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Physiology of endothelin and the kidney

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Abstract

Since its discovery in 1988 as an endothelial cell-derived peptide that exerts the most potent vasoconstriction of any known endogenous compound, endothelin (ET) has emerged as an important regulator of renal physiology and pathophysiology. This review focuses on how the ET system impacts renal function in health; it is apparent that ET regulates multiple aspects of kidney function. These include modulation of glomerular filtration rate and renal blood flow, control of renin release, and regulation of transport of sodium, water, protons and bicarbonate. These effects are exerted through ET interactions with almost every cell type in the kidney, including mesangial cells, podocytes, endothelium, vascular smooth muscle, every section of the nephron, and renal nerves. In addition, while not the subject of the current review, ET can also indirectly affect renal function through modulation of extrarenal systems, including the vasculature, nervous system, adrenal gland, circulating hormones and the heart. As will become apparent, these pleiotropic effects of ET are of fundamental physiologic importance in the control of renal function in health. In addition, to help put these effects into perspective, we will also discuss, albeit to a relatively limited extent, how alterations in the ET system can contribute to hypertension and kidney disease.

Keywords

blood pressure; sodium homeostasis; water homeostasis; acid base; microcirculation

The exciting discovery of ET, and in particular ET-1, stimulated a great deal of studies by the renal research community. Initial work demonstrated that the kidney produced ET-1 in relatively high amounts. For example, Kitamura et al found that the inner medulla of the kidney contained a much higher concentration of ET-1 as compared to multiple other tissues in the body (using the pig as a model) (209). Subsequently, it was determined that almost every cell type within the kidney synthesized ET-1. In addition, the kidney was noted to contain abundant ET receptors, particularly in the vasculature and the medulla. Indeed, as best as could be determined, every cell type within the kidney expresses ET receptors. The kidney is also extremely sensitive to ET-1, having up to 10-fold greater sensitivity to the vascular effects of the peptide as compared to other organ beds (272, 325). Given the almost ubiquitous expression of ET-1 and its cognate receptors within the kidney, it is perhaps not surprising that our current understanding of renal ET biology emphasizes that renal cell-derived ET acts primarily in an autocrine or paracrine manner. Thus, as the various effects

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of ET are discussed in this chapter, it is important to bear in mind that the renal ET system must be viewed within the context of the local microenvironment. In addition, given such high ET production and receptor expression, it was perhaps predictable that ET regulates multiple renal functional parameters. We now know that the ET system can affect total and regional renal blood flow (RBF), glomerular filtration rate (GFR), Na and water excretion, and acid/base handling. In addition, ET-1 can exert a variety of pathophysiologic effects such as regulation of cell proliferation, extracellular matrix accumulation, and inflammation. These latter effects of ET-1 have been shown to be of substantial importance in the development and/or maintenance of a number of forms of acute and chronic renal injury. This chapter will, however, primarily focus on the physiologic role of ET-1 in the kidney.

Although not the subject of this chapter, it is important to recognize that ET-1 may affect renal function through direct modulation of non-renal systems. ET-1 is produced and bound by, and exerts physiologic effects upon, the adrenal gland (both aldosterone and catecholamine synthesis), the heart (regulating inotropy, chronotropy and atrial natriuretic peptide production), the vasculature throughout the body, and the central nervous system (modifying vasopressin release and central mechanisms affecting blood pressure). Discussion of how ET affects these systems can be found elsewhere (37, 79, 363, 365, 366, 370).

I. Biology of ET peptides and receptors

A. ET synthesis and degradation

1. ET genes, mRNA and prepropeptide—There are three mammalian ET isoforms: ET-1, ET-2 and ET-3. Each of these peptides contain 21 amino acids, two intrachain disulfide bonds, vary by not more than 6 amino acids, and are highly conserved between species (Figure 1). The three isoforms are encoded by separate genes that do not undergo alternate splicing. Most studies examining ET regulation of renal function have focused on ET-1; hence this discussion will focus on ET-1. The human ET-1 gene consists of 5 exons distributed over 6838 base pairs (184), is located on chromosome 6 (17), and encodes a 2026 base pair mRNA (184). ET-1 production and secretion is largely controlled at the gene transcription level. Cooperation between a large host of tissue-specific transcription factors permits tissue-selective ET-1 gene transcription and helps ensure that ET-1 is appropriately activated (510). Such cooperation is facilitated by multiple regulatory elements in the ET-1 promoter, including activator protein 1 (AP-1), nuclear factor of activated T-cells (NFAT)-binding domains, GATA binding protein 2 (GATA-2), CAAT-binding nuclear factor-1 (NF-1) and many others (411).

ET-1 mRNA has a short half-life (~15 minutes) which is partly due to the presence of three destabilizing AUUUA motifs in the 3'-untranslated region (184). Alterations in ET-1 synthesis can be effected by modification of ET-1 mRNA stability (87, 283, 361). Human ET-1 mRNA encodes a 212 amino acid prepropeptide that undergoes removal of a short signal sequence by a signal peptidase to yield proET-1. ProET-1 is cleaved by dibasic-pair-specific endopeptidases, including furin and PC7, to yield the 38 amino acid Big ET-1 (279, 512).

2. Conversion of Big ET-1 to ET-1—Big ET-1 is present in the circulation, however it has at least two orders of magnitude less vasoconstrictor potency than ET-1 (71). Conversion of Big ET-1 to ET-1 occurs primarily by ET converting enzymes (ECE) (Figure 1). ECE are integral membrane zinc peptidases; three isoforms (ECE-1, -2 and -3) have been identified (71, 456). ECE-1 is present mainly in endothelial cells, has the greatest affinity for Big ET-1, and has a pH optimum of 6.8 (506). There are four ECE-1 isoforms (ECE-1a, -1b, -1c and -1d) that are derived from alternative splicing of a single gene (392, 397, 461) and

differ only at the amino terminus. ECE-1a is located in intracellular vesicles and on the cell surface; ECE-1b is located in the endosomal compartment near the trans-Golgi network, while ECE-1c and -1d are found primarily on the extracellular face of the plasma membrane (71, 278). The different ECE-1 locations indicate that ET-1 can be formed from Big ET-1 both intracellularly and extracellularly. Notably, Big ET-1 is sometimes present in the plasma in concentrations greater than ET-1, suggesting that extracellular conversion is of physiological importance. Since ECE is also localized to vesicles, the potential exists for ET-1 to be stored and secreted upon demand. Such a possibility has been confirmed in endothelial cells, wherein ET-1 can be found in Weibel-Palade bodies and released from vesicles upon stimulation (148, 371, 372).

ECE-2 has about 60% homology with ECE-1, hydrolyzes ET-1, and also consists of four isoforms with varying amino termini that may confer different intracellular cellular localization (99, 179). It's pH optimum is 5.5, indicating that ECE-2 is particularly involved with the trans-Golgi network (99).

Mice with combined knockout of ECE-1 and ECE-2 have measurable ET-1 levels, indicating that other proteases may catalyze ET-1 formation (511). ET-1 may also be generated by other enzymes, although their physiologic relevance is uncertain (71). There is no convincing evidence that ECE are rate limiting in mature ET-1 synthesis. Finally, Big ET-1 can be converted to ET-1 [1-31] by chymase; ET-1 [1-31] can potently vasoconstrict (amongst other properties) (71). This suggests that alternative processing of Big ET-1 may be of biologic relevance.

