following stimulation of the bradykinin receptors act through their specific receptors to mediate some of the effects of kinins on vascular tone and on mitochondrial respiration. Of potential relevance to the kidney, Kopp and Smith[439] demonstrated in a rat model of unilateral ureteral obstruction that indomethacin abolished BK-induced natriuresis and diuresis in the contralateral kidney.[439] Further studies are required to determine the role of bradykinin-induced prostaglandins in the healthy and diseased kidney, especially because renal diseases present with several characteristics including inadequate filtration of proteins and inflammatory cell recruitment.

Finally, recent evidence suggests that bradykinin participates in the regulation of neonatal glomerular function and acts as a growth regulator during renal development. An intact KKS is necessary for the normal functional development of the kidney.[440] During nephrogenesis, tubular and glomerular growth and differentiation, and acquisition of specialized functions, are coordinated in time and space with renal vasculogenesis, glomerulogenesis, and regional hemodynamic changes. The end result ensures that tubular structure and function are tightly coordinated with glomerular filtration during normal kidney development. To achieve this delicate task of glomerulotubular balance, the developing kidney produces growth factors and vasoactive hormones that act in a paracrine manner to regulate nephrovascular growth, differentiation, and physiologic functions. One such paracrine system is the KKS, which generates bradykinin. Bradykinin activates B2R to regulate RBF and salt and water excretion. Gene-targeting studies indicate that the fetal KKS plays an important role in the maintenance of terminal epithelial cell differentiation.[441] In fact, gestational salt loading induces abnormal renal development in B2R knockout mice.[442] It was also recently shown that B1R is unlikely to play a role in early nephrogenesis but its enrichment in the maturing proximal tubule suggests a potential role for this receptor in terminal differentiation of the proximal nephron.[443]

Clinical Pathophysiologic Role of the Kallikrein-Kinin System in the Kidneys

Diabetic nephropathy occurs in ~30% of all patients with diabetes. ACE inhibition is protective in many models of diabetic nephropathy, a protection partly mediated by the KKS. In fact, it has been shown in different diabetic models that the beneficial effects of ACE inhibitors were attenuated by a B2R antagonist.[444–447] The same findings were observed in diabetic mice lacking B2R.[448,449] Albuminuria, glomerular sclerosis, interstitial fibrosis, lipofuscin accumulation in proximal tubules, and lifespan shortening were enhanced in this model. Corroborating these findings, human tissue kallikrein gene delivery efficiently attenuated insulin resistance and prevented diabetic nephropathy in streptozotocin-induced diabetic rats.[450] Once again, NO seems to be mediating this renoprotective role. In fact, L-arginine, a substrate of NO synthase (NOS), reduces proteinuria associated with streptozotocin-induced diabetes.[451] Conversely, an NOS inhibitor as well as an endothelial NOS (eNOS) deficiency accelerates the severity of diabetic nephropathy.[452–455] Interestingly, cicaprost, a prostacyclin analog, also delays the pathogenesis of the diabetic nephropathy, suggesting that prostaglandins in addition to NO mediate the beneficial effects of the KKS.[456] It is noteworthy that some groups have reported that deletion of B2R protects against the streptozotocin-induced diabetic nephropathy.[457] In addition, it has been shown that glomerular kinin receptors are induced by diabetes and this may contribute to the development of glomerular injury and to the development of microvascular complications of diabetes.[458] Bradykinin also regulates the expression of connective tissue growth factor (CTGF), TGF-β receptor II, and collagen I in mesangial cells, which provides a mechanistic pathway through which B2R activation contributes to the development of diabetic nephropathy.[459] In addition, Christopher et al.[460] demonstrated that glucose by itself regulates the expression of B2R in vascular smooth muscle cells. These contradictory results may be attributed to the differences between strains of mice and/or the methods of induction of diabetes.

Furthermore, immune-mediated nephritis plays a major role in the pathogenesis of systemic lupus erythematosus (SLE) and Goodpasture syndrome, which is the experimental model of glomerulonephritis caused by antibodies against glomerular basement membrane (anti-GBM). Liu et al. recently showed that mouse strains with upregulated expression of renal and urinary kallikreins are less susceptible to anti-GBM antibody-induced nephritis and lupus nephritis.[461] In addition, administration of kallikreins decreased the anti-GBM antibody-induced nephritis, demonstrating a link between KKS and immune-mediated renal damage.[461] These findings corroborate the aforementioned results that attribute a renoprotective role for KKS in nephritis following insults such as salt imbalance and diabetes.

The KKS has also been shown to protect against aminoglycoside-induced renal injury. Aminoglycoside antibiotics have been used to treat infections by aerobic gram-negative bacteria. However, they cause ototoxicity and nephrotoxicity. Interestingly, administration of tissue kallikrein is protective against gentamicin-induced renal injury in rats partly by inhibiting the inflammatory response and apoptosis through suppressing of oxidative stress.[462] In addition, L-arginine also prevents gentamicin-induced tubular damage in rats, whereas a NOS inhibitor aggravates the renal failure.[463] Similarly to the diabetic nephropathy, endogenous prostacyclin production also prevented the apoptosis and oxidative stress induced by gentamicin.[464] Thus, the renoprotective effects of tissue kallikrein against gentamicin toxicity seems to be once more mediated by NO and prostacyclin.

Furthermore, KKS seems to play a protective role in ischemic acute renal failure (IARF). As previously discussed,

NO production induced by B2Rs is an important player in the protective effects of ACE inhibitors.[425] In addition, ARBs seem to be less protective than ACE inhibitors against ischemia-reperfusion injury,[465] suggesting that ACE inhibitors may partly mediate their beneficial effects by inhibiting the inactivation of the kinins than by suppressing angiotensin II formation. In addition, studies have reported that deleting B1R and/or B2R aggravates renal damage following IARF; however, the double knockout had more detrimental effects than a deficiency in B2R only, emphasizing that both B1R and B2R are necessary for protection in IARF.[466] In addition to NO, older studies have shown that prostaglandins E1, E2, and I2 are also protective mediators of the KKS in IARF.[467] Contrary to these findings, results from exogenously administered bradykinin on IARF are conflicting and suggest that it aggravates IARF, although suppression of the endogenous KKS is also detrimental.[468] Thus, it seems that the physiologic levels of bradykinin produced endogenously are important for the functional recovery after IARF, but the higher levels achieved with exogenously administered bradykinin are detrimental.

In support of the aforementioned results in animal models, genetic studies in humans revealed that polymorphisms in several KKS-related genes are associated with higher incidence of renal problems. In fact, ACE polymorphism seems to influence diabetic nephropathy[469] and a polymorphism in the human B2R gene has been correlated with a higher susceptibility for nephropathy in diabetic patients.[470] Both human SLE and spontaneous lupus nephritis were also recently found to be associated with polymorphism in the kallikrein gene family, particularly KLK1 and KLK3.[471] Other studies have shown that the ACE D/D genotype is a risk factor for progression to chronic renal failure in patients with IgA nephropathy.[472,473] In addition, this ACE D/D genotype is also a risk factor for patients with autosomal dominant polycystic kidney disease (ADPKD) to develop ESRD at an earlier age.[474] In fact, polymorphisms in most of the genes in the KKS have been associated with the progression of chronic renal failure to ESRD, including ACE,[475] B1R and B2R,[476] and eNO.[477]

ADENOSINE

Adenosine, a purine nucleoside, is a paracrine hormone that regulates cellular and physiologic functions in many tissues. Three major pathways produce adenosine: the intracellular pathway, the extracellular ATP pathway, and the transmethylation pathway. Intracellular generation of adenosine results from the action of 5′-nucleotidase on adenosine monophosphate (AMP) during hypoxia (sequential dephosphorylation of intracellular ATP to adenosine). In cells that rapidly consume ATP, enhanced utilization of ATP increases the intracellular production rate of adenosine. In the kidney there are two prime examples of the intracellular ATP pathway. Increased delivery of Na^+ to the thick ascending limb of loop of Henle stimulates Na^+-K^+-ATPase activity in the basolateral membrane of epithelial cells through the increased flux of Na^+ across the luminal membrane. Oxygen availability in the renal medulla is marginally adequate; consequently, increased Na^+-K^+-ATPase activity may deplete ATP levels and lead to dephosphorylation of adenine nucleotides to form adenosine. Reactive ischemia is a second example of the intracellular ATP pathway in the kidney. A short period of ischemia in the kidney triggers a brief increase in renal vascular resistance, a phenomenon known as reactive ischemia. Renal ischemia activates the intracellular ATP pathway of adenosine production and adenosine causes reactive ischemia via activation of A_1 receptors in the preglomerular microvessels.[478] Adenosine, produced intracellularly, can traverse cell membranes by facilitated diffusion and function in a paracrine or autocrine fashion.

The extracellular ATP pathway is yet another mechanism of adenosine production in the kidney. Extracellular production of adenosine from AMP is possible because of the presence of ecto-5′-nucleotidase on the surface of many cell types. Release of adenine nucleotides into the extracellular compartment from renal sympathetic nerve terminals, intrarenal platelets, renal endothelial cells, renal vascular smooth muscle cells, and/or renal epithelial cells exposes extracellular ATP to ecto-ATPases, ecto-ADPases, and ecto-5′-nucleotidases, and these enzymes metabolize adenine nucleotides to adenosine.[478] In the kidney, ecto-5′-nucleotidase activity is expressed on tubular luminal membranes, fibroblasts, and mesangial cells and is believed to be the major source of renal adenosine.[479]

When oxygen supply is adequate, enzymatic hydrolysis of S-adenosyl homocysteine (SAH) to L-homocysteine and adenosine constitutes the major production pathway. It is the transmethylation pathway of adenosine production. Approximately one-third of the adenosine release to the extracellular space by cardiomyocytes is through the transmethylation pathway, but the importance of this pathway in the kidney is unclear.[478]

Adenosine Receptors

Purinoceptors or adenosine receptors, also called P_1 receptors, are classic G protein-coupled receptors with four known subtypes (A_1, A_2A, A_2B, and A_3 receptors).[478,480] A_1 receptors (A1Rs) have a high affinity for adenosine, whereas the affinity of A_2A receptors for adenosine is approximately threefold less compared with that of A1R. A_2B and A_3 receptors are low-affinity adenosine receptors.[478,480–482]

A1Rs are present in afferent arterioles, glomeruli including mesangial cells, juxtaglomerular cells, vasa recta, as well as in various segments of the tubular and collecting duct system including proximal tubule, thin limbs of Henle, TAL, and collecting ducts.[483] They evoke vasoconstriction by inhibiting adenylate cyclase activity (via activation of G_i and G_o), thereby reducing cAMP generation in vascular smooth muscle and signaling.[478] In renal epithelial cells and isolated rabbit afferent arterioles, A1R activation also appears to stimulate phospholipase C activity. A_2A and A_2B receptors produce vasodilation by stimulating adenylate cyclase

activity to increase cAMP generation; A_2A signal by engaging G_s, G_{olf}, and p21ras and A_2B receptors are also known to stimulate phospholipase C via G_q. A_3 receptors are thought to exert their physiologic effects through activation of calcium signaling pathways (phospholipase via G_q families) and perhaps inhibition of cAMP accumulation (via G_i), but their role in regulating the renal microvascular and epithelial function has not been extensively examined.[478,480]

P_2 receptors were originally described as purinergic receptors, reflecting the idea that they responded to ATP released as a neurotransmitter from peripheral sympathetic nerves. Currently P_2 receptors are divided into two distinct families: P_2X and P_2Y.[480]

Distinct genes code for each receptor family and there are marked differences in the structural and signal-transduction characteristics between the two families.

Renal Actions of Adenosine

Adenosine regulates a wide array of physiologic functions, including cardiac rate and contractility, vascular smooth muscle tone, neurotransmitter release, lipolysis, leukocyte function, platelet function, and renal hemodynamics and electrolyte transport.[481,484,485]

Adenosine is produced in the kidney and acts in an autocrine or paracrine fashion.[479,481] Both high-affinity A1R and low-affinity A2R are widely distributed throughout the renal vasculature and the nephron.[481,486] The renal effects of adenosine are diverse and include alterations in RBF, GFR, hormone production, neurotransmitter release, and tubular absorption (Table 8.4).

8.4 Renal Actions of Adenosine

Function	Effect	Receptor
Renal blood flow	Transient ↑ Delayed slight ↑	A_1 A_2
GFR	↓↓	A_1 and A_2
Renin production	↓↓ ↑	A_1 A_2
Erythropoietin production	↓ ↑	A_1 A_2
Sodium excretion	↑↑ ↓	A_2 A_1
GMC production and proliferation	↓	A_2B

↓, decrease; ↑, increase; GFR, glomerular filtration rate; GMC, glomerular mesangial cells.

Effect on Renal Blood Flow and Glomerular Filtration Rate

Infusion of adenosine into animals' renal artery results in transient reduction of RBF secondary to A1R mediated afferent arteriolar vasoconstriction, followed by a delayed A2R mediated postglomerular vasodilation and return of RBF to normal.[487–489] Selective A2R agonists increase RBF via vasodilation of the medullary renal microcirculation. A1R importantly regulate renal function. Infusion of A1R agonists into the renal interstitium diminishes blood flow to both superficial and deep nephrons. In the outer cortex, A1R-induced vasoconstriction is most likely caused by contraction of preglomerular, rather than postglomerular, microvessels; however, in juxtaglomerular nephrons, A1R mediate vasoconstriction by contracting preglomerular microvessels, efferent arterioles, and outer medullary descending vasa recta. Ang II strongly enhances A1R-induced preglomerular vasoconstriction. Contraction of preglomerular microvascular smooth muscle cells by A1R underlies the mediator role of adenosine in tubuloglomerular feedback (TGF) (Fig. 8.7), explains the ability of adenosine to decrease GFR, and potentiates postjunctional vasoconstrictor responses to renal sympathetic neurotransmission in the kidney.[478] It is conceivable that A1R are present in endothelial cells along the renal vasculature and that adenosine causes the release of NO and perhaps other endothelial vasodilators when administered from the vascular, but not from the interstitial, aspect of the vessel. The resulting A1R-induced constriction would, therefore, be blunted by endothelial factors only when adenosine is given intravascularly. In a study in dogs, the administration of NOS inhibitors caused a marked augmentation in the constrictor response of RBF to bolus injections of adenosine, whereas the dilator effect of the A_2 agonist CGS-21680 was unaffected, indicating that adenosine may cause NOS activation through an A1R-mediated mechanism. It is now well recognized that the majority of vasodilator agents act by binding to their receptors on endothelial cells and by eliciting the generation and release of endothelial relaxing factors, most notably NO, endothelial hyperpolarizing factor, and prostaglandins. However, in a number of studies, adenosine appears to augment NOS activity and NO release through an A2R-mediated process, an action that would enhance the dilator component rather than diminish the constrictor component of the adenosine actions. Also adenosine has been shown to consistently stimulate the production of NO in cultured endothelial cells, usually through an A2AR-dependent mechanism.[489]

Adenosine induces a sustained decrease in GFR secondary to reduced P_{GC}.[490] Infused in humans, it results in an insignificant increase in RBF and a significant, moderate decrease in GFR.[491,492] It is postulated that adenosine-mediated reduction in GFR constitutes the underlying mechanism of TGF.[493,494] The hypothesis states that increased solute delivery to the MD stimulates sodium transport, resulting in ATP hydrolysis and generation of adenosine. Adenosine, in turn, completes the feedback loop by decreasing GFR and