3. ET catabolism—ET-1 is degraded by at least two enzymes. These include neutral endopeptidase (71, 463) and deamidase (189, 191) (Figure 1). The enzymes have different optimum pH profiles (deamidase at acid pH and neutral endopeptidase at neutral pH), suggesting different biologic roles. Renal catabolism of ET-1 may be of particular importance in that ET-1 causes prolonged BP elevation in bilaterally nephrectomized rats (224). In addition, circulating ET-1 does not appear in the urine (2).

B. ET receptors

1. Molecular biology of ET receptors—Mammalian ET receptors derive from two separate genes. The human ETA receptor (ETA) contains 427 amino acids, its gene is located on chromosome 4, and the receptor binds ET-1 ≥ ET-2 ≫ ET-3 (168). Splice variants have been described, however their relevance to kidney function has not been examined (150). The human ETB receptor (ETB) contains 442 amino acids, its gene is located on chromosome 13, and the receptor binds all ETs with equal affinity (15, 376). Several ETB splice variants have been described, including one with minimal signaling activity that may function as a clearance receptor (398). As for the ETA variant, the physiologic significance of these ETB splice variants in the kidney remains unknown. Finally, variable ET glycosylation has been described, but no functional significance has been identified (33).

2. ET receptor localization and signaling—ETA and ETB are widely expressed in the kidney; a given cell can express one or both receptor isoforms. In general, ETA predominate in vascular smooth muscle, while ETB predominate in endothelial cells and renal tubules. ET receptors activate multiple signaling systems that vary depending upon the cell type. ET receptors couple to members of the Gi, Gq, Gs and $Ga_{12/13}$ G-protein families (88, 181, 208) with resultant regulation of a variety of signaling cascades, including adenylyl cyclases, cyclooxygenases (COX), cytochrome P-450, nitric oxide synthase (NOS), the nuclear helix-loop-helix protein p8 (138), serine/threonine kinases, tyrosine kinases and others (411). ETA

and ETB often have opposing actions, i.e., in the vasculature, ETA activation causes vasoconstriction, while ETB activation, at least initially, causes vasodilation. However, many exceptions exist in which ETA and ETB elicit similar biologic responses. Given this complexity and cell-specific responses, detailed discussion of ET receptor signaling will be done in the context of each renal cell type.

A number of pharmacologic agents have been used to characterize ET receptor isoform function. However, substantial uncertainty exists about ET receptor isoform function. Part of this problem may relate to ET receptor dimerization (30). In vitro studies indicate that ETA and ETB can form homodimers (140) and heterodimers (139). Interestingly, ETA and ETB heterodimerized though a PDZ finger; mutation of the PDZ domain caused delayed ET receptor internalization and a prolonged increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_I$) in response to ET-1, suggesting that ETA/ETB heterodimerization affects receptor function (105). ETB may also heterodimerize with receptors other than ETA, including dopamine D3 and angiotensin II (AII) AT1 receptors (522, 523). However, to date there is no evidence that ET receptor heterodimers exist in vivo or subserve a biologic function.

ET-1 binding to its receptors causes prolonged biologic effects that are due, at least in part, to the almost irreversible binding of the peptide. In fact, ET-1 can remain bound to its receptor for up to 2 hours after endocytosis, suggesting that the peptide activates signal transduction long after internalization (63). ET receptors can also be present in the cell nucleus where they could conceivably exert different biologic effects than ET receptors on the plasma membrane (193).

C. Fundamental concepts about ET biology

A fundamental concept is that ET biology is best understood in the context of the local microenvironment. Plasma ET levels are generally too low to activate its cognate receptors. In contrast, local tissue ET concentrations are very likely much greater than that found in the circulation and can exert physiologic effects. Polarized cells, such as endothelial and renal tubular cells, secrete ET-1 predominantly towards the abluminal side. ET receptors are also mainly located on the abluminal side of polarized cells, thereby facilitating autocrine and/or paracrine regulation. Thus, ET appears to function primarily as an autocrine and paracrine regulator. Such considerations help explain how ET exerts such a broad range of effects, some of which can even oppose one another.

Another important concept is that ET-1 production is primarily regulated at the level of gene transcription. While alterations in mRNA stability, preproET-1 processing, ECE activity, or even vesicular trafficking have been described for ET-1, they have been infrequently identified as playing a significant role in the control of ET-1 synthesis and release. This control of ET-1 gene transcription involves numerous factors activating a panoply of intracellular signaling pathways. In general, vasoconstrictors tend to increase, while vasodilators decrease, ET-1 release. Further, since ET-1 release is largely dependent upon gene transcription, its regulation can lead to not only amplification of the magnitude of a given factor’s physiologic effect, but also substantial prolongation of the given factor’s duration of action. This latter concept may be particularly important in that ET-1 exerts long-lasting effects. Hence, the combination of stimulated gene transcription leading to sustained ET-1 production together with prolonged ET-1 binding to its receptors provides a powerful mechanism to lengthen the effect of a given stimulus (e.g. cell contraction) exerted by a given physiologic agent. This scenario may be relevant to all renal cell types; once the ET system is activated, it can exert potent and long-acting effects.

II. ET and the renal vasculature

A. Renal vascular ET receptor expression

ET-1 influences renal microvascular function by activation of ETA and/or ETB (Figures 2 and 3). The relative proportion and distribution of ETA and ETB expression varies between animal models and humans, possibly reflecting regional differences within the kidney. For example, in the canine renal cortex, the proportion of ETA/ETB expressed is approximately 22/78 based on binding studies using cortical membranes (36). The ratios in medullary and papillary tissues average 40/60 and 50/50, respectively (36). In contrast, the ETA/ETB distribution approaches 30/70 in the rat renal cortex and medulla alike (301). Descending vasa recta in the outer medulla express both ETA and ETB. The relative ETA/ETB proportion in porcine kidneys averages approximately 60/40 in glomerular membranes, but only ETB binding could be identified in papillary membranes (19). Approximately 30% of the receptors expressed in the human renal cortex and medulla are ETA (300).

While the renal microvasculature clearly expresses ET receptors, the fractional expression that vascular receptors represent of the total renal ET receptor expression is not well understood. Physiological regulation of renal microvascular ET receptor expression has not been thoroughly investigated. Functional evidence established that both receptor subtypes are expressed by preglomerular vessels and efferent arterioles (92, 101, 186, 249, 268), however there are only limited data pertaining to the relative distribution of receptors in specific renal microvascular segments. Edwards and Trizna (91) showed that preglomerular microvessels of rats and rabbits express ETA/ETB in approximately a 40/60 proportion and ^{125}I-ET-1 bound in a manner consistent with a single binding site. Dissociation constants were nearly identical across species and averaged approximately 20-21 pmoles/mg protein suggesting that preglomerular microvascular membranes from rats and rabbits exhibit nearly identical affinities for ET-1. ETA expression in rats (determined by ^{125}I-ET-1 binding) was lower in glomeruli and inner medullary collecting duct than in preglomerular microvessels, whereas the ETA/ETB proportion was similar for the microvasculature and inner medullary collecting duct of rabbits, but glomeruli exhibited primarily (80%) ETB binding. Davenport and colleagues used an ETA selective radioligand to demonstrate that ETA was expressed along human arcuate, interlobular arteries and veins and along arterioles and glomeruli (75). More recently, Wendel et al used immunofluorescence to survey rat renal ET receptor expression and found that ETA were detected on vascular smooth muscle cells of the large interlobar, arcuate and interlobular arteries and in veins (481). ETA immunoreactivity also appeared on smooth muscle cells of afferent and efferent arterioles, but not on endothelial cells of these vascular elements. Weak immunostaining for ETB was noted on endothelial cells of interlobular arteries, but ETB immunoreactivity was much stronger on the endothelial cells of peritubular capillaries. Importantly, endothelial cells of afferent or efferent arterioles did not exhibit detectable ETB immunostaining.

Vascular ET receptor expression can be influenced by changes in physiological status. For example, chronic increases in ET-1 suppress ETA expression while having little effect on ETB expression (240, 438). Surface flow and NO enhance vascular smooth muscle ETA expression and affinity (351, 352). Recently, chronic salt feeding was shown to increase renal vascular ETB, but not ETA, expression (382). The possibility that physiological challenges alter renal microvascular ET receptor expression is exciting because it implies a new level of regulation/compensation, which may reveal novel roles for ET in kidney function.

B. Renal microvascular ET production

There is little information defining which renal vascular cells actually produce ET peptides and under what conditions that production can be modulated. Immunocytochemistry studies confirmed that endothelial cells of human interlobular and arcuate arteries and adjacent veins produce mature ET-1 and Big ET-1 (198). Positive staining was also detected in glomerular capillary endothelial cells, but not endothelia from other intrarenal capillaries. Interestingly, no immunostaining was evident in the vascular smooth muscle cells of these endothelium-positive arterial segments.

ECE-1 was detected in human kidney on the endothelial surface of arcuate and interlobular arteries and on vascular smooth muscle and endothelial cells of glomerular arterioles (342). In the medulla, ECE-1 was detected in vasa recta bundles and tubular elements. Endothelial staining was confirmed by immunohistochemical detection with von Willebrand factor, which paralleled ECE-1 mRNA distribution (342).

ET-1 release occurs soon after it is formed by ECE-1 from pre-pro ET-1. Accordingly, secreting cells do not contain significant stores of biologically active ET-1. Endothelial cells produce biologically active ET-1 from pre-pro ET-1, mainly through the catalytic actions of ECE-1; however, other mechanisms are implicated under physiological and pathophysiologic conditions, and in tissue specific manners (71, 227). ET-1 production can come from many sources and conditions. Renal production is facilitated by conditions such as shear stress, inflammation, oxidative stress and the renin/AII system (30, 96, 130, 303). Most ET-1 is probably generated by tubular epithelial cells. How much renal ET-1 is derived directly from renal microvascular endothelial and smooth muscle cells, and how this ET-1 might influence renal microvascular or tubular function, is unknown.

C. Effect of ET on the renal microcirculation

The renal vascular effects of ET are preceded by activation of ETA and ETB. ET produces a powerful and prolonged renal vasoconstriction following either lumenal or adventitial peptide delivery (29, 80, 101, 134, 186, 249, 268, 332, 334, 335, 402). This vasoconstriction involves activation of either ETA or ETB and occurs in a segment specific manner (101, 186, 249, 268). ET also influences mesangial cell signaling, migration and proliferation, but does not appear to exert a direct influence on tubuloglomerular feedback (202, 411, 425). Therefore, the relationship between ET and regulation of renal hemodynamics or renal microvascular function are complex and highly varied. This section will highlight how ET influences renal microvascular function and how these actions translate into modulation of renal hemodynamics.

Probably the best information on the segment specific actions of ET on the renal microcirculation has come from *in vitro* studies using isolated arteries and arterioles from rat and rabbit and *in vivo* or *in vitro* hydronephrotic kidney models. The earliest work used isolated arterioles to assess microvascular reactivity to ET-1, ET-2 and ET-3, and revealed that ET-1 produced a long-lasting, concentration-dependent vasoconstriction of afferent and efferent arterioles (92). The ED_{50} averaged approximately 1.4 and 0.9 nM for afferent and efferent arterioles, respectively. ET-2 mediated vasoconstriction of these arterioles was similar to ET-1, but ET-3 was significantly less potent. In similar work, using isolated rat microvessels, efferent arterioles were approximately 10-fold more sensitive to ET-1 compared to afferent arterioles (249, 321). This implicates ET as a paracrine regulator of glomerular hemodynamics and glomerular filtration pressure.

1. Studies in the hydronephrotic kidney—Much of our knowledge of the renal microcirculation has benefitted from using the *in vitro* and *in vivo* hydronephrotic kidney.

This is a kidney model that is devoid of renal tubules while most of the vascular architecture is retained and visible for study (306). Hydronephrotic kidney studies provided the first in situ resolution of ET's actions on intrarenal microvascular elements; demonstrating that ET potently vasoconstricts afferent arterioles *in vitro* (268, 432, 433) and *in vivo* (119, 142, 413), whereas ET-1 exerts more modest, and more variable effects on the efferent arterioles. Variability in the efferent response may arise from data collected *in vitro* or *in vivo*. For example, ET-1 caused modest efferent arteriole vasoconstriction *in vitro* (268, 433), but evoked a much greater efferent response in the *in vivo* hydronephrotic kidney (101, 119). It is possible that ET-1-mediated afferent vasoconstriction in the *in vivo* hydronephrotic kidney reflects activation of both ETA and ETB (47, 101), whereas efferent vasoconstrictor responses may be through ETB (101). ETA blockade reduces afferent vasoconstriction to ET-1 without affecting efferent arteriolar responses. Conversely, ETB blockade, or ETB agonists influenced vessel diameter of both afferent and efferent arterioles. Using a different *in vivo* approach, Gulbins et al infused antibodies directed at ET-1 and ET-3 to scavenge endogenous ET peptides, and then monitored changes renal microvascular diameter (142). Anti ET-1/ET-3 antibody infusion evoked vasorelaxation from arcuate and interlobular arteries and the proximal portion of afferent arterioles. The diameter of efferent and distal afferent arterioles did not change. Thus ET-1 may produce a more prolonged vasoconstriction of distal afferent arterioles and efferent arterioles than more upstream preglomerular segments

2. Studies in the blood perfused juxtamedullary nephron preparation—The blood perfused juxtamedullary nephron preparation was developed in the mid-1980's by Daniel Casellas to evaluate inner cortical nephron function and microvascular reactivity (45, 46). The major advantage of this approach is that the kidney is perfused with blood and the vascular-tubular associations remain intact. Investigation of ET's effects on the renal microvasculature using this technique has clearly revealed that ET-1, ET-2 and ET-3 vasoconstrict both afferent and efferent arterioles (183, 186, 382). ET-1 and ET-3 constricted afferent arterioles more than efferent arterioles whereas the magnitude of afferent and efferent responses to ET-2 were similar (186). ET-1 is significantly more potent than ET-2 or ET-3 (183, 186). Accordingly, much of the vasoconstriction induced by lower concentrations of ET-1 is ETA-dependent, and is consistent with earlier *in vivo* studies showing that ETA blockade could completely block the ET-1-mediated decline in RBF and GFR (334, 335).