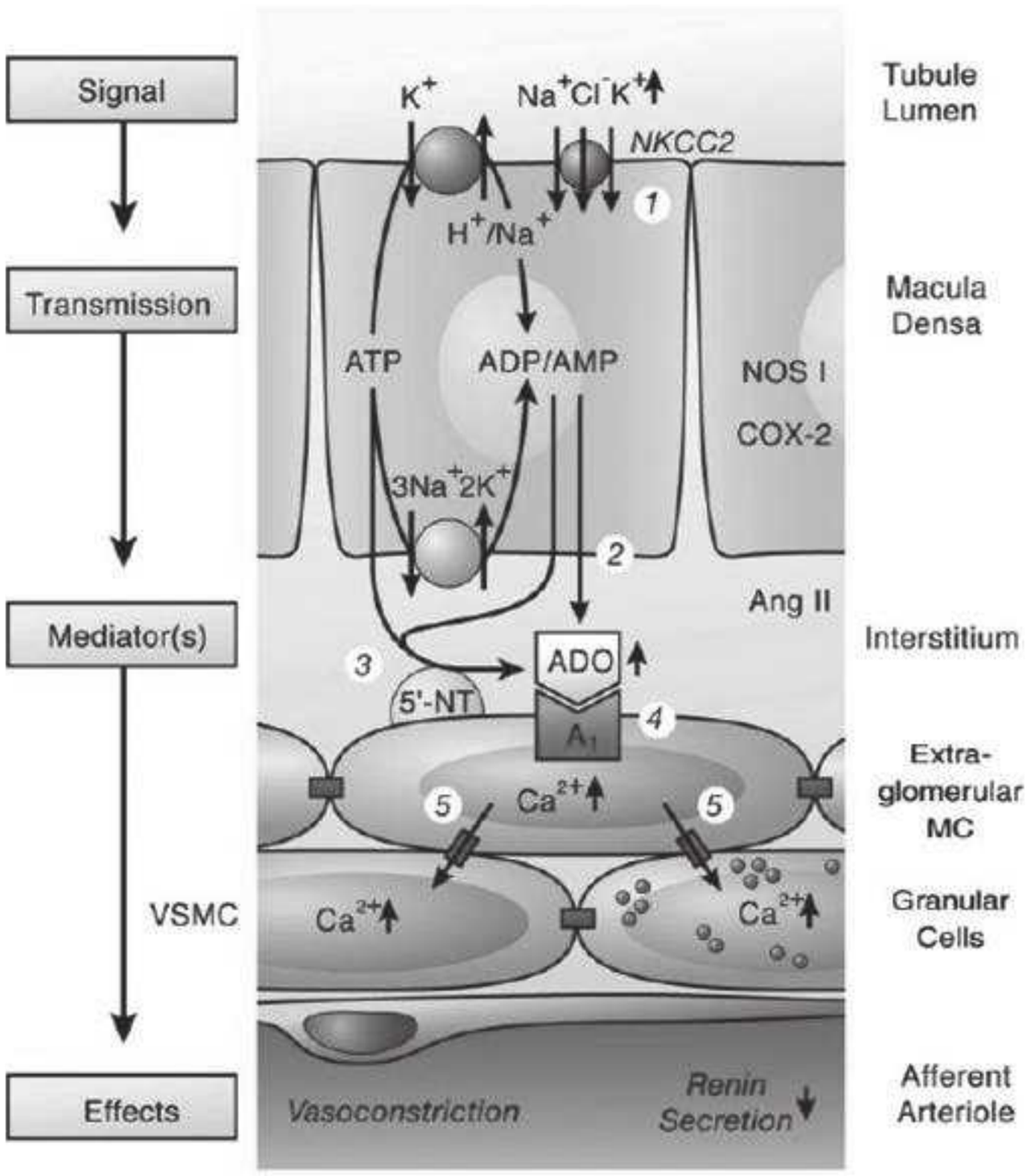

FIGURE 8.7 Proposed mechanism of adenosine acting as a mediator of the tubuloglomerular feedback. Numbers in circles refer to the following sequence of events. *1*, Increase in concentration-dependent uptake of nitrogen (N), potassium (K), and chlorine (Cl) via the furosemide-sensitive Na-K-2Cl cotransporter (NKCC2); *2* and *3*, transport-dependent, intra- and/or extracellular generation of adenosine (ADO); the extracellular generation involves ecto-5′-nucleotidase (5′-NT); *4*, extracellular ADO activates adenosine A1 receptors triggering an increase in cytosolic Ca^{2+} in extraglomerular mesangium cells (MC); *5*, the intensive coupling between extraglomerular MC, granular cells containing renin, and smooth muscle cells of the afferent arteriole (VSMC) by gap junctions allows propagation of the increased Ca^{2+} signal resulting in afferent arteriolar vasoconstriction and inhibition of renin release. Factors such as nitric oxide, arachidonic acid breakdown products, or angiotensin (Ang) II modulate the described cascade. *NOS I*, neuronal nitric oxide synthase; *COX-2*, cyclooxygenase-2. See text for further explanations. (Adapted from Vallon V, Muhlbauer B, Osswald H. Adenosine and kidney function. *Physiol Rev*. 2006;86(3):901–940.)

normalizing solute delivery to the distal nephron. The hypothesis is supported by experiments demonstrating that A1R blockade inhibits TGF.[495,496,497]

Effect on Sodium Reabsorption and Renal Tubular Transport

In contrast to A1R, which directly stimulate Na^+ reabsorption by increasing epithelial transport mechanisms, activation of A2R in microvessels of juxtaglomerular nephrons and in the medullary microcirculation enhances medullary blood flow, thus altering peritubular forces that modulate Na^+ reabsorption. The net result is an increase in Na^+ excretion.[478] Adenosine-induced decrease in solute excretion, particularly sodium, has been generally attributed to the concomitant reduction in GFR and urine flow. The presence of A1R and A2R on renal epithelial cells, however, suggests that adenosine has direct effects on tubular transport.[481] In rats, for example, infusing adenosine or adenosine receptor agonists in a dose that does not alter systemic blood pressure, RBF, or GFR still leads to sodium and water retention.[498,499] This effect was independent of renal enervation, at least for A1-specific agonists, and suggested a direct tubular effect of adenosine on A1R to stimulate sodium reabsorption.[499] A1R in the nephron are linked to Na^+ transport in several segments. However, the natriuresis and diuresis associated with systemic inhibition of A1R are due primarily to reduced proximal tubule (PT) reabsorption. Studies on kidney fluid and electrolyte transport show that activation of A1R stimulates NaCl reabsorption in cortical proximal tubule, which is a tubular segment with relatively high basal oxygen supply. In contrast, adenosine inhibits NaCl reabsorption in medullary TAL and IMCD—that is, nephron segments with relatively low oxygen delivery.[483] Caffeine and theophylline are nonselective adenosine antagonists, and reports suggest high levels of each induced diuresis.[500]

Adenosine acts as a mediator of the TGF, which establishes an inverse relationship between GFR and the NaCl concentration at the MD. In the juxtaglomerular apparatus, extracellular formation of adenosine by ecto-5′-nucleotidase contributes to the adenosine pool that mediates TGF-induced afferent arteriolar vasoconstriction. The TGF mechanism stablizes the NaCl load to the distal nephron, which facilitates fine regulation of body NaCl balance at these sites. Endogenous adenosine, the synthesis of which is increased by enhanced NaCl transport, limits via adenosine A1R activation the oxygen demand in relatively hypoxic nephron segments by directly and differentially affecting reabsorption along the nephron.[483]

Activation of basolateral P2 receptors in the collecting duct inhibits vasopressin-stimulated water reabsorption, and stimulation of apical P2 receptors can affect solute transport in both the proximal and the distal nephron: an in vivo micropuncture study in the rat showed that stimulation of apical P2Y1 receptors inhibits proximal tubular bicarbonate reabsorption through suppression of NHE3 activity,[1] and in vitro and in vivo evidence indicates that stimulation of apical P2 receptors in the distal nephron inhibits amiloride-sensitive sodium reabsorption[2,3] and reduces the activity of apical K secretory channels.[4,501]

Effect on Renin

Adenosine suppresses renin release by the kidney.[481] In sodium-depleted animals, renin release is inhibited by maneuvers that increase renal adenosine production,[502,503] an effect that results from direct action of adenosine on renin-producing cells.[504] Inhibition of renin release is most likely mediated by binding of adenosine to high-affinity A1R.[505] In this regard, A1R restrain renin release responses, a theory known as the adenosine-brake hypothesis. A1R are coupled to G_i and, therefore, inhibit adenylyl cyclase. Because stimulation of renin release from juxtaglomerular cells by many stimuli involves activation of adenylyl cyclase, activation of juxtaglomerular A1R attenuates renin release and antagonism of renal A1R increases renin release.[478] In contrast, agonists selective for the low-affinity A2R stimulate renin release, particularly when administered in high doses.[481,506] This suggests that adenosine regulates renin release by exerting either an inhibitory or stimulatory effect, depending on its local concentration. Studies employing acute blockade or chronic deficiency of adenosine A1R receptors rather indicate a modulating, tonic inhibition of the renin system by adenosine. In addition, an MD-dependent source of adenosine and activation of adenosine A1R contribute to renin release inhibition under conditions of high NaCl concentrations at the MD. An increase in intracellular cAMP is an important stimulator of renin release. Part of the cAMP could be released by renin-secreting cells and is extracellularly converted to adenosine, which acts as a negative feedback control or brake when renin secretion is stimulated.[483]

Effect on Renal Medullary Oxygenation

Renal medullary hypoxia is an obligatory part of the process of urinary concentration. When O_2 supply is further impaired, however, medullary hypoxic injury can develop. Various mechanisms act in concert to minimize medullary hypoxia. Adenosine-mediated actions like maintaining high proximal reabsorption, inhibiting reabsorption in the medullary TAL, and reducing GFR by the TGF mechanism, when distal NaCl concentrations increase, can be part of these mechanisms. Furthermore, in the deep cortex and medulla, adenosine via A2R activation causes vasodilation, which increases medullary blood flow and medullary oxygenation. Thus, adenosine through distinct actions on the vasculature and tubular transport system contributes to the stabilization of the O_2 demand-to-supply ratio particularly in the renal medulla.[483] Nishiyama and associates[480,507] demonstrated that hypoxia-induced renal vasoconstriction was associated with elevated interstitial adenosine levels and could be blocked by adenosine A1R antagonists. Adenosine plays a role in balancing oxygen supply and demand during renal hypoxia by regulating RBF, GFR, renin secretion, and solute transport.[493]

Pathophysiologic conditions associated with increased renal production of adenosine include ARF, myoglobinuric ARF, and mercuric chloride-induced ARF.[508–510] A1R may also be involved in other drug-induced nephrotoxicity. For example, selective antagonism of A_1 receptors attenuates nephropathy caused by nephrotoxins such as cisplatin, gentamicin, cephaloridine, glycerol, and radiocontrast media.[478]

A2R and Diabetic Nephropathy

Awad et al. showed that streptozotocin (STZ)-induced diabetes in rodents leads to marked proteinuria and decreased renal function that is attenuated with continuous subcutaneous administration of A2R agonists. Both nephrin and podocin mRNA levels were reduced after STZ-induced diabetes, an effect completely restored with A2R agonist treatment.[511] They also demonstrated that chronic administration of selective A2A agonists attenuates renal lesions and functional abnormalities characteristic of diabetic nephropathy. The renal tissue protective effect of the A2A agonist is believed to be mediated primarily by abrogating the inflammatory response associated with diabetes. Chronic A2R activation in diabetic rats ameliorates histologic and functional changes in kidneys induced by diabetes and causes reduced inflammation associated with diabetic nephropathy.[511]

Ischemia and Reperfusion Injury

Activation of A1R in many organs, including the kidney, initiates several cytoprotective kinase cascades including ERK MAPK, Akt, and PKC. Activation of cell surface A1R produces cytoprotective effects against ischemia and reperfusion (IR) injury in many organ systems including the heart, kidney, and brain. Joo et al. demonstrated that transient A1R activation produces both acute and delayed protective effects in the kidney including reduced renal cortical necrosis and apoptosis after IR injury. Renal apoptosis is an important component in the development of ARF after IR injury.[512] A2R exert important anti-inflammatory actions that may protect the kidneys from injury (Fig. 8.8). Their activation strongly inhibits neutrophil endothelial cell interactions in vitro and, in vivo, and markedly decreases the renal infiltration of neutrophils and attenuates renal dysfunction following IR injury.[478]

Adenosine 5′-tetraphosphate

Adenosine 5′-tetraphosphate (AP4) is the most potent vasoactive purinergic mediator identified to date, exerting the vasoconstriction predominantly through P2X1 receptor activation. The fact that AP4 is more resistant to degradation further favors potent and prolonged vasoconstrictive effects. The vasoconstrictive in vitro effects of AP4 are paralleled by hypertensive effects in vivo. Therefore, it may be speculated that AP4 is a vasoconstrictor secreted by human endothelial cells, which also plays a role in the regulation of systemic blood pressure under physiologic and pathologic conditions.[513]

Adenosine and Angiotensin II

Certain actions of adenosine, such as vasoconstriction of the renal afferent arteriole, are either dependent on or significantly enhanced by Ang II.[481,514] Evidence suggests that a reduction in, or prevention of, Ang II formation and action

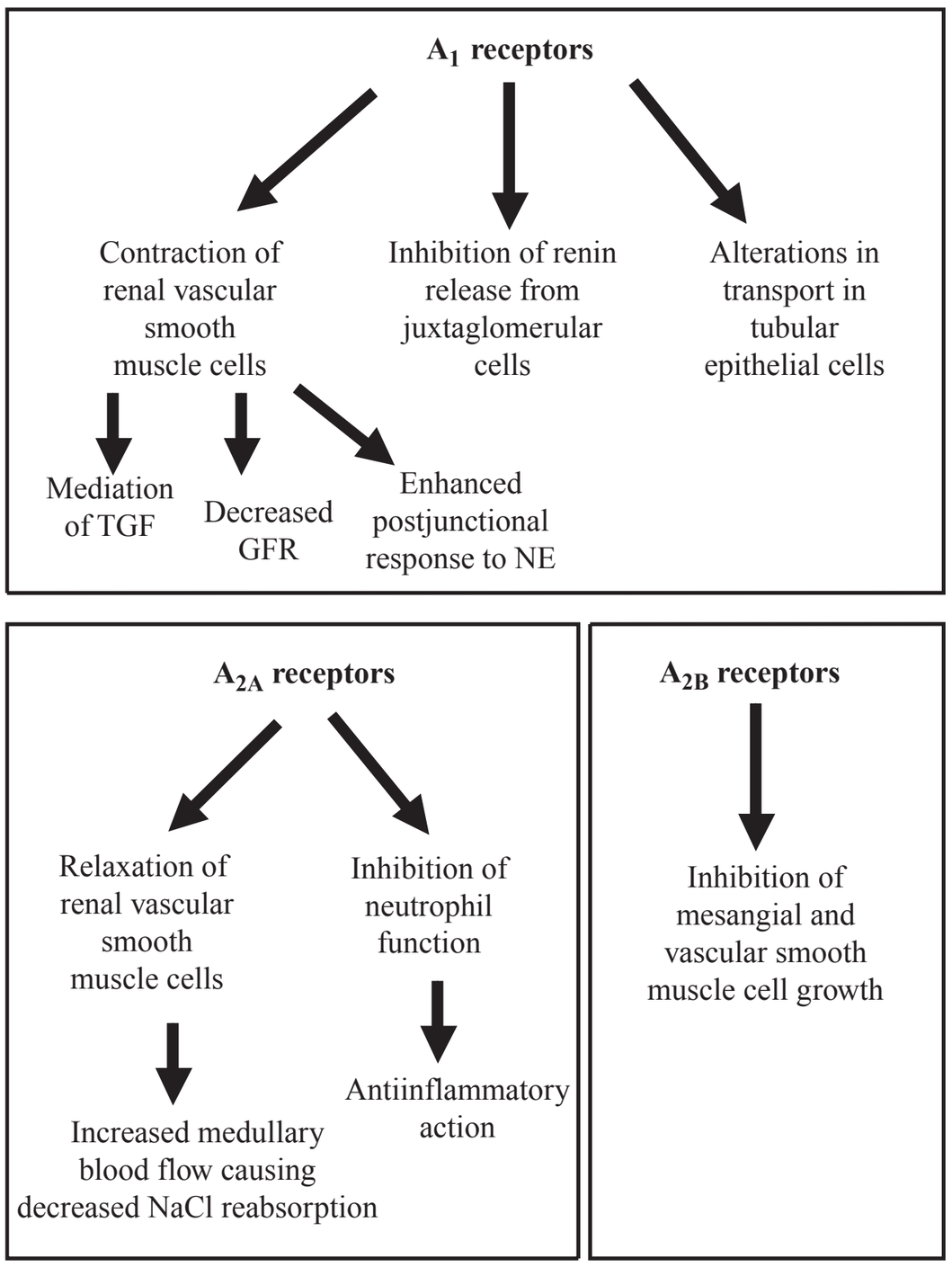

FIGURE 8.8 Regulation of renal function by adenosine. *TGF*, tubuloglomerular feedback; GFR, glomerular filtration rate; *NE*, norepinephrine. (From Bulut OP, Dipp S, El-Dahr S. Ontogeny of bradykinin B1 receptors in the mouse kidney. *Pediatr Res.* 2009;66(5):519–523.)

cause a marked attenuation of the vasoconstrictor response of the intact kidney to adenosine. Conversely, an elevation of ambient Ang II concentrations enhances the constrictor effect of A1R activation.[489]

Effects on Glomerular Mesangial Cells

A2B receptors' activation attenuates vascular smooth muscle cell proliferation and collagen and protein synthesis (Fig. 8.8). Studies with a number of adenosine receptor agonists and antagonists and with antisense oligodeoxynucleotides against the A2B receptor indicate that the growth inhibitory effects of adenosine on vascular smooth muscle cells are mediated by these receptors.[478]

Effect on Erythropoietin

A1R stimulation inhibits erythropoietin (EPO) synthesis, whereas that of A2R enhances EPO synthesis.[515]

Effect on Norepinephrine

Activation of A1R on sympathetic neurons in the kidney causes presynaptic inhibition of norepinephrine (NE) release.[516] Postjunctionally, however, adenosine seems to enhance sensitivity to NE.[516] Because renal denervation does not alter adenosine-induced changes in RBF and GFR, the hemodynamic actions of adenosine in the kidney are most likely independent of its effect on neurotransmitter release.[481]