Afferent arteriole vasoconstriction involves activation of both ETA and ETB. ET-1-mediated vasoconstriction of afferent arterioles is blunted by ETA blockade and abolished by combined ETA/ETB blockade (186). Efferent vasoconstriction also involves both ETA and ETB, but a more complex interaction may exist. Acute ETA blockade converts prominent efferent vasoconstriction to a modest vasodilation at lower ET-1 concentrations (10-100 pM) before a stronger vasoconstriction appears when the ET-1 concentration reaches 1 and 10 nM. Interestingly, blockade of ETB shifts the ET-1 concentration response curve slightly to the left suggesting increased ET-1 potency. The ETB agonist, S6c, also vasodilates efferent arterioles and reverts to a modest vasoconstriction during ETB blockade (186). Thus, these studies suggest that vasodilatory ETB present on vascular endothelium may exert a dominant role on the efferent arteriole and ETB-dependent constriction is only observed at higher agonist concentrations. This also suggests that vascular smooth muscle ETB might have lower affinity for ET-1 than endothelial ETB.

Data from the juxtamedullary nephron model suggest that ETB provide a vasodilatory influence on normal efferent arteriolar vascular tone whereas it is mainly a vasoconstrictor of afferent arterioles. These data may explain the variability noted in efferent arteriole responses in the hydronephrotic kidney models because efferent arterioles can respond to ET

with either vasoconstriction or vasodilation, depending on ambient conditions. Notably a high salt diet attenuates afferent arteriolar vasoconstrictor responses to ET-1, presumably by enhanced preglomerular microvascular expression of vasodilatory ETB (382).

3. Renal blood flow, renal hemodynamics, in vivo and in isolated perfused Kidneys—Whole kidney responses to systemic or intrarenal infusion of ET uniformly demonstrate profound vasoconstriction (20, 41, 104, 333, 375, 474, 480). Early *in vitro* and *in vivo* work demonstrate that intrarenal ET-1 infusion reduced RBF, increased renal vascular resistance and reduced GFR, all variables consistent with significant vasoconstriction of the preglomerular vasculature. However, whole kidney studies have limited utility for establishing which intrarenal microvascular elements respond to ET-1 and how they respond. Using intra-vital video-microscopy, Saito et al examined surface glomeruli and arterioles in isolated perfused kidneys from Munich-Wistar rats (375). They found that ET-1 potently vasoconstricted surface afferent arterioles at concentrations approaching 30 fM. Efferent diameter decreased by just 3% with 30 pM ET-1 (375). These findings in intact kidneys agree with *in vitro* studies suggesting that ET-1 is a more effective vasoconstrictor of pre-glomerular versus post-glomerular vessels.

Micropuncture studies uniformly support ET-1 as a preglomerular vasoconstrictor, but efferent arteriolar responses are equivocal with studies suggesting more, less, or no difference in the efferent vasoconstrictor response to ET-1. ET-1 reduces rat RBF and increases afferent and efferent arteriolar resistance (20, 205). ET-1 also decreases K_f and single nephron GFR declined significantly (20, 205). In other studies, K_f remained unchanged during ET-1 infusion but proportionally greater increases in afferent arteriolar resistance were observed compared to efferent changes (227, 228). Antagonist studies indicate that the renal microcirculation is under the influence of endogenous ET-1. Infusion of the combined ETA/ETB antagonist, bosentan, reduced arterial blood pressure slightly and significantly decreased glomerular capillary pressure (344). Under the same conditions, selective ETA blockade had no effect on mean arterial pressure or glomerular hemodynamics. These data suggest that endogenous ET exerts a tonic vasodilatory influence on the renal microcirculation that is of ETB origin. Endogenous NO contributes to ET-modulation of renal vascular resistance (57, 77, 343, 344).

In the canine kidney, intrarenal infusion of ET-1 or ET-3 reduced RBF and GFR (57, 153). This effect was enhanced by NOS inhibition, suggesting that NO buffers the renal vasoconstrictor actions of ET (57). Inhibition of COX augmented ET-1 mediated renal vasoconstriction but abolished the ET-3-mediated renal vasoconstriction (57). The renal microvascular response to ET appears to involve direct effects of ET-1 on microvascular resistance and indirect actions of ET-1 to stimulate production of other vasoactive mediators, such as thromboxane, adrenergic influences or AII.

D. Effect of ET on medullary blood flow

Thus far, discussion has focused on the effects of ET on afferent and efferent arteriolar resistance. These resistance changes can profoundly impact whole kidney and cortical blood flow, but how does ET influence medullary blood flow? The observation that ET-1 potently vasoconstricts both afferent and efferent arterioles of the juxtamedullary nephrons provide some clues to address this question (186). The juxtamedullary microvasculature provide blood flow to the vasa recta that perfuse the renal medulla (322), thus ET should reduce medullary blood flow in concert with reducing cortical blood flow. However, ET's influence on medullary blood flow seems more complex (107). Indeed, ET-1, ET-2 and ET-3 potently vasoconstrict isolated rat descending vasa recta with threshold effects visible at concentrations of approximately 10^{-16} M, 10^{-14} M, and 10^{-9} M, for the three peptides,

respectively (322). The constrictor effects of ET-1 and ET-2, but not ET-3, are attenuated during ETA blockade. In contrast, ET-3-mediated constriction is inhibited by ETB, but not ETA, blockade. Interestingly, PGE_2 could relax descending vasa recta preconstricted with ET-1 (1pM) or ET-3 (10nM) (399). ET also reportedly increases medullary blood flow in rabbit kidneys *in vivo*, while at the same time reducing whole kidney and renal cortical blood flow (106). ETA blockade decreased arterial blood pressure and increased RBF by increasing both cortical and medullary blood flow. ETB blockade increased arterial pressure and reduced renal and cortical blood flow while having no significant effect on medullary blood flow. ETB blockade also potentiated ET-1-mediated reductions in renal and cortical blood flow and abolished ET-1-mediated increases in medullary blood flow. Qualitatively similar results were observed in rats and mice (35, 298, 422, 462). These data argue that ETB are important regulators of the medullary blood flow response to ET-1, while ETA play a more important role in regulating ET-1's influence on renal cortical blood flow (Figure 3).

The role of prostanoid metabolites in modulating ET-1's influence on renal perfusion is unclear. Prostaglandins or NO appear to modulate ET-1's effects on RBF (57, 142, 155, 156, 347), but how they influence intrarenal regional blood flow is not well defined. While thromboxane A_2 is implicated in the dog kidney, it may not influence ET's actions on renal perfusion in the rat (57). Blockade of thromboxane receptors had no effect on ET-1-mediated reduction of cortical or medullary blood flow (496).