Pancreatohepatorenal Extracellular cAMP-Adenosine Pathway

In addition to an autocrine/paracrine role in the kidney, the extracellular cAMP-adenosine pathway may also function as an endocrine system by which the pancreas and liver regulate renal function. The pancreas releases glucagon directly into the portal circulation in response to appropriate stimuli. Glucagon in the portal circulation stimulates hepatic adenylyl cyclase, which results in secretion of cAMP by hepatocytes into the venous circulation. Liver-derived cAMP circulates to the kidney, where it is filtered into the proximal tubule and then metabolized to adenosine. Adenosine would then engage A1R in epithelial cells to enhance electrolyte transport. It is important to note that, in contrast to cAMP, which is stable in blood, adenosine has a half-life in human blood of less than 1 second. The liver has the capacity to release significant amounts of cAMP into the hepatic vein.[478]

The most recent studies strongly suggest that an autocrine/paracrine extracellular cAMP-adenosine pathway, in fact, does not participate in the regulation of Na^+ transport by proximal epithelial cells. It appears that the pancreatohepatorenal extracellular cAMP pathway is more important in modulating proximal tubular function. Although intrarenal infusions of glucagons do not reduce Na^+ excretion, intraportal infusions of glucagon in sheep cause a marked antidiuresis. Although speculative, it is conceivable that the pancreatohepatorenal cAMP-adenosine pathway participates in physiologic adjustments of renal transport, as well as in pathophysiologic processes. In normal mammals, both hypoglycemia and exercise are powerful stimulants to glucagon release. Activation of the pancreatohepatorenal cAMP-adenosine pathway by glucagon in response to hypoglycemia might increase Na^+ glucose symport in proximal tubules and, thus, increase the efficiency of glucose transport, an adaptive mechanism to combat hypoglycemia. Activation of the pancreatohepatorenal cAMP-adenosine pathway by glucagon during exercise might enhance Na^+ transport in the proximal tubules and thus increase the efficiency of Na^+ reabsorption, an adaptive mechanism to avoid volume depletion during sustained physical exertion. The pancreatohepatorenal cAMP-adenosine pathway might be overly activated in the metabolic syndrome. Although oral glucose normally strongly inhibits glucagon secretion by the pancreas, in animals and people with the metabolic syndrome, an oral glucose challenge markedly stimulates pancreatic glucagon secretion by approximately 200%. If the pancreatohepatorenal cAMP-adenosine pathway exists, each time such a patient ingests a high carbohydrate meal the renal tubules would be exposed to a wave of excess adenosine

production. Because adenosine causes increased reabsorption of Na^+ and vasoconstriction of the preglomerular microcirculation, this could contribute to the pathophysiology of hypertension in the metabolic syndrome. Importantly, adenosine receptors also inhibit lipolysis in fat cells and may reduce insulin sensitivity in skeletal muscle. However, at this time, both the physiologic and pathophysiologic roles of the putative pancreatohepatorenal cAMP-adenosine pathway are speculative.[478]

PARATHYROID HORMONE AND PARATHYROID HORMONE–RELATED PEPTIDE

In response to low levels of extracellular Ca, parathyroid glands secrete parathyroid hormone (PTH), an 84-amino acid polypeptide hormone.[517] PTH is initially synthesized as a 115-amino acid polypeptide, pre-pro-PTH, which is cleaved within parathyroid cells at the N-terminal portion first to pro-PTH (90 amino acids) and then to PTH (84 amino acids). PTH-related peptide (PTHrP) was first identified as a cause of humoral hypercalcemia of malignancy and is secreted predominately as a 141-amino acid peptide. PTH and PTHrP have sequence homology in the first 13 amino acids (the amino terminus).[518] Increased circulating PTH or PTHrP leads to mobilization of Ca from bone, enhancement of Ca reabsorption in the renal tubule, and increased production of 1,25-dihydroxyvitamin D_3 ($1,25[OH]_2D_3$) from 25 hydroxyvitamin D_3(25-OH D_3) by proximal tubule cells through 1α hydroxylase stimulation. $1,25(OH)_2D_3$, in turn, increases Ca absorption by the intestine and possibly Ca reabsorption by the kidney. The combined actions of PTH and $1,25(OH)_2D_3$ result in normalization of the extracellular Ca concentration. In addition to its regulatory actions on calcium balance, PTH can regulate phosphorus balance by inhibiting its reabsorption in the proximal and distal tubules of the nephron.

PTH synthesis and secretion by the parathyroid gland is tightly regulated.[517] Although a decreased extracellular Ca level stimulates PTH synthesis and secretion, increased extracellular levels of either Ca or $1,25(OH)_2D_3$ are inhibitory. The extracellular phosphorus level regulates PTH production directly at a posttranscriptional level[519] and indirectly by altering circulating Ca and $1,25(OH)_2D_3$ concentrations. Increased serum phosphorus secondary to renal insufficiency, for example, decreases Ca concentration and $1,25(OH)_2D_3$ production, leading to stimulation of PTH release, but can itself increase PTH level without alterations in ionized calcium or serum $1,25(OH)_2D_3$ levels.[520,521]

Magnesium also regulates PTH secretion and its depletion can decrease PTH secretion. Fibroblast growth factor 23 (FGF23) decreases PTH mRNA and secretion. Ben-Dov et al. showed that FGF23 acts directly on the parathyroid through the MAPK pathway to decrease serum PTH.[522]

The biologic activity of PTH resides in its amino-terminus. There is increasing evidence that the C-terminal fragment of PTH, PTH(7-84), exerts a hypocalcemic effect that is reversed by PTH(1-34) and PTH(1-84). PTH(7-84) inhibits PTH(1-84)-induced bone resorption. Nakajima et al. studied the effect of PTH(7-84) on PTH(1-34)-induced production of $1,25(OH)_2D_3$ in primary cultured murine renal tubules. PTH(1-34) stimulated the conversion of 25-OH D_3 to $1,25(OH)_2D_3$, and PTH(7-84) dose-dependently inhibited this process. Real-time polymerase chain reaction (PCR) revealed that PTH(1-34) increased the expression level of 1α-hydroxylase mRNA, whereas PTH(7-84) did not. This may at least partly account for the decreased serum level of $1,25(OH)_2D_3$ in patients with severe primary hyperparathyroidism with renal failure.[523]

Once secreted, PTH is rapidly cleared from plasma through uptake principally by the liver and kidney, where PTH(1-84) is cleaved into amino- and carboxyl-terminal fragments that are then cleared by the kidney. Hepatic clearance of PTH involves rapid proteolysis by Kupffer cells to N-terminal fragments and C-terminal fragments (CPTH). CPTH fragments can exert direct effects on bone cells via CPTH receptors. They are cleared predominantly by the kidney and accumulate disproportionately during renal failure.[524] Intact PTH has a plasma half-life of 2 to 4 minutes. In comparison, the C-terminal fragments, which are cleared principally by the kidney, have half-lives that are five to ten times greater.

Parathyroid Hormone and Parathyroid Hormone–Related Peptide Receptors

Two types of receptors exist. Type 1 PTH receptors (PTH1R) bind PTH and PTHrP. Binding to PTH1R occurs in the 15- to 34-amino acid region of both hormones (N-terminal sequence). It is interesting that these two peptides bind with almost equal affinity and yet do not share sequence homology in this region. The PTH1R mediates the biologic activity of PTH and PTHrP. PTH1R is heavily expressed in bone and kidney, and is also present in other tissues such as breast, skin, heart, blood vessels, pancreas, and other tissues. It activates multiple cellular signaling pathways including cAMP, PLC pathway, PKC, and release of intracellular calcium stores. Muller et al. showed also that activation of PTH1R engages major apoptosis signaling pathways, namely in apoptosis of differentiating embryonic cells.[525] Type 2 PTH receptors (PTH2R), which share 51% homology with PTH1R, can bind PTH but they do not bind PTHrP with high affinity. PTH2Rs are expressed in only a few tissues—their biologic significance is unknown.[518] Increasing evidence points to the presence of novel PTH receptors (CPTHR) with specificity for the carboxyl-terminal region of PTH. This portion of the hormone was previously thought to be biologically inert but has now been shown to possess hypocalcemic activity. The CPTHRs are present in various tissues but are most heavily expressed in bone.

Although PTH is a well-characterized endocrine regulator of mineral homeostasis, PTHrP is a key regulator of placental calcium transport in the fetus, and it appears to

be a physiologic modulator of smooth muscle tone. Current concepts indicate that PTHrP is a developmental and/or growth-regulating factor, much more similar to other known cytokines and growth factors than to PTH.[526] Under physiologic conditions, PTHrP levels are increased during pregnancy and lactation.[527] However, as described earlier, it appears to play a predominately pathophysiologic role in the adult, causing hypercalcemia.

Renal Actions of Parathyroid Hormone

PTH receptors and PTH-sensitive adenylate cyclase have been identified in glomeruli and basolateral membranes of epithelial cells in the proximal tubule, thick ascending limb of Henle's loop, and distal convoluted tubule (DCT).[7,528] PTH has three major effects on the kidney: increased Ca reabsorption, inhibition of phosphate reabsorption, and stimulation of $1,25(OH)_2D_3$ synthesis. Its other actions on the kidney include modulation of GFR, gluconeogenesis, magnesium reabsorption, and acid-base handling.

PTH decreases renal Ca excretion through multiple mechanisms. Ichikawa et al.[529] demonstrated that PTH infusion in rats decreases GFR by reducing K_f. A decreased GFR leads to decreased filtered load of Ca and, therefore, Ca excretion. PTH also enhances tubular Ca reabsorption by stimulating active Ca transport in the thick ascending limb of Henle's loop and distal tubule.[530,531] The effect of PTH on Ca transport in the proximal tubule varies and is probably related to Na and water reabsorption in this nephron segment.

PTH causes phosphaturia primarily by inhibiting phosphate transport in the proximal tubule, specifically by inhibiting sodium-phosphate (Na-P) cotransport.[532] Two different renal Na-P cotransporters have been identified and have been termed type 1 (Npt1) and type 2 (Npt2). Npt2 is a target for regulation by PTH and decreases Na-P transport by endocytic retrieval and lysosomal degradation of the Npt2 protein.[533] This endocytic retrieval can occur either from proximal tubules exposed to apical or basolateral PTH and can signal via either the cAMP-PKA or the PLC-PKC pathway.[534] Mice that are Npt2 null have profound phosphate wasting.[535] Npt2-null mice are resistant to further phosphaturic effects from exogenous PTH.[536] α_2-Adrenergic receptor stimulation blunts the phosphaturic response to PTH.[537] PTH-stimulated synthesis of $1,25(OH)_2D_3$ in the proximal tubule is discussed in the next section.

Although no single hormone has been specifically shown to regulate Mg homeostasis, PTH appears to increase Mg reabsorption in the kidney.[538] PTH also plays a role in acid–base homeostasis by enhancing urinary acid excretion.[539] Although PTH inhibits bicarbonate reabsorption in the proximal tubule, it indirectly stimulates distal hydrogen ion secretion and titratable acid excretion by increasing phosphate delivery to the distal nephron. PTH has also been shown to enhance proximal tubular gluconeogenesis[540] and renin secretion by juxtaglomerular cells.[541]

Renal Actions of Parathyroid Hormone–Related Peptide

In the kidney, PTHrP appears to modulate RPF and GFR, and induces proliferative effects on both glomerular mesangial and tubuloepithelial cells. PTHrP is known to be upregulated in several experimental nephropathies such as acute renal failure, obstructive nephropathy, as well as diabetic nephropathy. In transgenic mice models and in the former condition, PTHrP appears to contribute to the progression of renal damage by increasing tubulointerstitial cell survival, inflammation, and renal fibrogenesis. In diabetic nephropathy, PTHrP can promote renal hypertrophy and proteinuria. Ang II, a critical factor in the progression of renal injury, appears to be, at least in part, responsible for endogenous PTHrP upregulation in these pathophysiologic settings.[526] PTHrP also participates in the hypertrophic signalling triggered by high glucose on podocytes. In this condition, Ang II induces the upregulation of PTHrP, which in turn might induce both TGF-β1 and p27Kip1 expression and thereby promotes the hypertrophy of podocytes.[542]

Conventional renal cell carcinoma (CRCC) originates from the renal proximal tubular epithelium, a target tissue for PTHrP proliferation effects.[543] It was shown that PTHrP, acting through its receptor PTH1R, is an essential growth factor for CRCC in vitro and in vivo and a new target for the VHL gene products.[544,545] It seems that PTHrP induces tumor cell survival through inhibition of cell apoptosis.[546]

VITAMIN D

Along with PTH, vitamin D plays a central role in calcium and phosphate homeostasis. The active form of vitamin D, $1,25(OH)_2D$, is a steroid molecule synthesized from either vitamin D_3 (cholecalciferol) or vitamin D_2 (ergocalciferol). These two forms of vitamin D differ only by the side chain to the sterol skeleton. Vitamin D_3 is present in the diet (animal sources, mainly fish oil) and is also synthesized by the skin from 7-dehydrocholesterol upon exposure to ultraviolet light. Vitamin D_2 is available only from dietary sources (plants, yeast, and fungi). Vitamins D_3 and D_2 are biologically inactive. They require activation in the liver and kidney. After binding to carrier proteins, in particular, vitamin D-binding protein (DBP), vitamin D is transported to the liver where it is enzymatically hydroxylated to 25-hydroxyvitamin D (calcidiol, 25[OH]D) through the action of hepatic microsomal and mitochondrial cytochrome P450 vitamin D–25-hydroxylase. Subsequently, 25(OH)D, bound to DBP, is transported to the kidneys where it is hydroxylated exclusively in the proximal tubule by the mitochondrial 25(OH)D–1α-hydroxylase.[547] 1α-Hydroxylation is the rate-limiting step in the formation of the most abundant active metabolite $1,25(OH)_2D_3$.[548–550] This step is tightly regulated through multiple feedback mechanisms,[549,550] mainly PTH, calcium, phosphate, fibroblast growth factor 23 (FGF23), and $1,25(OH)_2D_3$ itself (Fig. 8.9). An increase

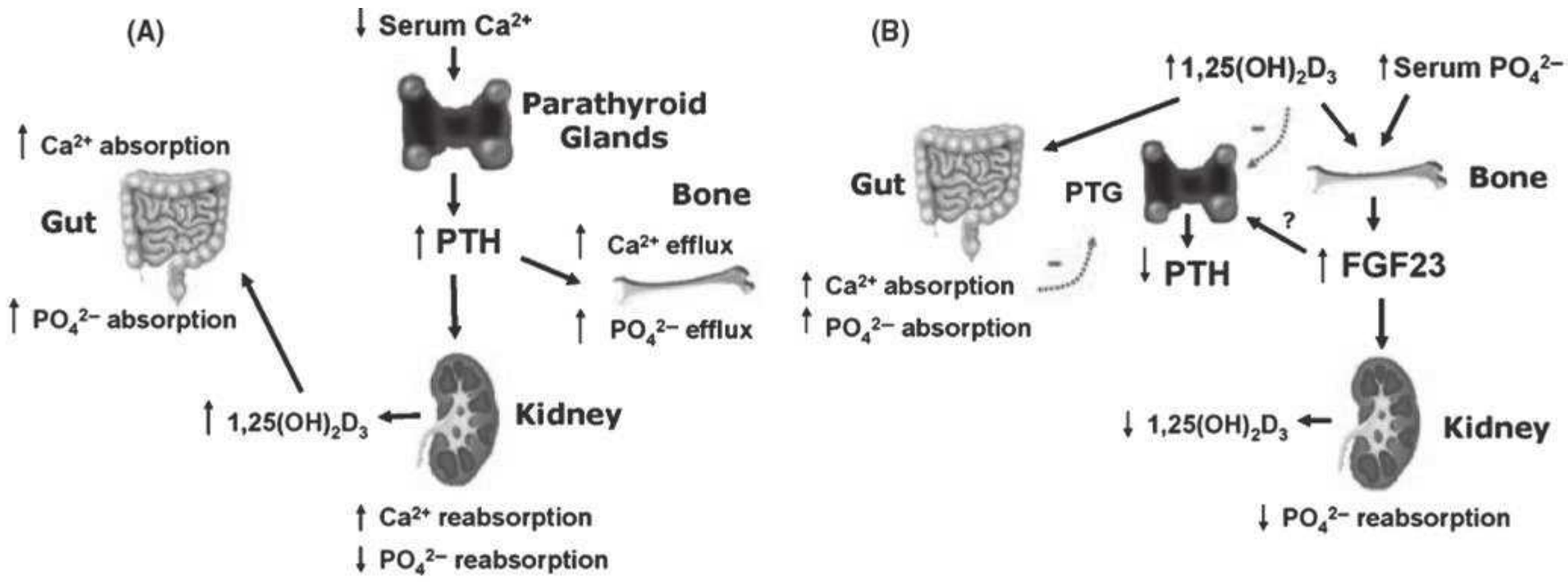

FIGURE 8.9 **A:** Calcium–parathyroid hormone (PTH)–vitamin D axis. The calcemic hormone PTH produced by the parathyroid gland targets kidney to increase calcium absorption and $1,25(OH)_2D_3$ production and bone to increase calcium efflux. $1,25(OH)_2D_3$ stimulates calcium absorption from the gut, which, along with renal and bone calcium, restores serum calcium to normal. **B:** Fibroblast growth factor 23 (FGF23)–bone–kidney axis. FGF23 produced by bone osteocytes has phosphaturic effects and suppresses $1,25(OH)_2D_3$, thereby providing a means to lower serum phosphate in a PTH-independent manner. (From Stubbs J, Liu S, Quarles LD. Role of fibroblast growth factor 23 in phosphate homeostasis and pathogenesis of disordered mineral metabolism in chronic kidney disease. *Semin Dial*. 2007;20(4):302–308.)

in PTH levels, secondary to decreased serum Ca, stimulates 1α-hydroxylase activity in the kidney. A low serum phosphorous or $1,25(OH)_2D_3$ concentration also activates 1α-hydroxylase, whereas elevated $1,25(OH)_2D_3$ levels and the phosphaturic FGF23 are inhibitory. Other less established stimulators of 1α-hydroxylase activity include calcitonin, growth hormone, insulin, insulin-like growth factor, estrogen, and prolactin.[548–550]

In addition to the kidney, extrarenal sites of 1α-hydroxylase activity have been identified. These include macrophages, keratinocytes, hepatocytes, and human placenta, as well as skeletal muscle cells[551] and various bone cell preparations,[552,553] although the regulatory processes for this conversion are not well understood. Extrarenal production of $1,25(OH)_2D_3$ can lead to hypercalcemia in certain pathologic situations, as in patients with active sarcoidosis or in patients with lymphoma.

The first step in the inactivation and catabolism of vitamin D is hydroxylation of 25(OH)D and $1,25(OH)_2D$ by 24-hydroxylase, which is present in the kidney, intestine, and several other tissues that possess $1,25(OH)_2D_3$ receptors.[547,550] Importantly, kidney 24-hydroxylase and 1α-hydroxylase are reciprocally regulated.[547,550,554] $1,25(OH)_2D_3$ and hypophosphatemia increase 24-hydroxylase activity whereas vitamin D deficiency and PTH (via CAMP) suppress it.[554]

25(OH)D has a long half-life (approximately 3 weeks) and is the best measure of vitamin D status. Calcitriol has a short half-life (4 to 6 hours) and exists at circulating levels 1/1,000 of those of 25(OH)D. $1,25(OH)_2D_3$ exerts its biologic actions by binding to intracellular vitamin D receptors (VDR), which in the unliganded form are located in the cytosolic and nuclear compartments.[555] Like other members of the steroid-thyroid family of receptors, the liganded form of VDR functions as a transcription factor in the nucleus. The VDR–$1,25(OH)_2D_3$ complex regulates transcription of more than 60 genes by interacting with DNA sequences known as vitamin D response elements. Central to its role in Ca homeostasis, $1,25(OH)_2D_3$ induces the transcription of genes coding for Ca-binding proteins.[556] Vitamin D-dependent Ca-binding proteins (CaBP-Ds) are found in high concentrations in Ca-transporting tissues, such as the kidney, intestine, and placenta. CaBP-Ds bind calcium with high affinity and are associated with Ca transport in these organs.

Another potential regulatory site for vitamin D signaling, other than the synthesis and degradation of $1,25(OH)_2D_3$, is by regulation of VDR expression. Receptor regulation has been shown to be physiologically important, as $1,25(OH)_2D_3$ signaling is dependent on both the number and occupancy of VDRs on the cell surface membrane.[557]

Aside from its biologic effects in the kidneys, calcitriol is transported by DBP to other vitamin D receptor VDR-positive target tissues (mainly bone, intestine, and parathyroid gland) to act in a genomic or nongenomic manner. Regulation of gene expression by calcitriol is mediated by VDR and takes place within hours. By contrast, nongenomic responses of calcitriol are probably mediated by a specific membrane-bound VDR and occur within seconds to minutes. Nongenomic effects of calcitriol include rapid changes in phosphoinositide metabolism, increases in intracellular calcium levels, stimulation of intestinal calcium transport and phosphate fluxes, elevation in cyclic guanosine monophosphate (cGMP) levels, and activation of protein kinase C.[558] These activities have been found in many cells, including keratinocytes, enterocytes, muscle cells, osteoblasts, and chondrocytes. VDR seems to be necessary for some of these

nongenomic transduction processes; however, another protein named 1a,25-dihydroxy-membrane associated rapid response steroid binding (MARRS) is also seemingly involved in these rapid nongenomic actions.[558]

Physiologic Actions of $1,25(OH)_2D_3$

$1,25(OH)_2D_3$ participates in a hormonal system that tightly regulates the extracellular Ca concentration.[556] A decline in serum Ca stimulates PTH release, which acts on the kidney to increase production of $1,25(OH)_2D_3$. $1,25(OH)_2D_3$, in turn, stimulates intestinal absorption of Ca and decreases its excretion by the kidneys. $1,25(OH)_2D_3$ also acts on bone to stimulate Ca mobilization.[559] Normalization of serum Ca shuts off this cascade by suppressing 1α-hydroxylase activity in the kidney and release of PTH from the parathyroids. Increased $1,25(OH)_2D_3$ also contributes to turning off Ca-correcting mechanisms by inhibiting its own production.[560] In addition to its effects on Ca homeostasis, $1,25(OH)_2D_3$ also enhances phosphate absorption in the intestine and kidney.

About 50% to 60% of filtered Ca is reabsorbed in the proximal tubule. This process is Na-dependent, and the majority of Ca is reabsorbed via a paracellular pathway.[561,562] Approximately 20% of filtered Ca is reabsorbed in Henle's loop, 10% to 15% in the distal tubule, and 5% in the collecting duct. Unlike the proximal tubule, Ca reabsorption in the distal tubule appears to be Na-independent.[561] In addition to VDR, distal tubule epithelial cells contain CaBP-Ds and ATP-dependent plasma membrane Ca pumps.[563] It has been postulated, therefore, that $1,25(OH)_2D_3$ enhances renal Ca reabsorption by direct action on the distal tubule in a manner analogous to stimulation of Ca absorption by intestinal cells.[556] Several experimental studies support this hypothesis: Concentrations of CaBP-Ds and Ca transport rates in renal cells are increased by vitamin D, whereas vitamin D deficiency abolishes CaBP-D synthesis and decreases Ca absorption.[556] Experimental studies also suggest a role for $1,25(OH)_2D_3$ in phosphate handling by the kidney. In isolated perfused proximal tubule segments, low concentrations of $1,25(OH)_2D_3$ antagonize the phosphaturic action of PTH.[563] In rats in which vitamin D deficiency was induced, but the diet was manipulated to maintain normocalcemia, normophosphatemia, and normal PTH levels, $1,25(OH)_2D_3$ stimulated tubular reabsorption of phosphate.[564] It was thought that $1,25(OH)_2D_3$ regulates phosphate reabsorption by direct modulation of Na-P cotransport in renal tubule cells.[565] However, data on rats subjected to a low phosphate diet suggest that the Na-P cotransport in the kidney cannot be explained by the $1,25(OH)_2D$–VDR axis.[566]

In patients with renal failure requiring dialysis, serum phosphate levels increase as a result of the decreased capacity of the kidney to excrete phosphate; the elevated serum phosphate inhibits $1,25(OH)_2D_3$ formation and leads to decreased serum Ca levels and to increased PTH secretion (secondary hyperparathyroidism). PTH would lead to worsening of hyperphosphatemia with more phosphate released from bone than excreted in the kidney with diminished PTH sensitivity, ultimately leading to renal osteodystrophy and possible calcium phosphate precipitation in tissues and vessels with an associated increase in cardiovascular events. The use of active vitamin D analogs in an attempt to remedy secondary hyperparathyroidism may increase Ca while worsening hyperphosphatemia, therefore increasing the Ca × P product and rendering CaP precipitation more likely. Phosphate binders can help decrease serum phosphate levels.

A new set of agents called calcimimetics have been approved in this setting (e.g., cinacalcet). They bind to CaSR in the parathyroids and increase its sensitivity to Ca, therefore counteracting the excessive PTH secretion in a dose-dependent manner and decreasing the Ca × P product.[567]

The presence of VDR on monocytes/macrophages and activated lymphocytes suggests that $1,25(OH)_2D_3$ plays a role in regulating the functions of these cells.[568]

Renoprotective Effects of Vitamin D

It has been demonstrated that $1,25(OH)_2D_3$ possesses renoprotective property against hyperglycemia-induced renal injury by suppressing the renal RAS. Evidence suggests that $1,25(OH)_2D_3$ is a negative endocrine regulator of renin biosynthesis and directly transrepresses renin gene transcription. $1,25(OH)_2D_3$ suppresses renin biosynthesis in mice, and vitamin D deficiency stimulates renin production. VDR knockout mice and those missing the 1α-hydroxylase enzyme develop hypertension and cardiac hypertrophy and high renin levels.[569] Also, diabetic mice lacking VDR develop more severe renal damage than wild type mice because of more robust activation of the intrarenal RAS, including more induction of renin and angiotensinogen.[570] Deb et al. demonstrated that $1,25(OH)_2D_3$ suppresses hyperglycemia-induced angiotensinogen expression in the kidney by blocking NF-κB activation of the angiotensinogen gene transcription.[571] Forman et al. showed that, among normotensive individuals, lower 25(OH)D levels were associated with higher circulating Ang II levels and a blunted renal plasma flow response to exogenous Ang II infusion, both findings consistent with activation of the RAS in the setting of lower plasma 25(OH)D.[572] Melamed et al. showed that low 25(OH)D levels are associated with the development of ESRD.[573] In animal studies, vitamin D and VDR agonists (VDRA) were shown to ameliorate glomerulosclerosis, glomerular hypertrophy and inflammation, podocyte hypertrophy, mesangial proliferation, albuminuria, and interstitial fibrosis.[574,575] These effects may be independent of BP and PTH. In the kidney, vitamin D may be important for maintaining podocyte health, preventing epithelial-to-mesenchymal transformation, and suppressing renin gene expression and inflammation. In human studies, CKD is associated with a very high prevalence of 25(OH)D deficiency. Emerging evidence in patients with CKD show that vitamin D can reduce proteinuria or albuminuria even in the presence of ACE inhibition.

In addition to reducing proteinuria, VDRA may reduce also insulin resistance, BP, and inflammation and preserve podocyte loss providing biologic plausibility to the notion that the use of VDRA may be associated with salubrious outcomes in patients with diabetic nephropathy.[575]

Fibroblast Growth Factor 23

FGF23, a 30-kDa protein primarily synthesized by osteoblasts and osteocytes, controls renal phosphate excretion by regulating renal Na-dependent phosphate cotransporters (NaPi2a and NaPi2c). It is phosphaturic and decreases 1α-hydroxylase levels by a VDR independent mechanism, and induces 24-hydroxylase activity, therefore reducing $1,25(OH)_2D_3$ by a VDR-mediated mechanism.[576] In vivo studies have shown that FGF23 is one of the most potent phosphatonins that induces renal phosphate wasting and reduction of $1,25(OH)_2D_3$.[577] Another unique characteristic of FGF23 is that this molecule derives from bone and exerts its hormonal effects in the kidney despite the ubiquitous presence of its receptors (FGFRs).

FGF23 directly acts on parathyroid glands and attenuates secretion of PTH in the presence of Klotho, an antiaging protein, as a cofactor. Klotho mutant mice display a phenotype identical to that of FGF23 null mice, both of which are characterized by premature aging–related phenotypes associated with hypercalcemia, hyperphosphatemia, and paradoxically high $1,25(OH)_2D$ levels. Klotho is predominantly expressed in the distal tubule of the kidney. Aside from its function as a cofactor for the stimulation of FGF-23, it also colocalizes with epithelial Ca channel transient receptor potential vallinoid-5 (TRPV5). Mice overexpressing the Klotho gene age slowly through a mechanism that involves insulin and oxidant stress resistance.[574] Klotho is expressed in limited tissues such as the kidney, parathyroid, and pituitary gland.[577]

The identification of FGF23 and Klotho as a physiologic regulator of phosphate and vitamin D metabolism has considerably advanced the understanding of the mineral and bone disorder in CKD. It is now clear that FGF23 plays a central role in the pathogenesis of altered mineral metabolism and secondary hyperparathyroidism in CKD patients.[577] The primary systemic stimuli of FGF23 secretion are increased $1,25(OH)_2D$ levels and increased dietary phosphorus intake. In kidney failure, FGF23 levels increase early and steadily rise with progression of kidney disease, likely as an appropriate physiologic adaptation to maintain normal phosphorus balance by helping to augment urinary phosphate excretion in conjunction with increased PTH levels and by decreasing gut phosphorus absorption through decreased $1,25(OH)_2D$. In the long term, this compensation may become maladaptive by causing a progressive decline in $1,25(OH)_2D$ levels with attendant consequences such as secondary hyperparathyroidism. Moreover, excess FGF23 levels have been independently linked with cardiovascular disease and mortality, suggesting that chronically elevated FGF23 levels may directly contribute to adverse CKD outcomes.[578]

FGF23 has been also implicated in the pathogenesis of X-linked hypophosphatemic rickets/osteomalacia (XLH), tumor-induced osteomalacia (TIO), and autosomal-dominant hypophosphatemic rickets/osteomalacia (ADHR)—all entities with common features, including hypophosphatemia because of renal phosphate wasting and impaired mineralization of bone with normal serum Ca and PTH.[579,580]

EICOSANOIDS

The eicosanoids are a group of locally acting hormones or autacoids that are derived from dietary polyunsaturated fatty acids. In humans, arachidonic acid, an essential fatty acid esterified into cellular membrane phospholipids, is the most abundant and important precursor. After deesterification by phospholipases, free arachidonic acid may either rapidly reesterify into membrane lipids, avidly bind intracellular proteins, or undergo enzymatic oxygenation to yield the various biologically active molecules referred to as eicosanoids. The type of product formed depends on the enzymes involved in the oxygenation process (Fig. 8.10).[581] Oxygenation of arachidonic acid by cyclooxygenase results in prostaglandin and thromboxane (TX) synthesis. Oxygenation by lipoxygenase generates hydroxyeicosatetraenoic acids and leukotrienes. These two major enzymatic pathways are all expressed in the kidney.[582,583] The specific nature of the products generated varies with both cell type and initial stimulus for arachidonic acid release. Eicosanoids have diverse biologic effects in the kidney, the significance of which will be discussed later.

Cyclooxygenase Products

Prostaglandins

Prostoglandins (PGs) are a unique group of cyclic fatty acids with diverse biologic effects that are produced throughout the body. The kidney is a major site of PG production, metabolism, and action.[584,585] PGs are important modulators of renal function in both physiologic and pathophysiologic settings. The spectrum of their effects in the kidney encompasses modulation of RBF, GFR, salt and water transport, and the release of renal hormones. It is within the setting of compromised renal status that maintenance of renal function is most dependent on PGs. Under these circumstances, inhibition of PG synthesis with nonsteroidal anti-inflammatory drugs (NSAIDs) is likely to impair renal function.[586]

Structure and Synthesis of Prostaglandins Arachidonic acid (eicosatetraenoic acid) is the major substrate for the synthesis of PGs in humans. The initial step is catalyzed by cyclooxygenase (COX), a major therapeutic target of analgesic, antipyretic, and anti-inflammatory actions of NSAIDs. COX converts arachidonic acid to PGH_2, which is subsequently metabolized by various PG synthases to more stable, biologically active, prostanoids, namely PGE_2, prostacyclin (PGI_2), $PGF_{2\alpha}$, PGD_2, and thromboxane A_2 (TxA_2) (Fig. 8.10). For a detailed description of the biosynthetic pathways leading to the

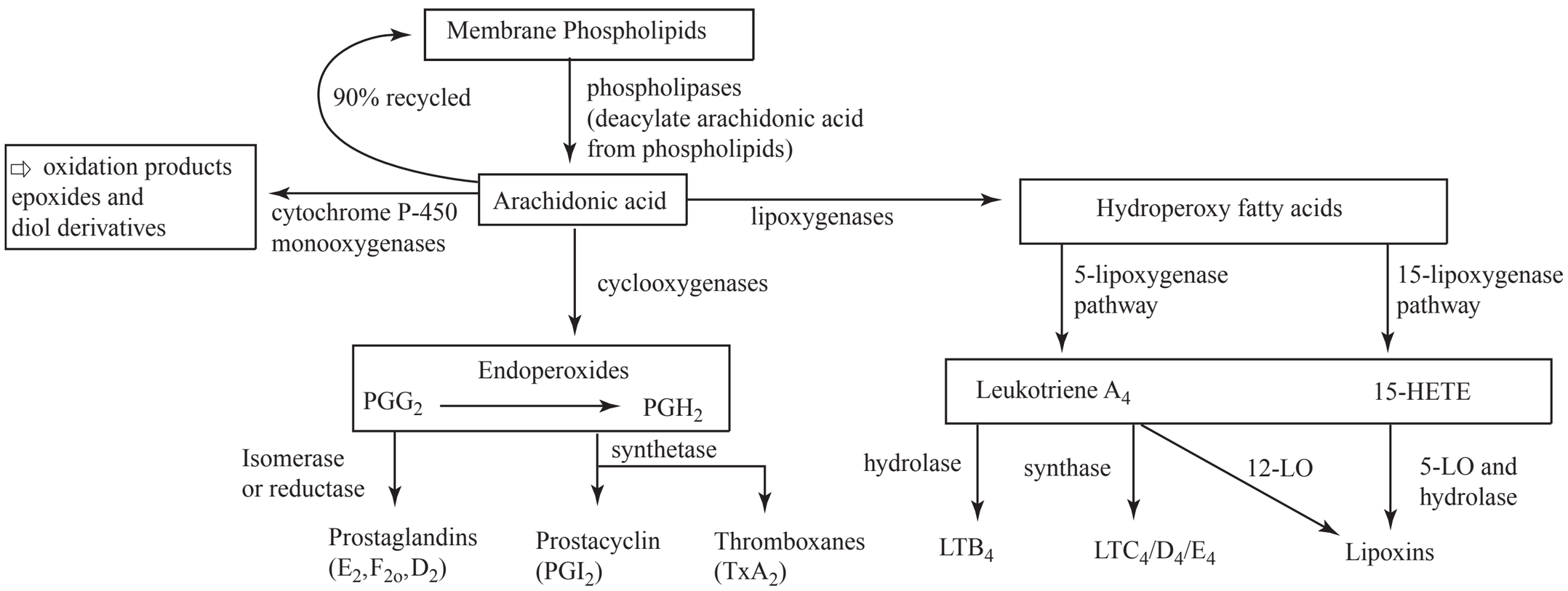

FIGURE 8.10 Renal eicosanoid synthesis. The oxygenated products of arachidonic-acid (eicosatetraenoic-acid) metabolism are referred to as eicosanoids. These include lipoxygenase, cytochrome P450 monooxygenase, and cyclooxygenase products. The lipoxygenase pathway yields hydroxy fatty acids and leukotrienes. The cytochrome P450 monooxygenase pathway yields ω-oxidation products and diol derivatives. The cyclooxygenase pathway yields the prostanoids, which include the prostaglandins (PGE_2, PGF_2, PGD_2, and prostacyclin) and thromboxane. The most important prostaglandins are dienoic (i.e., possessing two double bonds outside the ring structure)—hence the subscript 2.