The impact of ET-1 on medullary perfusion is influenced by gender and environmental conditions. Infusion of ET-1 directly into the renal medulla had no detectable effect on medullary blood flow in normal or ETB-deficient female rats, but produced a marked reduction in medullary blood flow in male rats of both strains (298). Ovariectomy eliminated this gender difference. Big ET-1 decreases cortical and medullary blood flow in rats fed a normal salt diet, but the medullary vasoconstriction is abrogated on a high salt diet (462). Notably, ECE-1 expression is significantly enhanced in the renal medulla of rats fed high salt. In addition, the sensitivity of juxtamedullary afferent arterioles to ET-1 was shifted to the right in rats fed high salt. This shift is accompanied by increases in ETB expression by the preglomerular microvasculature (382). These data support involvement of medullary ECE-1 and ETB activation in the medullary perfusion response to ET precursors and peptides.

E. ET signaling pathways in the renal circulation

This section focuses on the intracellular signaling mechanisms responsible for ET-mediated renal microvascular vasoconstriction. Studies have clearly shown that renal microvascular vasoconstriction is strongly linked to elevation of $[Ca^{2+}]_I$ and that changes in $[Ca^{2+}]_i$ involve both Ca^{2+} influx and Ca^{2+} mobilization signaling cascades (16, 303) (Figure 2). Interestingly, afferent and efferent arterioles often use different Ca^{2+} signaling mechanisms to produce vasoconstriction evoked by the same agonist (43, 44, 152, 266, 267, 269, 303).

At the vascular smooth muscle cell level, ET increases $[Ca^{2+}]_i$ rapidly. ET-1, ET-2 and ET-3 stimulate peak increases in cytosolic Ca^{2+} concentration in preglomerular smooth muscle cells with a rank order potency of ET-1>ET-2≫ET-3 (389). This pharmacological potency profile suggests that ET-mediated elevations in $[Ca^{2+}]_i$ arise primarily through activation of ETA, with perhaps a smaller component arising through ETB stimulation. The peak response to ET-1 and ET-2 was followed by a smaller but sustained plateau elevation of $[Ca^{2+}]_i$. Peak Ca^{2+} responses were unaffected by depletion of extracellular Ca^{2+}, but the sustained increases in Ca^{2+} were abolished. The peak responses to ET-1 are primarily generated by mobilization of Ca^{2+} from intracellular stores, whereas the sustained increases in Ca^{2+} reflects influx of extracellular Ca^{2+}. ETA- and ETB-stimulated Ca^{2+} responses were corroborated by Fellner and Arendshorst who noted that ET-1, and the ETB agonist,

IRL-1620 both stimulated increases in $[Ca^{2+}]_i$ in preglomerular smooth muscle cells and isolated rat afferent arterioles (112). The relative ETA- and ETB-dependent responses were attenuated by their respective receptor antagonists, and combined ETA/ETB blockade virtually eliminated the response, demonstrating select receptor-dependency.

Early studies performed in hydronephrotic kidneys provide the first data using intact, pressurized arterioles. ET-1-mediated vasoconstriction of afferent arterioles was inhibited by blockade of L-type voltage-gated Ca^{2+} channels while having a more modest effect on efferent arterioles (268). Activation of sarcolemma chloride channels may initiate the depolarization necessary to activate voltage-dependent Ca^{2+} channels. Indeed, Takenaka showed that inhibition of voltage-gated Ca^{2+} channels or chloride channels reversed ET-1-mediated vasoconstriction of afferent arterioles in hydronephrotic kidneys, *in vitro*(432, 433). *In vivo* however, Fretschner and co-workers found no effect of Ca^{2+} channel blockade on the afferent or efferent response to ET-1 (119), whereas Pollock et al. showed that nifedipine significantly attenuated the renal vasoconstriction evoked by ET-1, or the ETB agonist, S6c (332). Ca^{2+} channel blockade attenuated Ca^{2+} signaling events in preglomerular smooth muscle cells and blunted afferent arteriolar vasoconstriction to lower (1.0 and 10 pM), but not higher (100 pM), ET-1 concentrations.

Collectively, ET peptides activate ETA and ETB to increase $[Ca^{2+}]_i$ in preglomerular smooth muscle cells by stimulating Ca^{2+} influx and Ca^{2+} release mechanisms. Voltage-dependent Ca^{2+} influx may occur through ET receptor-mediated opening of chloride channels leading to membrane depolarization and subsequent activation of L-type, voltage-dependent Ca^{2+} channels. The explanation for discrepant results pertaining to the efficacy of Ca^{2+} channel blockers to blunt or eliminate ET-1 mediated signaling *in vivo* and *in vitro* is unclear, but may reflect differences in physiological or hemodynamic status among preparations.

Ca^{2+} mobilization from intracellular stores involves activation of several receptor-specific Ca^{2+} signaling cascades (303). ET-mediated Ca^{2+} release in the renal microcirculation appears to involve activation of Ca^{2+} -induced Ca^{2+} release/cADP-ribose mechanisms, reactive oxygen species, Rho-kinase, PKC, chloride channels and cytochrome P450 metabolites (16, 48, 111, 183, 196, 207, 303, 433, 443). Preglomerular smooth muscle Ca^{2+} signaling experiments suggest that release of Ca^{2+} from intracellular stores is an important signaling mechanism employed by ET. Activation of renal microvascular ETA or ETB presumably stimulates ADP-ribosyl cyclase to produce cyclic ADP-ribose (cADP-ribose) and nicotinic acid adenine dinucleotide phosphate (NAADP) leading to Ca^{2+} release (111, 443, 444). cADP ribose activates ryanodine receptor-dependent Ca^{2+} release and NAADP may stimulate Ca^{2+} release through a lysosome dependent pathway. ET-1 or S6c-stimulated Ca^{2+} signaling events and reductions in RBF were attenuated during inhibition of ADP-ribosyl-cyclase activity and during ryanodine receptor blockade (111, 444). Mice with defective ADP-ribosyl cyclase exhibit markedly reduced renal hemodynamic sensitivity to ET-1 infusion compared to wild type controls.

More recent work implicates a novel lysosomal Ca^{2+} signaling mechanism (443). Interventions such as inhibition of NAADP actions, or disruption of lysosomal pH and Ca^{2+} regulation, simultaneously blunt ET-1 and norepinephrine-mediated increases in $[Ca^{2+}]_i$ in rat afferent arteriolar smooth muscle. Thus, ET-1 employs novel mechanisms to stimulate Ca^{2+} signaling events in renal microvascular smooth muscle.

Reactive oxygen species are important modulators of renal microvascular function and appear to influence preglomerular responsiveness to ET (111, 196). ET-1 increases $[Ca^{2+}]_i$ and superoxide accumulation in preglomerular smooth muscle cells, and this effect was

markedly diminished in the presence of the free radical scavenger, Tempol (111). ETB activation with S6c also increases $[Ca^{2+}]_i$, but only slightly influences superoxide accumulation. At the whole kidney level, the NADPH oxidase inhibitor, apocynin, attenuated ET-1 or S6c's ability to reduce RBF (196). Thus, oxidative status in the renal microvasculature can significantly influence renal microcirculatory responses to ET.