different types of PGs and thromboxanes, collectively called prostanoids, the reader can refer to following reviews.[587,588]

The COX pathway is also the major pathway for arachidonic acid metabolism in the kidney.[582,583] In both animals and humans, two separate COX enzymes have been identified that are encoded by two separate genes: COX-1 (589) and COX-2 (590). The human COX-1 enzyme is constitutively present in the renal vasculature (arterial and arteriolar endothelial cells, mesangial cells),[583,587,591–593] glomerular epithelial cells,[594] renal interstitial cells,[587,595] along most segments of the tubule, although in markedly varying concentrations,[596–598] and in the medullary and papillary collecting ducts in humans, monkeys, dogs, rabbits, and rats.[587] The COX-2 enzyme, first thought to be only inducible in inflammatory responses, was found to be constitutive in the kidney.[599] Its expression is consistently focal and limited to the MD of the juxtaglomerular apparatus, epithelial cells of the thick ascending limb, and papillary interstitial cells of rats, rabbits, and dogs. In mice, COX-2 expression varied with developmental stages, with high levels of expression in the MD and thick ascending limbs of fetal kidneys and minimal expression upon renal maturation, suggesting a putative role for COX-2 in nephrogenesis.[600] In the adult human kidney, expression of the COX-2 protein has been observed in endothelial and smooth muscle cells of arteries and veins, and intraglomerularly in podocytes, but not in MD cells.[587] It is noteworthy that the distribution of prostanoid synthases within the kidney remains incompletely characterized.[601]

Physiology of Prostaglandins in the Kidneys The rate of PG production is dependent on the release of free arachidonic acid from tissue stores by phospholipase A_2 (PLA_2). Arachidonate tissue stores vary with dietary intake of essential fatty acids and can be depleted when intake is deficient.[602] Fish oil diets (rich in omega-3 polyunsaturated fatty acids) will compete for the arachidonate oxidation process and inhibit formation of active products.[603] Table 8.5 lists several modulators of the key steps involved in PG synthesis. Although under basal conditions both COX-1 and COX-2 contribute to prostanoid production in the kidney, some stimuli have been shown to initiate a more selective response. Evidence indicates that Ang II, through AT_1 receptors, increases MD COX-2 expression.[604,605] In addition, conditions associated with activation of the renin-angiotensin system, such as a low-salt diet or diuretic administration, all significantly increase MD COX-2 expression.[606,607] Recently, pressure was also shown to be an important promoter of renal COX-2 expression in renal medullary interstitial cells subjected to mechanical stress in vitro as well as in rats subjected to ureteral obstruction.[608] In contrast to COX-2, cortical expression of COX-1 is independent from Ang II but relies on hemodynamic changes.[604] Several renal pathophysiologic states such as glomerulonephritis, in addition to ureteral obstruction, are associated with increased prostanoid production.[609–611]

Prostanoids are rapidly degraded, which limits their effects to the immediate vicinity of their site of synthesis and accounts for their autocrine or paracrine function. They mediate diverse actions, in part related to their site of synthesis and the cells on which they act (Tables 8.6 and 8.7). Their principal physiologic role is mediation and/or modulation of hormone action at these locations.[583,587,592,612,613] Thus, cortical production by arterioles and glomeruli is related to regulation of RBF, GFR, and renin release. Other cortical sites of PG production affect ammoniagenesis[614] and calcium

8.5 Modulators of Prostaglandin Synthesis[a]

Modulator	Site of Action
Promoters	
Angiotensin II	PLA_2
AVP	PLA_2
Bradykinin	PLA_2
Norepinephrine	PLA_2
PAF	PLA_2
Interleukin-1	PLA_2 and COX
TNF-α	PLA_2
PDGF	COX
EGF	COX
Calcium	PLA_2
Diabetes	PLA_2
Ischemia	PLA_2
Chronic AVP therapy	COX
Ureteral obstruction	COX and TX synthase
Venous obstruction	COX
Glomerulonephritis	COX
Nephrotic syndrome	TX synthase
Inhibitors	
Glucocorticolds	PLA_2 and COX
Potassium	PLA_2
Urea	PLA_2
Mepacrine	PLA_2
NSAIDs	COX

[a]Note that hormones are important physiologic modulators of prostaglandin production. AVP, arginine vasopressin; PAF, platelet-activating factor; TNF-α, tumor necrosis factor-α; PDGF, platelet-derived growth factor; EGF, epidermal growth factor; NSAIDs, nonsteroidal anti-inflammatory drugs; PLA, phospholipase A; COX, cyclooxygenase; TX, thromboxane.

and phosphate transport.[615] Medullary PG production is directed to regulating vasa recta blood flow, tubular sodium and chloride transport, and the response of the collecting duct to vasopressin. Inhibition of COX activity in the absence of exogenous administration or endogenous release of hormones such as Ang II, NE, or vasopressin has little effect on renal functional parameters.[616] Once their local release is enhanced, COX products may themselves stimulate the local generation of other hormones. Under pathophysiologic conditions, such as inflammatory injury, local release of prostanoids may mediate some of the functional derangements that characterize these conditions.[609–611]

Prostanoids act through specific and distinct receptors.[617,618] These receptors are members of the G protein-coupled family of receptors. In the kidney, they mainly include the E-prostanoid (EP), F-prostanoid (FP), I-prostanoid (IP), and T-prostanoid (TP) receptors, which respectively interact with PGE_2, $PGF_{2\alpha}$, PGI_2, or TxA_2 (Fig. 8.1). Multiple subtypes of each of these prostanoid receptors may exist, as in the case with the PGE_2 receptor (EP receptor), thus explaining the apparently contrasting effects mediated by PGE_2 on smooth muscle and collecting duct permeability to water.[619] The differential sensitivity of tissues to several structural PGE analogs has led to the identification of at least four distinct EP receptors: the two vasodilator receptors, EP_2 and EP_4, and the two vasoconstrictor receptors, EP_1 and EP_3.[620] EP_1 receptors signal mainly by IP_3-mediated increased intracellular Ca^{2+}.[621–623] In contrast, the vasodilator receptors EP_2 and EP_4, signal through increased cAMP.[624–626] EP_3 receptors constrict smooth muscle, probably by inhibiting cAMP generation via a pertussis toxin-sensitive, G_i-coupled mechanism.[627,628] In mesangial cells, the $PGF_{2\alpha}$ receptor (FP receptor) seems to be coupled to increased intracellular Ca^{2+}. At higher concentrations, $PGF_{2\alpha}$ also stimulates EP receptors.[629,630] The TXA_2 receptor (TP receptor) appears to signal via phosphatidylinositol hydrolysis, leading to increased intracellular Ca^{2+}.[631] There is pharmacologic evidence for existence of TP receptors in the glomerulus.[629] The PGI_2 receptor (IP receptor) signals via stimulation of cAMP generation.[632,633] PGI_2 has been demonstrated to play an important vasodilator role in the glomerular microvasculature, where the effects of PGI_2 and PGE_2 to stimulate cAMP generation were distinct and additive.[634] Thus, because multiple PGs can be synthesized through the COX pathway and because these PGs can interact with different receptors, their pathophysiologic effects are further diversified and depend on which prostanoid is produced and which receptor is available locally.

Renal Hemodynamics There are some species differences in the renal actions of PGs, and this must be taken into account when extrapolating data from animals to humans. Although acute inhibition of PG synthesis does not change arterial pressure in normal circumstances, it does produce both an increase in renal vascular resistance and a decrease in sodium and water excretion.[635–637] In general, PGE_2 and PGI_2 are vasodilators in most species, whereas TXA_2, $PGF_{2\alpha}$, and PGE_2 (in certain circumstances) are vasoconstrictors.[584,638,639] The contribution of these vasoactive properties of COX products to the regulation of renal vascular tone under normal physiologic conditions is probably minimal.[640–645]

In contrast, the local release of vasodilator PGs (PGE_2 and PGI_2) in response to renal vasoconstrictors plays an important role in maintaining RBF and GFR. There is compelling evidence indicating that mesangial cell synthesis and release of PGE_2 and PGI_2 modulate the constrictor actions of Ang II, NE, and AVP.[583,584,587,629,646] Activation of the renin-angiotensin and sympathetic nervous systems leading to enhanced release of angiotensin, catecholamines, and AVP occurs in conditions, such as hemorrhage, volume depletion, general anesthesia, cirrhosis, and cardiac failure. While serving to maintain the systemic blood pressure, these hormones constrict mesangial cells and glomerular

8.6 Renal Actions of Eicosanoids

	Product Pathway		
Action	**Cyclooxygenase**	**P450 Epoxygenase**	**Lipoxygenase**
Vascular			
Constriction	TXA_2	5,6-EET 20-HETE	LTD_4, LTC_4 LXA_4, LXB_4
Dilation	PGE_2, PGI_2	5,6-EET	LXA_4, cyclooxygenase-dependent
Mesangial			
Contraction	TXA_2, $PGF_{2\alpha}$	LTD_4, LTC_4	LTC_4
Relaxation	PGE_2, PGI_2		
Mitogenic	$PGF_{2\alpha}$, TXA_2		
Antimitogenic	PGI_2, PGE_2		
Na transport			
Inhibition	PGE_2	5,6-EET	
Na-K-ATPase			
Inhibition	PGE_2	11,12-DHT	
Stimulation		19-HETE	
Water transport			
Inhibition	PGE_2	EETs, DHTs	

TXA, thromboxane A; PGE, prostaglandin E; PGI, prostaglandin I; PGF, prostaglandin F; EET, epoxyeicosatrienoic acid; HETE, hydroxyeicosatetraenoic acid; DHT, dihydrotestosterone; LTD, leukotriene D; LTC, leukotriene C; LXA, lipoxin A; LXB, lipoxin B. See text for references.

8.7 Renal Actions of the Different Prostanoids

Mediator	**Main Source**	**Primary Effects**
PGE_2	Tubular epithelial cells Interstitial cells	Renal vasodilation Relaxation of mesangial cells Modulation of glomerular capillary ultrafiltration coefficient Stimulates renin release from juxtaglomerular apparatus Antagonizes hydroosmotic effect of ADH in collecting tubular epithelial cells Inhibits sodium chloride reabsorption Mediates renal response to loop diuretics
PGI_2	Vascular and glomerular endothelial cells	Renal vasodilation Relaxation of mesangial cells Stimulates renin release from juxtaglomerular apparatus
$PGF_{2\alpha}$	Mesangial cells	Contracts smooth muscle Glomeruli
TXA_2	Glomeruli	Contracts smooth muscle Contracts mesangial cells

ADH, antidiuretic hormone; TXA, thromboxane A; PGE, prostaglandin E; PGI, prostaglandin I; PGF, prostaglandin F.

arterioles. Fortunately, their enhancement of renal PG release locally opposes their constrictor effects. The vasodilatory action of PGs on the afferent arteriole serves to maintain renal perfusion, whereas their relaxant effects on mesangial cells maintains the effective surface area for filtration.[638] Inhibition of PG generation in these circumstances is associated with a dramatic fall in RBF and GFR.[645–648] Vasodilator PGs, in particular PGI_2, may also counteract the vasoconstrictor responses to calcium in human subjects.[638] In addition to modulating the effects of vasoconstrictors, endogenous PGs mediate the actions of some vasodilator agents. These include a role for PGI_2 in mediating the vasorelaxant actions of dopamine[650] and magnesium[651] in humans.

Finally, PGs synthesized from the MD can trigger renin release,[652] which leads to increased Ang II levels. Ang II preferentially constricts the glomerular efferent arteriole, thus increasing intraglomerular pressure and, ultimately, maintaining GFR in volume-contracted conditions.[653] This response is further reinforced by the PGE_2-induced afferent vasodilation. In contrast, TXA_2 exerts a negative effect on renin release.[654] However, inhibition of COX activity reduces plasma renin activity, suggesting that the predominant influence of prostanoids is stimulatory. PG-mediated renin release is independent of β-adrenergic mechanisms.[655] It has been recently reported that a decrease in extracellular tonicity leads to renin release through a mechanism involving aquaporin 1–mediated water influx in juxtaglomerular cells and PG-dependent formation of cAMP and activation of PKA.[645]

Solute Excretion Infusion of arachidonic acid or the COX products PGE_2 or PGI_2 directly into the renal artery results in natriuresis.[656,657] Natriuresis is largely a direct tubular phenomenon originating in the distal nephron.[657] PGE_2 has mild or no effects on sodium transport in the proximal tubule and most segments of the ascending limb of Henle, with the exception of the medullary thick ascending limb in some species.[658] This lack of effect is in keeping with both the low rates of PG production and the low density of PG receptors in these nephron segments.[597,598] Under normal circumstances, inhibition of COX does not result in alteration of sodium delivery out of the loop of Henle to the early distal tubule.[659] PGE_2, however, has significant effects on sodium transport in the collecting duct, where it inhibits transepithelial sodium transport.[656,658] In fact, in most mammalian species, the collecting ducts are the major nephron segments responsible for PG synthesis[597,598] and, along with the MTAL, express the majority of receptors for PGE_2 in the kidney.[660,661]

There is evidence that PGE_2 exerts its inhibitory effect on rabbit CCD sodium transport by at least two mechanisms. The first involves inhibiting principal cell basolateral Na^+-K^+-ATPase activity[662–664] and the second by directly decreasing the open probability of the apical amiloride-sensitive sodium channels.[665,666] PGE_2 utilizes multiple signal transduction pathways in the CCD. These include increase in intracellular Ca^{2+}, activation of PKC, and modulation of cAMP levels.[584] The inhibitory effects of PGE_2 on sodium transport in the thick ascending limb probably involve inhibition of adenyl cyclase.[667] Through G_i-coupled EP_3 receptor expressed in the thick ascending limb,[668,669] PGE_2 also blocks the phosphaturic action of PTH in the proximal tubule.[670] Recent evidence obtained from a randomized, placebo-controlled, crossover study in healthy humans suggest that PGs may modulate sodium excretion through ENaC regulation in the distal nephron.[671] Natriuresis may also be regulated by renal medullary COX-derived prostanoids acting in a paracrine manner. The prostanoid receptors regulating renal medullary blood flow through the descending vasa recta seem to be EP2, EP4, and/or IP receptors.[672] The importance of EP2 and IP receptors has been confirmed to be associated with salt-sensitive hypertension in animal models of EP2 and IP receptor deficiency.[673,674] Expression of EP3 in the renal medulla was shown to be induced by hypertonicity, suggesting a role for this receptor as well in natriuresis and protection of the renal medulla. EP3 activation leads to inhibition of Na^+-K^+-$2Cl^-$ transporter and aquaporin 2.[675]

Sodium loading is associated with an increase in urinary PG excretion, yet PGs are not important in the regulation of sodium balance in normal euvolemic subjects. However, in circumstances associated with sodium retention and compromised renal function, PGs play a significant role. In fact, high-salt diet increases renal medullary COX-2 and microsomal prostaglandin E synthase-1 (mPGES-1) expression to maintain blood pressure homeostasis.[676–678] Inhibition of PG synthesis or blocking their effects in such conditions is associated with sodium retention.[647,679,680] Administration of furosemide is associated with increased PG excretion, which is, in part, mediated by a direct action on tubular cells.[681,682] Administration of NSAIDs diminishes the natriuretic action of furosemide and other loop diuretics, suggesting a role for PGs in mediating the action of these agents. This cannot be the sole mechanism, however, for the natriuretic response to diuretics outlasts the increase in PG excretion.

Water Excretion PGs, especially PGE_2, affect water transport in the collecting duct in many ways. PGs may indirectly regulate water excretion by a reduction of the corticomedullary osmotic gradient via inhibition of solute transport in the thick ascending limbs or by increase in renal medullary blood flow. In fact, during physiologic stress, PGE_2 dilates descending vasa recta, thereby buffering the constrictor effects of Ang II, AVP, and catecholamines, which is vital to prevent hypoxic damage to renal medullary cells.[683] Moreover, PGs of the E series blunt the hydraulic conductivity response of the collecting duct to AVP.[684,685] In fact, in vivo infusions of arachidonic acid or PGE_2 induce water diuresis, whereas inhibition of PG synthesis potentiates the urinary hyperosmolality caused by AVP.[686] However, in the absence of vasopressin, basolateral PGE_2 actually increases osmotic water reabsorption.[687,688] These effects on water conductivity in the collecting ducts have been explained by changes in cAMP accumulation. AVP mediates the increase in water conductivity in the collecting duct through increased cAMP generation.

Studies on the effect of PGE_2 on cAMP metabolism in this nephron segment demonstrated that PGE_2 could both stimulate basal cAMP generation and suppress AVP-stimulated cAMP generation.[689,690] The inhibitory effects of PGE_2 on AVP-stimulated cAMP generation and water conductivity in the collecting duct are probably mediated through the EP_3 receptor, as discussed previously.[675,690,691] In addition to affecting water flow via modulation of cAMP levels, PGE_2 has been shown to inhibit AVP-induced water conductivity by activation of PKC and elevation of intracellular calcium.[619,692]

Application of basolateral PGE_2 probably increases water absorption in the collecting duct by stimulating cAMP production.[687,688] The EP_4 receptor, which is found on the epithelial cells of the ureter, bladder, and collecting duct, is coupled to the G_s-stimulated cAMP signaling pathway.[625,693] This suggests that an EP_4 receptor mediates cAMP-stimulated water absorption in the collecting duct. Recently, PGE_2 was shown to mediate lithium-induced polyuria by downregulating the expression of aquaporin 2 and the Na^+-K^+-$2Cl^-$ cotransporter (NKCC2) in the medulla but not in the renal cortex.[694]

Another facet of the PGE_2-AVP interaction is that AVP acutely stimulates endogenous PGE_2 production by the collecting duct. This effect has been demonstrated in rats[695,696] and the current consensus is that it also occurs in humans.[696,697] It also suggests that PGE_2 participates in a negative feedback loop, whereby endogenous PGE_2 production dampens the action of AVP. In agreement with a functional role for the increase in urinary PGE_2 production seen during AVP infusions are numerous observations of enhanced renal concentrating ability in animals or humans pretreated with inhibitors of PG production.[698,699] Given that the concentration of AVP needed to stimulate PGE_2 production is 10 to 100 times the concentration needed to maximally stimulate water conductivity, it is controversial whether AVP plays a physiologic role in PGE_2 generation.[700] At these concentrations, AVP has been shown to acutely increase intracellular calcium and activate PKC, via activation of phospholipase C.[700,701]

Other Effects on Renal Function The tubuloglomerular feedback (TGF) response is modulated by multiple autacoids and hormones including ATP, Ang II, NO, and PGs, including PGE_2, PGI_2, and TxA_2.[702,703] Under basal conditions, MD COX-2 directly modulates TGF response, particularly through TXA_2,[702] with little contribution of COX-1, as well as via inhibition of nNOS-dependent NO.[704] When subjected to low-dose chronic Ang II, the increase in TGF response is mediated by the local release of vasoconstrictive COX-1 PGs.[705] These studies suggest that: (1) both COX isoforms regulate TGF but (2) their contribution differs in various settings.

Clinical Pathophysiologic Role of Prostaglandins in the Kidneys

PGs, through their vasodilator effects, play a salutary role in maintaining RBF and GFR in several prerenal conditions such as hemorrhage, septic shock, cirrhosis, and low cardiac output states. Studies in patients with congestive heart failure have confirmed that enhanced PG synthesis is crucial in protecting kidneys from the effects of elevated vasoconstrictor levels in these patients.[706] Renal artery stenosis is another condition associated with increased renal PG secretion[707] that may locally act to enhance renal perfusion. Administration of COX inhibitors in these settings with renal hypoperfusion is associated with adverse effects on RBF and GFR.[708]

With regard to intrinsic renal diseases, COX products have been implicated in modulating or mediating renal injury (or both). Single nephron GFRs increase significantly after renal ablation and are associated with increased glomerular synthesis and urinary excretion of prostanoids by the remaining nephron.[709,710] In this model of renal ablation, increased expression of COX-2 has been described and inhibition of COX-2 was associated with amelioration of the renal functional changes associated with renal ablation.[709,710] Similar results were observed with omega-3 fatty acid[711] or flax oil[712] supplementation after renal ablation. Selective inhibition of TXA_2 synthesis is associated with an increase in GFR, lessening of proteinuria, and preservation of renal histology.[713,714] In addition, COX-2 inhibition was also found to slow progression in the rat model of polycystic kidney disease.[715] Dietary soy protein was recently shown to decrease production of prostanoids and expression of COX in a model of polycystic kidney disease and to be associated with reduced disease progression.[716]

Enhanced TXA_2 production has been implicated in the pathophysiology of the intense vasoconstriction that characterizes the obstructed kidney[717,718] and in mediating the decrease in RBF and GFR that occurs in the early phase of nephrotoxic serum nephritis.[609,610,719,720] In patients with lupus nephritis, an inverse relation between TXA_2 biosynthesis and GFR has been proposed.[721,722] In this setting, renal function improved after short-term therapy with a TX receptor antagonist, but not with aspirin.[721,723] In addition, administration of TXA_2 synthesis inhibitors or receptor antagonists has been associated with improved renal function in animals with allograft rejection and cyclosporine toxicity.[638] Although basal COX-2 levels are important for podocyte survival, overexpression of COX-2 in podocytes leads to increased albuminuria and glomerular injury, partly through activation of the thromboxane receptor.[724,725] Jia et al. also recently showed that cisplatin-induced renal injury is mediated by activation of the COX-2/mPGES-1 pathway, which may offer a new therapeutic target for management of the adverse effect of cisplatin chemotherapy.[726]

Ischemia/reperfusion injury has been shown to be worsened by COX-2 inhibitors or in COX-2 knockout mice, suggesting that PGs protect the kidney against acute renal injury.[727] Recent studies show that EP4 and EP2 receptor agonists improve renal function and/or increase survival rate of a rat model of acute renal failure, supporting a protective role of EP2 and EP4 receptors in preventing the progression of kidney failure.[728] Lithium treatment was also shown to improve outcome of renal ischemia/reperfusion

injury through NO and/or COX pathways and represents a promising therapeutic approach to boost renal viability and function after ischemia/reperfusion injury in the setting of transplantation.[729] However, other groups reported a beneficial effect of COX-2 inhibitors that could be acting through immune modulation.[730,731] These opposite findings could be partly explained by differences in the experimental models.

The role of COX products in mediating diabetic nephropathy remains controversial. Vasodilator PGs may contribute to the hyperfiltration that occurs in early stages of diabetic nephropathy, whereas TXA_2 may play a role in the subsequent development of albuminuria and basement membrane changes.[732,733] MD COX-2 expression is increased in models of hyperfiltration, such as high-protein diet and diabetes. COX-2 inhibition decreases hyperfiltration and proteinuria, and inhibits development of glomerular sclerosis in experimental diabetes.[734,735] Interestingly, inhibition of COX-2 in patients with type 1 diabetes mellitus reduces, but does not correct, hyperfiltration in subjects whose baseline GFR was $\geq$135 mL/min^{-1}/1.73 m^{-2}.[736] However, in response to COX-2 inhibition, women with type 1 diabetes mellitus exhibited a significant renal hyperfiltration response suggesting that women have a greater dependence on vasodilatory PGs than men.[737] A role for decreased PGI_2 synthesis in type IV renal tubular acidosis associated with diabetes mellitus has also been suggested.[738] The increased renal production of TXA_2 and PGI_2 in type 2 diabetes has also been suggested as a role for these compounds in the pathogenesis of diabetic nephropathy.[733,739,740] Recently, the lipocalin-type PGD2 synthase (L-PGDS) knockout mouse was shown to develop structural changes associated with diabetic nephropathy, such as glomerular hypertrophy, fibrosis, and basement membrane thickening.[741] Urinary excretion of L-PGDS, found at elevated levels in type 2 diabetic patients, correlates with the progression of diabetic nephropathy and reflects the underlying early increase in glomerular damage.[742]

Diminished vasodilator renal PG synthesis has also been implicated in the pathogenesis of the severe sodium retention that occurs in patients with the hepatorenal syndrome.[743] Pregnancy is associated with increased glomerular synthesis and urinary excretion of PGE_2, $PGF_{2\alpha}$, and PGI_2.[744] Augmented renal vasodilator PG production does not appear to regulate GFR and RBF in normal pregnancy; however, diminished synthesis of PGI_2 has been demonstrated in human and animal models with pregnancy-induced hypertension.[745–747] A beneficial effect of reducing TXA_2 generation, while preserving PGI_2 synthesis, by low-dose (60 to 100 mg per day) aspirin therapy has been proposed in patients at risk for pregnancy-induced hypertension.[748,749] In patients with hypertension, COX inhibition by NSAIDs is associated with increased salt retention and resistance to the diuretic action of thiazides and furosemide.[750,751] Short-term use of some NSAIDs was found to increase the mean arterial pressure of hypertensive patients.[752,753] On the other hand, attempts to treat hypertension with PG analogs have generally been disappointing.[754,755]

Finally, chronic inhibition of COX by regular use of NSAIDs leads to gastrointestinal toxicity and may increase the risk of chronic renal disease, especially in older patients and patients with heart disease.[756–758] Selective COX-2 inhibitors have been developed and have been shown to spare gastric PG production. These nontraditional COX-2 selective anti-inflammatory agents might have represented a significant advance for the treatment of acute and chronic inflammatory disorders[759–761]; however, the safety of their use has been placed into question after two large prospective cohorts in elderly patients showed an increased risk of cardiovascular events in patients on selective COX-2 inhibitors versus those on NSAIDs.[762,763] Clinical studies have also demonstrated that selective COX-2 inhibitors can even reduce GFR and RBF in physiologically stressed volunteers or patients.[764,765]

In summary, prostanoids exert diverse and complex functions in the kidney under physiologic and pathologic conditions. Further understanding of pathways involving and regulating COX, prostanoid synthases, and prostanoid receptors should provide targets for pharmacologic treatments of renal disease.

LIPOXYGENASE PRODUCTS

Biosynthesis and Metabolism

Lipoxygenases (LOs) comprise a family of enzymes capable of mediating selective lipid oxidation.[766] Enzymatic lipoxygenation of arachidonic acid leads to the generation of leukotrienes (LTs), lipoxins (LXs), and hydroxyeicosatetraenoic acids (HETEs). Formation of these compounds is initiated by 5-, 12-, or 15-lipoxygenase, whereby a hydroperoxy group is introduced onto arachidonic acid at carbon-5, carbon-12, or carbon-15, respectively, to yield the corresponding 5-, 12-, or 15-hydroperoxytetraenoic acid (HPETE). HPETEs are unstable compounds that are transformed into the corresponding 5-, 12-, and 15-HETE, which, in turn, undergo enzymatic modification leading to the generation of the various LTs and LXs. The 5-lipoxygenase pathway is a major route of arachidonic acid metabolism in the polymorphonuclear cells and macrophages leading to the formation of 5-HETE and LTs.[767–769] 5-Lipoxygenase requires activation by a cell membrane-bound protein called the 5-lipoxygenase-activating protein (FLAP).[770] The 15-lipoxygenase enzyme catalyzes the production of 15-HETE and initiates another major pathway of arachidonic acid metabolism in leukocytes. In activated neutrophils and macrophages, sequential lipoxygenation of arachidonic acid at carbons-15 and -5 yields trihydroxy derivatives, the LXs.

Renal Actions of Lipoxygenase Products

In the rat, 5-LOX FLAP + 12-LOX mRNA are present in the glomerulus as leukotriene B_4 (LTB_4) and leukotriene D_4 (LTD_4) receptors.[771] 15-LOX is localized to the distal nephron only.[771] Products of lipoxygenase are classically proinflammatory;

however, lipoxins, 15-HPETE, and 15-HETE exhibit anti-inflammatory activity.[674]

The LTs are potent proinflammatory molecules. LTB_4 has minimal spasmogenic properties, but is the most potent chemotactic substance yet described for polymorphonuclear cells, and promotes their activation and adhesion to the endothelium.[767] It has no significant effects on renal hemodynamics in normal animals, but amplifies glomerular inflammation and proteinuria in animals with glomerulonephritic injury.[773] The peptidyl LTs contract vascular, pulmonary, and gastrointestinal smooth muscle and increase vascular permeability to macromolecules.[767] LTC_4 and LTD_4 exert potent effects on glomerular hemodynamics. In rats, systemic administration of LTC_4 leads to reduction in RBF and GFR.[774] Similarly, infusion of either LTC_4 or LTD_4 in the isolated perfused kidney results in dramatic increase in renal vascular resistance and reduction in GFR.[775] LTD_4 mediates these effects by causing a significant increase in efferent arteriolar resistance, leading to a fall in glomerular plasma flow rate (Q_A), and a rise in glomerular capillary hydraulic pressure (P_{GC}). In addition, it markedly reduces the glomerular capillary ultrafiltration coefficient (K_f) and, therefore, its overall effect is to decrease single nephron GFR.[776] LTC_4 and LTD_4 contract mesangial cells[777,778] and LTD_4 stimulates neutrophil adhesion to these cells.[779] In both rats and humans, specific mesangial cell LTD_4 receptors have been identified. Intracellular signaling for LTD_4 in these cells involves receptor-activated phosphatidylinositol diphosphate (PIP_2) hydrolysis, release of inositol phosphates, and increased intracellular calcium concentrations.[780,781]

LXA_4 attenuates LTB_4-induced neutrophil chemotaxis and inhibits natural killer cell cytotoxicity.[767,769] The effects of LXA_4 are mediated primarily by functional high-affinity LXA_4 receptors.[782] In rat glomerular mesangial cells, LXA_4 competes with LTD_4 at a common receptor whereby LXA_4 mediates partial agonist–antagonist effects.[783] Different LXs display distinct effects on renal hemodynamics.[769,784,785] In rats, LXA_4 causes a selective decrease in afferent arteriolar resistance, thereby increasing RBF, glomerular capillary pressure, and GFR. The LXA_4-induced increase in GFR, however, is partially offset by its mild effect in decreasing K.[783,785] The vasodilator actions of LXA_4 are mediated by prostaglandins.

Role of Lipoxygenase Products in Kidney Disease

LTs are increasingly recognized as major mediators of glomerular hemodynamic and structural deterioration during the early phases of experimentally induced glomerulonephritis.[784,786,787]

Mesangial cell (MC) proliferation is a central event in the pathogenesis of glomerulonephritis. LTD_4-induced proliferation of mesangial cells is modulated by LXA_4.

Increased glomerular generation of LTB_4 and peptidyl-LTs has been demonstrated in several models of glomerular injury.[784,786,787] LTB_4 probably worsens glomerular injury by augmenting leukocyte recruitment and activation and the peptidyl LTs, by depressing K_f and GFR.[773–779] Selective blockade of the 5-lipoxygenase pathway, in the course of glomerular injury, is associated with significant amelioration of the deterioration of renal hemodynamic and structural parameters.[788,789] In addition, dietary deprivation of essential fatty acids, which results in arachidonic acid and eicosanoid deficiency, confers protection against the histopathologic and the functional consequences of immune-initiated injury in the glomerulus.[790] In hemodialysis patients, 5-LOX activity and expression are significantly increased in peripheral blood monocytes, and can be markedly suppressed by polyunsaturated fatty acid supplementation.[1] In human glomerulonephritis, 5-lipoxygenase and 5-LO-activating protein (FLAP) mRNA expression have been detected in kidney biopsy specimens from patients with immunoglobulin A (IgA) nephropathy and mesangial proliferative glomerulonephritis and were associated with a clinically worse renal status.[791] Urinary LTE_4 levels are also elevated in patients with active SLE.[792] A pathophysiologic role for LTs has also been described in experimental acute allograft rejection,[793] cyclosporine toxicity, and acute ureteral obstruction.[787] LXA_4 and 15-S-HETE are also generated during experimental glomerular injury and may exert salutary effects on glomerular function by antagonizing the proinflammatory actions of LTs.[784,794–797] In animals with experimental glomerulonephritis, 5-lipoxygenase inhibition results in marked reduction in proteinuria and preservation of GFR.[786,798] The binding of 5-lipoxygenase to FLAP is a prerequisite for subsequent formation of leukotrienes from arachidonic acid.[799] The use of a FLAP antagonist has been shown to reduce proteinuria and restore glomerular size selectivity in human glomerulonephritis.[800] 12/15-lipoxygenase (12/15-LO) expression is increased in high glucose (HG)-stimulated MC and in experimental diabetic nephropathy.[801–803]

ENDOTHELIN

Endothelin (ET), originally isolated from porcine aortic endothelial cells, is an extremely potent and long-lasting vasoconstrictor.[804] Initially, ET's effect on vascular tone regulation was the focus of research. Later, other actions—such as ET effects on cell growth and proliferation, ion transport, eicosanoid synthesis, renin and ANP release, fibrosis, and inflammation—emerged as important factors linking ET to diseases.[771,805,806] The kidney is an important site of ET production and expresses a high density of ET receptors.[807] Endothelin may, therefore, act in an autocrine and paracrine manner to influence renal hemodynamics, tubular function, and mesangial cell biology.