ET-1 binding to ETA and ETB also stimulates phospholipase A2 activation, arachidonic acid release, and production of COX and cytochrome P450 metabolites from renal tubular and vascular cells (86, 182, 183, 319, 380, 505). Cytochrome P450 and COX metabolites contribute to ET's renal vasoconstrictor actions, but comparatively little is known about the vascular sites of action and cellular signaling mechanisms involved. In pioneering studies, Imig et al. determined that COX and cytochrome P450 metabolites modulate Ca^{2+} signaling events in preglomerular smooth muscle cells and directly influence afferent arteriolar vasoconstrictor responses to ET-1 (182, 183). Inhibition of COX or cytochrome P450 hydroxylase activity attenuated ET-1 mediated afferent arteriolar vasoconstriction. Conversely, inhibition of cytochrome P450 epoxygenase activity enhanced ET-1 mediated afferent arteriolar vasoconstriction. Inhibition of COX or cytochrome P450 hydroxylase activity attenuated ET-1- mediated increases in $[Ca^{2+}]_i$ in preglomerular smooth muscle cells, but cytochrome P450 epoxygenase inhibition had no effect. These data establish that ET-1 stimulates production of COX and CYP450 hydroxylase metabolites by renal microvascular smooth muscle cells, and these metabolites contribute to the ET-1–mediated vasoconstriction. In contrast, inhibition of the CYP450 epoxygenase pathway enhanced the vasoconstrictor response to ET-1. Thus ET-1 mediated production of vasodilatory epoxyeicosatrienoic acids (EETs) may counteract the vasoconstrictor actions of ET-1.

While ET-1-mediated increases in $[Ca^{2+}]_i$ are important signaling mechanisms by which ET influences renal microvascular resistance, changes in Ca^{2+} sensitivity can also regulate vascular function (409). Presently, two major mechanisms appear to alter Ca^{2+} sensitivity; these include PKC and receptor-mediated activation of the RhoA/Rho-kinase pathway, which inhibits myosin light chain phosphatase (8, 270, 326). In two separate studies, different PKC inhibitors did not alter ETA (ET-1) or ETB (IRL-1620) mediated vasoconstriction of afferent arterioles (48, 433). PKC does not appear to play a major role in mediating renal microvascular vasoconstriction by ET. In contrast, the data on Rho-kinase is more interesting and deserves more study. Rat afferent arterioles express elements of the Rho-kinase signaling pathway and arteriolar reactivity is influenced by inhibitors of Rho-kinase activity (48, 185). In addition, ETB activation reportedly activates RhoA of the Rho-kinase signaling pathway (208). Acute exposure to Rho-kinase inhibitors rapidly reduces microvascular resistance in normal and hydronephrotic kidneys. Furthermore, pretreatment with Rho-kinase inhibitors virtually eliminates the preglomerular vasoconstriction induced by the ETB agonist, IRL-1620, and attenuates IRL-1620-mediated vasoconstriction of the efferent arteriole. Unfortunately, ETA-dependent effects have not been examined, so the contributions of the Rho-kinase system on ETA-mediated renal microvascular responses remain to be determined. Nevertheless, the limited data available thus far support a role for Rho-kinase activity in ET-1-mediated renal microvascular reactivity.

Integration of the data presented on the microvascular effects of ET-1 argues that ET-1 is a potent vasoconstrictor of the renal microcirculation and may act in an important, segment-specific manner. Renal microvascular vasoconstriction involves both ETA and ETB subtypes, and may be altered under differing environmental conditions, such as high salt diets or hypertension. The physiological implications of regional influences along the vascular tree remain to be determined. There is general agreement that ET regulates microvascular tone by modulating $[Ca^{2+}]_i$, and may also modulate Ca^{2+} sensitivity, thus

providing a remarkably sensitive mechanism for ET-1-dependent regulation of renal cortical and medullary resistance.

III. ET and glomerular function

ET can modify glomerular cell function, although most of the peptide's actions have been described in the context of pathophysiologic conditions associated with glomerular sclerosis, cell proliferation and/or proteinuria (25). There is limited data that suggests the ET system can alter GFR through control of glomerular cell function; this section focuses on this topic. Please note that endothelial cell ET biology is discussed in the context of the renal vasculature in the previous section.

A. Glomerular epithelial cells

1. Glomerular epithelial cell ET production and receptor expression— Glomerular podocytes from rat, human and mouse can synthesize ET-1 (67, 70, 117, 200, 292). Rat glomerular epithelial ET-1 production is increased by activation of PKC and inhibited by blockade or depletion of PKC (70). An interesting study using mouse podocytes reported that reorganization of the actin cytoskeleton via Rho kinase-dependent focal adhesion kinase (FAK) activation of nuclear factor- KB (NF-KB) and activator protein-1 (AP-1) led to increased ET-1 synthesis (292). Thus, podocytes release ET-1; such production may be regulated by factors associated with changes in podocyte conformation.

Glomerular epithelial cells from human and rat express ET receptors (121, 350) (Figure 3). There is limited information on the ET receptor isoforms in these cells, however ETB have been localized to podocytes in rat glomeruli (507), while ET-1 induction of thrombin receptor internalization in human glomerular epithelial cells occurred by ETA activation (55).

2. ET actions in glomerular epithelial cell—There is no direct evidence that ET modulation of glomerular epithelial cell function leads to alterations in GFR or RBF. However, if one can speculate that contraction of these cells might alter glomerular surface area or glomerular sieving, then the possibility does exist that ET-1 could affect glomerular hemodynamics. Indeed, ET-1 has been demonstrated to modulate alterations in the cytoskeleton in glomerular epithelial cells. For example, ET-1 induces nephrin shedding from glomerular epithelial cells, in part due to cytoskeleton redistribution. In addition, ET-1 caused cytoskeletal rearrangement leading to increased protein permeability in mouse podocytes (293); this effect was mediated via ETA activation, and phosphatidylinositol-3 kinase (PI3K) and Rho-kinase pathways. This group also noted that shigatoxin-stimulated podocyte cytoskeletal changes were mediated by ET-1, raising the possibility of an autocrine ET-1 function in these cells. ET-1 increases $[Ca^{2+}]_I$ in podocytes (350) and parietal cells (277); this latter effect was associated with contraction of the parietal sheet. Taken together, the above studies suggest that ET-1 can contract glomerular epithelial cells, most likely via ETA activation; whether this impacts glomerular function remains to be determined.

B. Mesangial cells

1. Mesangial cell ET production and receptor expression—Mesangial cells have been well described to produce ET-1 (Figure 4). A wide variety of agents modulate mesangial cell ET-1 gene synthesis, including vasoactive substances, growth factors, cytokines, reactive oxygen species, and others. Factors that enhance ET-1 synthesis include ET-1 itself (via ETB) (190), AII (178, 222), AVP (178, 377, 424), thromboxane A_2 (529), thrombin, tumor necrosis factor (TNF) and interleukin-1 (IL-1). These stimulatory effects are mediated by a number of signaling systems. Typically, preproET-1 expression is

increased by activation of p38 mitogen-activated protein kinase (MAPK) and PKC, while extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinases/stress-activated protein kinase (JNK/SAPK), or intracellular Ca^{2+} release are typically not involved (115, 158). Subsequent to p38 MAPK activation in mesangial cells, TAK1 kinase, TAK1 binding protein-1 (TAB1), TNF receptor associated factor 2 (TRAF2) and several mitogen activated protein kinase/extracellular signal regulated kinase kinases (MEKKs) play a role in ET-1 gene transcription. Finally, atrial and brain natriuretic peptides decrease mesangial cell ET-1 production (225).

Mesangial cells express both ETA and ETB (Figures 3 and 4). Initial studies, conducted before anti-ET receptor antibodies and a large variety of receptor-specific agonists and antagonists were available, demonstrated that mesangial cells expressed ET receptor mRNA, bound ET, and that ET elicited Ca^{2+} signaling and cGMP production, however the specific isoforms involved were uncertain (6, 23, 66, 318, 405, 420, 423, 429, 516). Subsequently, strong evidence for both ETA- and ETB-mediated actions in mesangial cells has been obtained. In addition, ETA and ETB are expressed by cultured human mesangial cells (158, 315), while prominent mesangial cell ETA immunostaining is present human kidney sections (481). A notable aspect of mesangial cell ET receptors is that their binding and signaling are downregulated by pre-incubation with ET-1 (receptor desensitization). ET-1 markedly reduced ET-1 binding capacity without affecting its affinity in cultured rat mesangial cells (23). Similar desensitization, in terms of evoked $[Ca^{2+}]_I$ responses, was observed in these cells (403).

2. ET actions in mesangial cells—ET-1 exerts multiple effects on mesangial cells, including cell contraction, hypertrophy, proliferation and extracellular matrix accumulation (411). The latter responses may be important in the pathophysiologic effects of ET-1, however this discussion will focus primarily on cell contraction as this may be involved in modulating GFR and/or RBF. ET-1 causes mesangial cell contraction primarily through ETA activation (20, 401, 428) (Figure 4). ET-1 activates phospholipase C (PLC) (194, 406, 407) and PKC (403), leading to augmented inositol triphosphate levels, increased Na/H exchange, cell alkalinization and elevated $[Ca^{2+}]_I$ (20, 403, 405, 406). The increased $[Ca^{2+}]_I$ derives from intracellular stores and influx through dihydropyridine-insensitive pathways (403, 516). Low ET-1 concentrations (0.1-10 pM) cause slow sustained increases in $[Ca^{2+}]_I$ that are dependent upon Ca^{2+} influx through a voltage channel-independent mechanism, whereas higher ET-1 concentrations (≥ 100 pM) elicit a rapid and transient increase that is dependent upon Ca^{2+} release from intracellular stores through activation of PLC and PKC (406). The increase in $[Ca^{2+}]_I$ is primarily due to ETA (516); ETB activation can increase $[Ca^{2+}]_I$, albeit much less than that seen with ET-1 (516).

Several pathways involved in cell contraction downstream of ET-1-induced increases in $[Ca^{2+}]_I$ in mesangial cells have been identified. Proline-rich tyrosine kinase-2 (Pyk2), the only cytoplasmic tyrosine kinase activated by mobilization of $[Ca^{2+}]_I$ (255), undergoes ET-1-stimulated autophosphorylation in a Ca^{2+}-dependent manner in mesangial cells (412). Pyk2 causes p38 MAPK activation in mesangial cells, another kinase known to mediate cell contraction (412). Pyk2 can also phosphorylate p130Cas, causing increased interaction with BCAR3, a protein with a GDP exchange-factor-like domain; this may lead to BCAR3-mediated GTP-loading of Rap1 with resultant alterations in the actin cytoskeleton and cell contraction (367). ET-1 can also increase CrkII adapter protein association with BCAR3 in mesangial cells, another potential mechanisms for regulating cell contraction (368). In addition to the Pyk2 pathway, ERK5 may be involved since ET-1 activates ERK5 in human mesangial cells, while ERK5 knockdown inhibits mesangial cell contraction (85). ET-1 may also modulate mesangial cell contraction through activation of Src tyrosine kinases; this may involve ß-arrestin-1-mediated recruitment of Src to complex with the ET receptor (181),

adhesion-dependent activation of Src by interaction with focal adhesion kinase (49), and Ca^{2+}/CaM-dependent protein kinase II (CaMK II) (473). In addition, ET-1 actions on mesangial cells may relate, at least in part, to its transactivation of the EGF receptor, an effect that has been shown to activate the adaptor protein p66Shc, $G\alpha_{i3}$, ß1Pix and ERK1/2 (51, 171). Finally, ET-1 induces platelet activating factor (PAF) release by mesangial cells, while inhibition of PAF release decreases ET-1-mediated mesangial cell contraction (265, 289).

ET-1-induced mesangial cell contraction could be partially mitigated by the vasorelaxants prostaglandin E_2 (PGE_2) and NO. ET-1, via ETA, increases phospholipase A_2 and COX2 (but not COX1) activity, leading to elevated PGE_2, and to a lesser extent, thromboxane A_2 (120, 174, 404). ET-1 stimulated COX2 activity in mesangial cells depends upon intracellular Ca^{2+} release, CAMK, non-receptor linked protein tyrosine kinases, and nuclear factor of activated T cell 2 (NFAT2) (68, 419). ET-1 may also stimulate NO production by mesangial cells. ET-3 rapidly increases NO-dependent cGMP production by isolated rat glomeruli and cultured rat mesangial cells though activation of ETB, release of Ca^{2+} from intracellular stores, and CaM (89, 318, 423). However, the system is clearly more complex in that prolonged exposure (many hours) to ET-1 inhibits cytokine-induced NOS2 activity in rat mesangial cells (via ETA) (27, 162). The explanation of these diverse effects of ET on NO production is unknown, however it seems likely that, in contrast to the likely inhibition of NOS2 gene transcription, the rapid induction of NO occurs through activation of NOS1 or NOS3 and does not involve regulation of gene transcription.

All of the above studies have been done using in vitro preparations, hence the physiologic relevance of ET regulation of mesangial cell function is an open question. Given this limitation, it is notable altered mesangial cell ET-1 production has been observed in hypertension. In particular, Ikeda et al. reported that phorbol ester, AII, and vasopressin (AVP) increased ET-1 secretion to a greater extent in mesangial cells from SHR hypertensive as compared to WKY normotensive rats (178). These findings suggest that heightened ET-1-mediated mesangial cell contraction, resulting in reduced GFR, might pay a role in impaired renal Na excretion in some hypertensive states.

IV. ET and sodium transport

A. Overview of ET regulation of Na transport

As has been alluded to previously, ET in the kidney exerts complex regional actions, involving paracrine and autocrine pathways. This has generally confounded interpretation of studies that either: 1) examined the effects of systemically or intrarenally administered ET agonists or antagonists; or 2) analyzed changes in renal ET-1 levels or urinary ET-1 excretion in response to stimuli. Nonetheless, an abbreviated review of these types of studies can provide some insight into the role of renal ET in the regulation of Na transport, as well as the problems encountered with using these types of approaches.