Biochemistry, Synthesis, and Receptor Biology

The term endothelin refers to a family of homologous 21-amino acid vasoconstrictor peptides found in three distinct isoforms: ET-1, ET-2, and ET-3. In humans, ET isoforms

are encoded by three separate genes located on chromosomes 6, 1, and 20, respectively.[808,809] The initial ET peptide translation product is a large (approximately 200 amino acids) isopeptide-specific prohormone named preproendothelin. Posttranslational processing of this prohormone to mature ET requires two steps. The first involves its proteolytic cleavage by dibasic pair-specific endopeptidases on Lys-Arg and Arg-Arg pairs, which respectively flank the N- and C-terminals of the preproendothelin molecule, to yield an intermediate 38- or 39-amino acid proET polypeptide. The subsequent step is accomplished by proteolytic cleavage of proET between Trp^{21} and Val^{22} by a putative endothelin-converting enzyme (ECE).[810] All ET isopeptides have a hairpin loop configuration structure imparted by two intrachain disulfide bonds bridging amino acid residues 1 through 15 and 3 through 11, the reduction of which leads to a twofold loss of biologic activity.[811] The two endothelin isoforms ET-2 and ET-3 differ from ET-1 in 2 and 6 amino acid residues, respectively. The three ET isoforms are highly homologous in their amino acid sequences and tertiary structure to certain scorpion and snake venoms, the sarafotoxins, which suggests common genetic evolutionary origins.[812] Although all isoforms of ET are potent vasoconstrictors, there are significant cell- and tissue-specific differences in the secretion of, and biologic responses to, different isoforms.[813,814]

ECEs are metalloproteases that belong to the M13 group of proteins, a family including several proteins such as neutral endopeptidases, X-converting enzyme, ECEs, and others.[815] Three major ECE isoforms have been identified to date and named ECE-1, ECE-2, and ECE-3, of which ECE-1 and ECE-2 are the most prominent.[820] The ECEs differ from each other regarding cell/tissue distribution, localization, pH of optimal activity, and substrate specificity.[815] Four variants of ECE-1 have been reported in humans (ECE-1a, ECE-1b, ECE-1c, and ECE-1d), and two ECE-2 variants (ECE-2a and ECE-2b).[809] Both ECE-1 and ECE-2 cleave big ET-1 more efficiently than either big ET-2 or big ET-3. ECE-1 is expressed ubiquitously with highest expression in endothelium, lung, ovary, testis, and adrenal medulla, whereas ECE-2 is expressed in neural tissues. ECE-3, which selectively cleaves ET-3, has been found in the bovine iris.[816] ECE-1 was located at the cell surface and on intracellular vesicles.[817] ECE-1 also hydrolyzes BK, substance P, and insulin.[809] Not all the enzymes responsible for the final step of posttranslational processing of ET-1 have been identified. Current evidence suggests that other proteases may be involved in the final processing of ET, because mice lacking ECE-1 and ECE-2 can still produce mature ET-1.[818] In addition, alternative, ECE-independent pathways have been suggested possibly involving tissue chymases and non-ECE metalloproteinases.[819] Recently, several inhibitors specific for the ET-converting enzyme have been reported.[820]

Initial studies identified ET on the basis of its release from large-vessel endothelial cells. Since then, ET immunoreactivity has been detected in the kidney, spleen, skeletal muscle, and lung.[821] In the kidney, the arcuate arteries, veins, glomerular arterioles, and capillaries are a rich source of ET.[20] In the glomerulus, there is evidence for ET secretion by mesangial, endothelial, and epithelial cells.[823] In the rest of the nephron, the internal medullary collecting duct (IMCD) has been demonstrated to be a major site of ET-1 and ET-3 production.[823–825]

Normally, blood vessels produce very little ET, and the normal circulating level of ET is extremely low.[24] Secretion of ET by endothelial cells is controlled at the level of transcription and these cells do not store ET for future release.[810,827] Thus ET-1 probably acts primarily as a paracrine/autocrine mediator and not as a circulating hormone.[809] ET peptide secretion is upregulated by various humoral mediators, such as thrombin, BK, insulin, Ang II, AVP, endotoxin, IL-1, TGF-β, and tumor necrosis factor (TNF).[828] These mediators may be responsible for the increase in ET observed in various pathophysiologic states. Hypoxia is also an important stimulus for ET production.[829] In the kidney, increasing osmolarity serves as a stimulus for tubular production of ET.[830] On the other hand, NO, ANP, and prostacyclin exert inhibitory influences on ET synthesis and release.[831] In summary, mesangial cells' ET-1 release is under complex regulation, with vasoconstrictor, profibrotic, inflammatory, and proliferative agents augmenting its release, whereas vasorelaxant agents tend to inhibit its production.[832]

Endothelins exert their actions through two major receptor subtypes known as ET_A and ET_B receptors. These belong to the superfamily of G-protein coupled receptors and have been identified in a variety of tissues.[833] A third type of ET receptors, ET_C, has been cloned from Xenopus laevis.[834] Both ET_A and ET_B receptors have widespread distribution and are abundantly expressed in the kidneys. The ET_A receptor is believed to be involved in vasoconstrictive and proliferative responses to ET-1 and binds endothelins with the following affinity: ET-1 > ET-2 > ET-3.[809] ET_B receptor, on the other hand, is a nonisofrom selective receptor and recognizes all three ET isoforms with equal affinity. Its activation induces transient vasodilation. The recently cloned ET_C receptor binds preferentially ET-3 and its stimulation causes NO release.[823,833,834] Both ET_A and ET_B receptors are expressed on vascular smooth muscle.

The kidney expresses abundant mRNA transcripts for ET_A and ET_B receptors.[823,833,835] Expression of ET receptors is especially prominent in the renal artery, glomerular arterioles, endothelium, mesangium, vasa recta bundles, and collecting duct.[771,823,833] Both receptor subtypes are expressed in the glomerulus. Vascular smooth muscle cells of the arcuate arteries and the renal medullary interstitial cells display ET_A receptors. Epithelial cells of the cortical, inner medullary, and outer medullary collecting ducts have ET_B receptors.[823]

ET receptor activation leads to diverse cellular responses involving a chain of receptor-mediated amplification of effectors. At the ET_A receptor, these responses include the phospholipase pathway (PLC) leading to the formation of inositol triphosphate and diacylglycerol and to the release of

stored calcium into the cytosol. This causes cellular contraction and vasoconstriction. ET-mediated effects persist after dissociation of ET from its receptor, probably because of persistently high intracellular calcium or prolonged activation of signaling pathways.[815] Endothelial cells can express ET_B receptors linked to formation of NO and prostacyclin and mediate endothelium-dependent vasorelaxation.[836] In nephron segments and other renal structures, ET mediates its effects via a multiplicity of intracellular signal-transduction pathways that involve phospholipase activation, tyrosine phosphorylation of proteins, and elevation of intracellular free calcium.[837]

Biologic Effects of Endothelin in the Kidney

Endothelin effects on the kidney are broadly divided into vascular and tubular. Endothelin is a potent renal vasoconstrictor, as much as 30-fold more potent in this regard than Ang II.[771,804,805,836,837] Indeed, the renal vasculature is more sensitive than other vascular beds to the vasoconstrictive effects of ET-1.[838] In the isolated perfused kidney, ET-1 administration reduces GFR and causes a dose-dependent increase in renal vascular resistance. In whole animals, systemic ET infusion induces a decline in cortical blood flow, GFR, and urine volume[771,805]; however, some studies have shown differential regulation of blood flow between the cortex and the medulla with exogenous ET-1 infusion, showing cortical vasoconstriction and NO-dependent medullary vasodilation.[839,840] The direct effects of ET-1 on preglomerular and postglomerular resistances are quantitatively similar at lower doses, so the glomerular transcapillary hydraulic pressure and GFR are maintained.[841] However, at higher doses, a greater increase in preglomerular resistance occurs that, in addition to a decrease in glomerular capillary ultrafiltration coefficient (K_f), leads to a decline in GFR.[841,842] Dihydropyridines inhibit ET-mediated vasoconstriction exclusively in the afferent arterioles.[841] Renal hemodynamics may also be influenced by indirect effects of ET, such as modulation of arachidonic acid metabolism and renin release.[842] Local generation of prostaglandins (PGs), such as $PGF_{2\alpha}$, may mediate some of the vasoconstrictor effects of ET.[843] ET-1 directly inhibits renin release, but the net renin secretory response in vivo varies with the ET-1 dose, as well as with the state of activation of intrarenal baroreceptors and the MD-mediated pathway.[842] In humans, similar effects have been shown on renal vasculature, with renal vasoconstriction and reduction in RBF and GFR, whereas no studies addressed the effect of ET-1 on intrarenal distribution of blood flow.[838]

At the tubular level, ET-1 seems to play an important role in volume regulation. Despite compromise of RBF and GFR, infusion of nonpressor doses of ET in animals is associated with an increase in urinary flow and Na^+ excretion.[771,805] In addition, studies in the isolated perfused kidney have shown that ET increases Na^+ excretion despite a dramatic decline in GFR.[805] These effects on Na^+ and water balance are largely due to the ability of ET to reduce Na^+-K^+-ATPase activity and reversibly inhibit AVP-stimulated cAMP generation and water transport in the IMCD.[805,844] In addition, a natriuretic role for ET-1 is demonstrated in animals through ET_B receptors engaging NO and leading to inhibition of chloride transport in the MTAL of Henle's loop.[845] Furthermore, ET effect on epithelial amiloride-sensitive sodium channel is dose-dependent including activation and inhibition through both ET_B-mediated and non–ET_B-mediated effects.[846,847] The high concentration of ET receptors in the human inner medulla[835] and the recent observations suggesting ET production by human IMCD cells[825] justify the assumption that a similar physiologic role for intrarenal ET may also be operative in humans. ET also affects Na^+ balance indirectly by stimulating release of ANP.[848]

ET is well known to induce contraction of MCs in culture and results of micropuncture experiments demonstrate that ET-1 directly reduces the coefficient of ultrafiltration.[849] ET is also recognized as a growth factor with mitogenic effects on MCs in culture, inducing changes in MC phenotype and gene expression.[771,805,833] Abundant evidence points to a pivotal role for ET-1 in the biology and, particularly, the pathology of the renal mesangium. The peptide is produced by MC and can, in turn, act on MCs to elicit proliferation, hypertrophy, contraction, and/or extracellular matrix accumulation. These effects are mediated in large part through activation of ET_A and particularly involve PKC and MAPK. Excessive ET-1 production by, and action on, MCs is of pathogenic importance in glomerular damage in animal models of glomerulonephritis (GN), diabetes, and hypertension (Fig. 8.11).[832]

Studies with ET receptor antagonists demonstrated that, in the animal kidney, ET-1-induced reductions in total RBF are mediated by ET_A receptor, whereas selective medullary vasodilation is mediated by ET_B receptor.[850,851] In humans the situation is less clear. Antagonism studies have suggested that ET-1 effects through ET_A receptors may not be major contributors to the maintenance of renal vascular tone in health, whereas ET-1 vasodilatory effects through ET_B receptors are important.[852]

Endothelins in Kidney Disease

Endothelins have been implicated in a variety of diseases including cardiovascular (CV) and renal diseases, neoplasia, wound healing, and others. ET-1 has been implicated in the pathophysiology of congestive heart failure, showing cardiac pro-arrhythmic effects and promoting fibrogenesis and ventricular remodeling.[853,854] Despite its central role in CV disease pathogenesis, antagonism did not show any clear beneficial effect.[815]

The role of ET-1 in the pathogenesis of hypertension has been evoked by several studies showing a cross-talk between all pressor and vasoconstrictor systems including ET, the renin-angiotensin system, and the sympathetic nervous system.[815] Collectively, study results suggest that dysregulation of the endothelin system contributes to multisystem complications of hypertension.[855–857]

At the renal level, various diseases were associated with a dysfunctional endothelin system, including progression

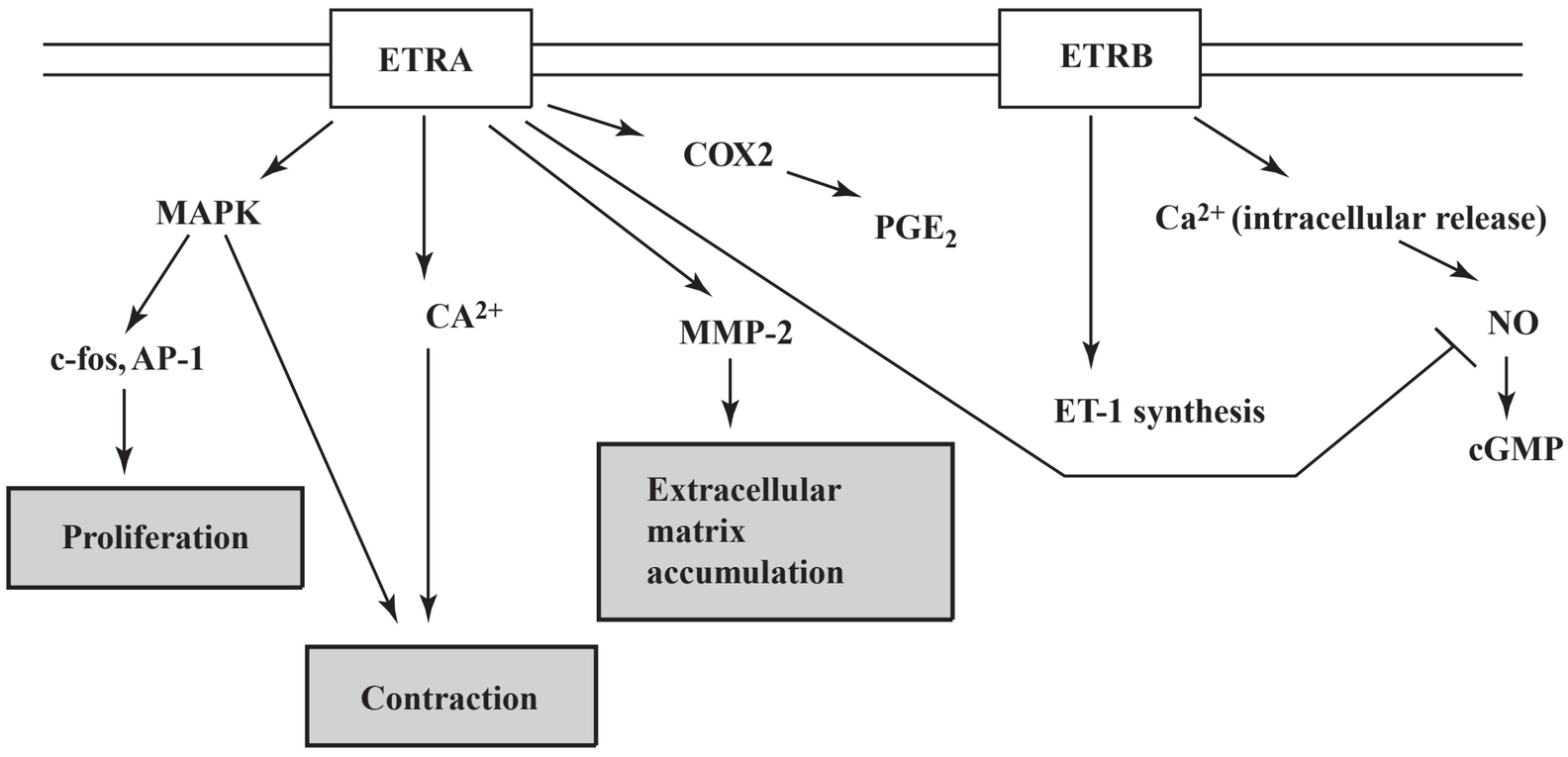

FIGURE 8.11 Schematic representation of biologic effects mediated by endothelin receptor A (ETRA) and endothelin receptor B (ETRB) in mesangial cells. The net effect of ETRA activation is mesangial cell contraction, extracellular matrix accumulation, and proliferation. The net effect of activation of ETRB tends to be vasorelaxant as well as causing autostimulation of ET-1 production. *AP-1*, activator protein-1; *MMP-2*, matrix metalloproteinase-2. (From Sorokin A, Kohan DE. Physiology and pathology of endothelin-1 in renal mesangium. *Am J Physiol Renal Physiol.* 2003;285:579, with permission.)

of chronic kidney disease, hypertension, and proteinuria. Declining renal function is associated with an increase in plasma ET levels.[858] Patients undergoing hemodialysis have higher ET levels than do patients undergoing peritoneal dialysis or uremic patients not yet on renal replacement therapy.[859] Erythropoietin administration, as well as acute volume contraction during hemodialysis, may contribute to the elevation of ET-1 level in patients undergoing hemodialysis.[860] Although the significance of elevated plasma levels of a primarily autocrine or paracrine hormone (ET) remains questionable at present, ET-secreting hemangioendotheliomas have been shown to produce marked hypertension.[861]

A pathophysiologic role for ET has been reported in several conditions affecting the kidney.[805,823,862] Urinary ET-1 excretion increases in patients with several forms of chronic progressive glomerulopathies.[862] MCs' ET-1 production is increased in rat models of immune complex GN, nephrotoxic serum nephritis, and mesangial proliferative GN. In addition, MC ET-1 production is augmented in human SLE and urinary ET-1 excretion is proportional to the severity of human mesangial proliferative GN.[832]

Although there is no direct evidence in vivo that MC ET-1 production is increased in diabetic nephropathy (DN), there are in vitro data suggesting that MC ET-1 synthesis is increased by hyperglycemia.[832] Studies suggest that MC ET-1 production is enhanced in DN and that excessive ET-1 action in the diabetic glomerulus can cause enhanced matrix accumulation, proteinuria, and reduced GFR.[832]

In animals subjected to surgical reduction of renal mass, ET-1 gene expression increases in parallel with proteinuria and glomerulosclerosis.[863] Proteinuria is currently known to be a renal and CV risk factor, and its reduction may confer CV protection.[838] Upregulation of the renal ET system exacerbates proteinuria. Implicated mechanisms include increased glomerular capillary hydrostatic pressure and permeability.[838] Chronic selective ET_A receptor blockade was associated with reduction of microalbuminuria in diabetic patients.[62] Renal ischemia, on the other hand, is a potent stimulus for ET-1 production.[63] ET-1 is upregulated after renal ischemia/reperfusion injury and may contribute to the injury by prolonging vasoconstriction. It is known that ET_A-selective, but not ET_B-selective, antagonist is protective against renal IR injury.[64] ET-1 aggravates cell damage through the activation of Na^+/Ca^{++} exchanger suggesting that Ca^{++} may play a critical role in hypoxia/reoxygenation-induced renal tubular injury.[65] Other renal diseases involving the ET system include: radiocontrast-induced renal injury,[66,823] cyclosporine-mediated nephrotoxicity,[67] immune nephritis, and the rat remnant kidney model.[68] However, data supporting a role for ET antagonists in the treatment of acute or chronic kidney disease in humans are currently lacking.[815]

In summary, ET is a potent vasoconstrictor peptide. In the kidney, it reduces RBF and GFR, contracts mesangial cells, and may function as a paracrine–autocrine factor in modulation of sodium and water balance. It is a potential mediator of growth and proliferative changes within the kidney. It is thought to play a pathophysiologic role in a number of kidney diseases. ET receptor antagonists may prove to be beneficial in certain conditions.

NITRIC OXIDE

NO is a paracrine mediator with a wide spectrum of physiologic actions, including the control of vascular tone, antithrombotic actions, cell cycle regulation, neurotransmission, signal transduction, and inflammation. NO is synthesized during conversion of its physiologic precursor L-arginine

(L-Arg) to L-citrulline.[864,865] This reaction is catalyzed by a family of enzymes known as NO synthases (NOS).[864,866–868] Three NOS isoforms (neuronal [nNOS, NOS1], inducible [iNOS, NOS2], and endothelial [eNOS, NOS3]) have been identified in mammalian tissues. Neuronal nitric oxide synthase (nNOS) was first found in the neuronal cells of the brain, but is also constitutively expressed in the kidney and may be of physiologic importance.[867] iNOS is expressed upon activation of macrophages and other cells. The third isozyme is found in endothelial cells (eNOS) and, like nNOS, is constitutive in nature.[868,869] NO produced from endothelial cells (eNOS-derived) is important as a tonic vasodilator and inhibitor of platelet aggregation and adhesion.

Renal Action of Nitric Oxide

All three NOS isoforms are expressed in the medulla and medullary NO production exceeds that in the cortex.[864] eNOS is found predominantly in renal vasculature, whereas iNOS immunoreactivity has been shown in the preglomerular portion of the afferent arteriole[871] and in glomerular mesangial cells. Isolated rat proximal tubule and inner medullary collecting duct cells express iNOS following stimulation with TNF-α and IFN-γ.[872]

Studies at the Single Nephron Level

NO has been shown to participate in the regulation of renal hemodynamics. The administration of a competitive inhibitor of NO production, L-NMMA, to normal rats causes dramatic glomerular hemodynamic changes, including reduced single nephron plasma flow, augmented afferent and efferent arteriolar resistances, decreased ultrafiltration coefficient, and increased glomerular capillary pressure.[873–876] Chronic oral supplementation with an L-arginine inhibitor in rats caused proteinuria, increased glomerular capillary pressure, and glomerular hemodynamic changes as described previously.[875] These observations suggest that NO might be an important regulator of glomerular capillary pressure and that its dysregulation might be involved in the development of glomerular sclerosis through increases in glomerular capillary pressure.

Dietary supplementation with L-arginine ameliorates the progression of renal disease in rats with subtotal nephrectomy,[876] at least in part because of its inhibitory effects on the development of glomerular hypertension.[877]

Role in Renal Injury

Increasing evidence implicates a role for decreased NO and increased peroxynitrite production in the pathophysiology of reactive oxygen species (ROS)-induced acute kidney injury.[878–880] Furthermore, Ang II promotes the production of O_2 and Ang II synthesis is increased in the kidney when there is a deficiency of NO. Once initiated, these events create a cycle that continues to increase Ang II levels in the glomerular circulation and to raise glomerular capillary pressure.[881] A locally activated renal RAS, in conjunction with increased TGF-1 expression, was shown to be a major feature of renal injury in rats with chronic inhibition of NO synthase.[881] Both exogenous and endogenous NO have protective effects against ischemia/reperfusion-induced renal dysfunction and tissue damage, probably through the suppression of endothelin-1 overproduction in postischemic kidneys.[882]

Therapeutic Implications

Not only do ACE inhibitors decrease Ang II synthesis, they also prevent the degradation of bradykinin, which is an important physiologic molecule involved in the release of NO. With ARBs, blocking the AT_1 receptor favors the synthesis of NO and stimulates factors that allow NO to be biologically more active.[881]

nNOS is abundantly expressed in MD cells, and its expression is stimulated in various high-renin states including salt restriction, administration of loop diuretics, or inhibition of the renin-angiotensin system—some of the same interventions that augment COX-2 expression. Direct evidence in support of MD NOS, presumably nNOS, acting as a positive regulator of renin secretion came from studies in the in vitro perfused juxtaglomerular apparatus (JGA). In this preparation, administration of L-arginine-stimulated renin secretion and NOS blockers almost completely abolished the stimulation of renin secretion by low levels of NaCl.[883] Studies have also demonstrated that tubuloglomerular feedback control of afferent arteriolar resistance is influenced by MD NO production, thereby enhancing autoregulation of RBF, GFR, and renin secretion.[884]

ERYTHROPOIETIN

Erythropoietin (EPO) is a 30.4-kDa glycoprotein hormone that acts on the bone marrow to stimulate red blood cell production.[885] The kidneys produce 85% to 90% of circulating erythropoietin in adults and the liver accounts for the remainder.[885,886] The liver is the major source of erythropoietin in the fetus.[886] In situ hybridization studies performed in anemic or hypoxic animals and erythropoietin-transgenic mice demonstrated that EPO is synthesized by peritubular cells of the renal cortex, particularly at the corticomedullary junction.[886–889] Other tissues were also found to produce EPO (peripheral endothelial cells, vascular smooth muscle cells, neurons, astrocytes, microglia, and cardiomyocytes). EPO receptors (EPO-R), members of the cytokine receptor superfamily, are localized in different parts of the kidney, as well as in the CNS, endothelial cells, solid tumors, liver, and uterus.[890] In erythroid progenitor cells, EPO binds to EPO-R, leading to activation of the JAK2 and downstream signal transduction pathways including STAT5, PI3 kinase, and MAPK.[891] The main stimulus for EPO production and secretion is decreased oxygen supply to renal tissue which most commonly results from anemia or hypoxemia. Decreased oxygen triggers a cascade of reactions mostly mediated by the so-called hypoxia-inducible factors (HIF), which activate a wide set of genes involved in protecting the

kidney from hypoxia including EPO gene.[892] This autocrine/paracrine secretion of EPO helps by decreasing apoptosis and cell necrosis in mesangial and tubular cells subjected to hypoxic (ischemia reflow injury) stress and toxic insult (cisplatinum), suggesting a potential therapeutic use of EPO or EPO analogs in tubular necrosis.[893–895] Extensive evidence indicates that EPO is a pleiotropic cytokine that confers broad tissue-protective properties as part of an innate response to stressors, promotes angiogenesis, and modulates wound healing responses.[896] It seems that SGK1 might contribute to the mediation of EPO effects under ischemic conditions.[897] Conversely, when the kidney is hyperoxygenated, as occurs after red cell transfusion, EPO production is reduced. In addition to modulation by oxygen availability, EPO production is influenced by several cytokines. IL-1 and TNF-α were shown to inhibit EPO mRNA levels and EPO formation in human hepatoma cell cultures and to reduce EPO production in isolated perfused rat kidneys.[898] Secretion of these cytokines by macrophages could contribute to defective EPO production and anemia in infectious or inflammatory diseases. Wang et al. showed that EPO has antioxidative properties in organs affected by diabetes and may prevent incipient microvascular damage in the diabetic retina.[899] Schiffer et al. studied the effects of different EPO molecules on podocyte signaling in vitro and on podocyte survival in an experimental model of diabetic kidney injury. EPO activates pro-survival intracellular pathways in podocytes in vitro, and ameliorates diabetes-induced podocyte loss in vivo.[900]

EPO has the potential to modulate oxygen delivery through regulation of endothelial NO production. In endothelial cell cultures, although short-term exposure to EPO decreases or leaves unchanged eNOS and endothelin-1 expression, the combination of EPO and hypoxia increases EPO-R and eNOS expression, and nitric oxide (NO) and cGMP production, demonstrating a direct effect of EPO on endothelial eNOS and NO production. EPO administration for 14 days in healthy rats increased hematocrit as well as eNOS expression and augmented NO-dependent vasodilatation.[901]

In healthy volunteers, Ang II injection increases EPO secretion in a dose-dependent manner. This effect is neutralized by a selective AT_1 receptor blocker, inferring that the stimulation of EPO by Ang II is probably via AT_1 receptors.[902] It has been postulated that EPO has antinatriuretic action, which could account for the worsening hypertension observed in some patients receiving recombinant EPO. In one study in isolated Wistar rat kidneys, EPO decreased Na excretion, possibly by increasing Ang II production.[904]

Cyanate, a compound that could spontaneously form from urea, reacts with EPO leading to carbamylated EPO, an EPO protein with reduced activity. In renal insufficiency, cyanate can reach levels high enough to reduce the activity of both endogenous and exogenous EPO. This might explain one mechanism of suboptimal responses to recombinant EPO in patients with ESRD on inadequate dialysis. It might also explain the superiority of continuous peritoneal dialysis over hemodialysis in terms of decreasing blood urea nitrogen (BUN) and, at the same time, improving anemia.[903]

INSULIN

Besides inhibiting gluconeogenesis in the proximal tubule, insulin exerts a significant vasodilatory effect on the kidney, thus increasing RPF; this effect appears to be mediated by PGs and partially counteracts the vasoconstrictor effect of Ang II.[905] In contrast, insulin appears to enhance the contractile effect of Ang II on mesangial cells.[906] It also potentiates AVP action in terms of water reabsorption at the collecting ducts by increasing the gene transcription of aquaporin-2 (AQP2).[907] In rats' renal proximal tubule cells, insulin and dopamine receptors interact to regulate renal sodium transport.[908] Studies using primarily cell culture have demonstrated that insulin can directly increase activity of the epithelial sodium channel, the sodium-phosphate cotransporter, the sodium-hydrogen exchanger type III, and Na-K-ATPase.[909]

C-peptide

C-peptide, or connecting peptide, for a long time thought of as an inert by-product of the conversion of proinsulin to insulin, has revealed multiple biologic roles by partially reversing or preventing complications of insulin-dependent diabetes.[910] Physiologic concentrations of C-peptide in diabetic rats activates pathways involved in cellular proliferation, and limits or prevents the glomerular hypertrophy and the mesangial matrix expansion seen in the posthyperfiltration phase of early diabetic nephropathy.[911] In the kidney, C-peptide reduces diabetes-induced glomerular hyperfiltration, albuminuria, and renal hypertrophy. C-peptide may induce constriction of afferent arterioles in diabetic mice thus reducing GFR—one of the renoprotective mechanisms of C-peptide in diabetes.[912] Following in vivo administration of C-peptide to patients with type 1 diabetes (T1DM), microvascular blood flow to tissues and organs, including muscle, skin, and kidney, is consistently augmented and likely relates to stimulatory effects on NO pathways.[913] One month treatment with C-peptide in T1DM patients results in a 6% decrease in GFR, and a 50% decrease in urinary albumin excretion.[914]

C-peptide reduces diabetes-induced hyperfiltration via a net dilation of the efferent arteriole and inhibition of tubular Na reabsorption, both potent regulators of the glomerular net filtration pressure.[915] In several studies, increased renal Na-K-ATPase activity has been linked to hyperfiltration and to the increase in oxygen consumption. Via inhibition of Na-K-ATPase, C-peptide may contribute to a normalization of the basal oxygen consumption of proximal tubules in diabetic animals. C-peptide may also influence oxygenation through effects on NO release. In addition, C-peptide can improve diabetes-reduced erythrocyte deformability. This has the potential to improve capillary blood flow, thus improving oxygen availability in the kidney, and

other affected tissues.[914] In vivo, C-peptide supplementation for 1 month improves body weight in STZ-induced diabetic rats and decreases urinary sodium wasting.[916] TGF-β1, overexpressed in renal cells in diabetes, has been suggested as a major malefactor in the development of morphologic changes in diabetes by stimulating the mesenchymal formation of collagen IV, and eliciting fibrosis in renal tissues. It has been reported that C-peptide has a protective effect on early diabetic glomerular changes in response to TGF-β1 in STZ-diabetic mice. In addition, an inhibitory effect of C-peptide on TGF-β1-induced gene expression has been demonstrated in a mouse podocyte cell line. C-peptide is reported to effectively reverse TGF-β1-induced structural changes in proximal tubular cells and to inhibit TGF-β1-induced gene expression in a mouse podocyte cell line. The mechanism by which this occurs is not fully understood. It has also been reported that C-peptide, via activation of NF-κB regulated survival genes, protects against TNF-α–mediated renal tubular injury.[914]

RENAL DEGRADATION OF HORMONES

Hormones fall in general into four structural groups: peptides and proteins, steroid hormones, amino acid derivatives, and fatty acid derivatives. Peptide hormones such as insulin have generally a short half-life and are extracted by the kidney, which, on average, removes between 16% and 40% of the hormone entering the renal circulation.[917] In exceptional cases, the kinins for example, more than 90% is removed during a single passage. The removal of biologically active and inactive peptides from the renal circulation occurs predominantly by glomerular filtration.

The rate of filtration is influenced by the size, shape, and charge of the molecule. After filtration, peptide hormones are degraded in the proximal tubule via two mechanisms. Larger peptides, such as insulin, require absorption by epithelial cells and degradation in lysosomes or endosomes. Growth hormone, for example, is also absorbed by tubules where it undergoes peritubular degradation.[918] Smaller peptides, such as bradykinin, angiotensin, and ANP, are degraded by hydrolysis on the brush border. Urinary hormone excretion accounts for less than 1% to 2% of the filtered load.[918] In most cases, the liver contributes significantly to peptide hormone metabolism. A few hormones, however, undergo negligible hepatic extraction and the kidneys are their predominant site of degradation.[917] Examples of these hormones are calcitonin, the amino-terminal fragment of PTH, and the C-peptide of proinsulin. Complete removal of insulin is also dependent on intact renal function.[919] Glomerular filtration accounts for approximately 60% of all the insulin removed by the kidney and the remaining is extracted from the peritubular circulation. Uptake and degradation occurs largely by receptor-mediated endocytosis of insulin on the basolateral membrane of tubule epithelial cells.[920,921] The kidneys contribute significantly to disposal of glycoprotein hormones, such as erythropoietin, follicle-stimulating hormone, and luteinizing hormone.[922,923]

Steroid hormones are derivatives of cholesterol and are typically eliminated by inactivating metabolic transformations and excretion in urine or bile. Examples include testosterone, cortisol, and vitamin D. Their half-lives vary considerably between a few minutes and a few hours. With the exception of vitamin D, the kidney plays only a minor role in the metabolsim of steroid hormones.[920]

Two major hormone groups are derivatives of amino acids: thyroid hormones and catecholamines. These were discussed in detail in previous sections of this chapter. Thyroid hormones are inactivated primarily by intracellular deiodinases and catecholamines are rapidly degraded by enzymes such as monoamine oxidase and catechol-O-methyl transferase.

Fatty acid derivatives include mainly eicosanoids and were discussed in other sections of this chapter. These hormones are rapidly inactivated by metabolism and have short half-lives.

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