Exogenously administered ET-1, if given at a sufficient dose, typically reduces RBF and GFR in experimental animals and humans (5, 166, 201, 334, 345, 410). Such renal hemodynamic effects are usually associated with reduced urinary Na and water excretion, particularly when RBF is reduced by at least 25% (64, 201). However, when ET receptor agonists were given at doses with only modest or no effects on RBF or GFR, urinary Na excretion either increased (81, 147, 163, 387) or did not change (118, 137, 197, 383). One group found that renal decapsulation or maintaining renal perfusion pressure at baseline values with an aortic clamp prevented ET-1-induced natriuresis, suggesting that the natriuretic effect of exogenous ET-1 was due to increased BP (460). In addition, as will be discussed in the section on Na transport, inconsistent findings about ET agonist-induced

natriuresis may relate to differential activation of ET receptor isoforms. The bottom line from these studies, however, is that the role of the ET system in controlling renal Na excretion cannot be clearly defined by maneuvers that exert generalized renal effects.

Changes in renal ET levels or urinary ET-1 excretion have been measured in response to alterations in fluid volume status. While a few studies have seen either decreased (in humans) (287, 349, 394) or unchanged (in humans) (13, 114, 165) urinary ET-1 excretion following Na loading, the majority of studies have found increases in urinary ET-1 excretion (in humans and experimental animals) (4, 69, 170, 176, 192, 220, 274, 374, 381). Thus, taken together, the bulk of evidence indicates that volume expansion is associated with increased renal ET-1 production. This conclusion suggests that endogenous renal ET-1 exerts a net natriuretic effect; as will be seen from the discussion below, this does indeed appear to be the case.

B. ET regulation of proximal tubule Na transport

1. ET production by the proximal tubule—Although early studies did not routinely detect ET-1 mRNA in the proximal tubule (PT) (458, 459), the majority of studies have demonstrated that this nephron segment synthesizes ET-1 (Figure 5). Proximal tubule ET-1 protein release and/or mRNA content have been confirmed using LLC-PK_1 cells (a porcine PT cell line) (396), cultured rabbit PT cells (214), isolated or in situ rat PT (54, 291, 495), and cultured human PT cells (313, 514). In addition, ECE-1 protein was detected in human PTs (342). Despite this evidence for PT ET synthesis, the available data suggests that PT produce ET peptides in relatively small amounts compared to most other nephron segments. In cultured rabbit tubular cells, PT released much less ET-1 and ET-3 as compared to thick ascending limb and collecting duct (214).

ET-1 production by the PT can undergo regulation, however the identified factors may be more involved in disease than physiologic control. The only agents shown to inhibit PT ET-1 release are epidermal growth factor (EGF) and hepatocyte growth factor (HGF), factors typically associated with renal injury (151). In contrast, a variety of substances and conditions associated with renal injury or inflammation enhance PT ET-1 production, including hypoxia (305), thrombin, transforming growth factor-ß (TGF-ß), TNF-α and IL-1ß (308). Additionally, high density lipoproteins stimulated ET-1 release by human proximal tubular cells (313), while plasma proteins such as albumin and immunoglobulin G increased ET-1 release by a rabbit PT cell line (528); these findings suggest that nephrotic syndrome may lead to enhanced PT ET-1 production. Finally, activation of PKC increases ET-1 secretion by LLC-PK_1 cells (308). Taken together, the above studies indicate that PT ET-1 production is subject to regulation, however whether or not this is involved in control of Na transport is unknown. That such alterations might occur is suggested by one study in which an increase in ET-1 mRNA and protein was observed in PTs of uninephrectomized SHR rats as compared to WKY controls (250). Clearly, studies on the effect of blood pressure, extracellular fluid volume (ECFV), interstitial pressure and vasoactive factors on PT ET-1 production are needed.

2. ET receptor expression by the proximal tubule—Peptide binding, immunostaining, RT-PCR and functional studies convincingly demonstrate that the PT expresses ET receptors, albeit in smaller amounts than more distal nephron segments (226, 304, 431) (Figure 3). Despite some disparate results, the bulk of evidence indicates that PT (rat and human) likely express both ETA and ETB. ETB mRNA, protein and/or binding patterns in PT have been generally, albeit not unequivocally detected (314, 320, 439, 481, 509). In addition, as described below, ET-1 modulation of PT function via ETB activation has been repeatedly demonstrated. Proximal tubules in rat and human also likely express

ETA (314, 508), although this has not been universally observed (481). In summary, although expression is low, the PT appears to express both ETA and ETB.

ET receptor expression by the PT may be regulated, both in terms of degree of expression and interaction with other plasma membrane receptors. Dopamine D3 receptors may interact with ETB; D3 and ETB in rat PT co-immunoprecipitated, while WKY PT cell ETB expression was increased by D3 activation (this was dependent upon extracellular Ca^{2+} or dihydropyridine-sensitive Ca^{2+}-channels) (517). Notably, SHR PT ETB levels were reduced as compared to WKY, and were also decreased by D3 activation, raising the possibility that D3 regulation of ETB is aberrant in some forms of hypertension (517). AT1 receptors may also interact with ETB; WKY PT AT1 and ETB co-localize and co-immunoprecipitate (523). Further, AT1 activation increased ETB cell surface expression in WKY, but not SHR, PT cells, while ETB activation, in turn, reduced AT1 receptor expression in WKY, but not SHR, PT cells (523, 524). Thus, ETB may physically associate with D3 and AT1 receptors. Further, alterations in ETB regulation, leading to diminished ETB activity, may occur in some forms of hypertension.

3. ET actions in the proximal tubule—ET-1 modulation of PT Na transport is complex (Figure 5); conflicting results have been obtained by several laboratories. Some groups have found that ET-1 reduces PT Na and fluid transport. Whole animal studies, using lithium clearance, found that intravenous ET-1 decreased rat PT fluid reabsorption (147, 324). In support of this, ET-1 (1 nM) reduced fluid and bicarbonate absorption, in part by inhibition of Na/K ATPase activity, in microperfused isolated rat proximal straight tubule (127). ET-1 also decreased rat PT brush border membrane Na-glucose co-transporter activity (273), while both ET-1 and ET-3 inhibited Na/K ATPase activity in isolated rat PT (312). However, other groups have found no effect of ET-1 on PT Na reabsorption using lithium clearance in humans (410) or isolated PT Na/K ATPase activity (520). Finally, yet other investigators have reported that ET-1 enhances PT Na reabsorption. ET-1 (given apically) increased rat PT fluid reabsorption in micropuncture studies, albeit SNGFR was also greatly augmented (362). ET-1 also increased Na/H antiporter and Na/HCO3 co-transporter activity in rabbit renal cortex plasma membrane vesicles (93). In addition, ET-1 stimulated Na/H exchange and Na/P_i co-transport by rat renal cortical slices (via activation of protein kinase A (PKA) and PKC (144) and increased Na/H exchange activity in PT-like OKP cells (via PKC) (469).

The reasons for the divergent results on ET-1 regulation of PT Na transport are not fully understand, but may relate, at least in part, to the concentration of the peptide. In a key study, Garcia and Garvin found that low concentrations of ET-1 (0.1 pM) enhanced PT fluid absorption (via PKC), while high concentrations of ET-1 (1 nM) reduced fluid transport (via PKC-, COX-, and lipoxygenase-dependent mechanisms) (123). In agreement, blockade of 5-lipoxygenase or leukotriene C4/D4 abrogated ET-1-induced natriuresis in rats (as assessed by lithium clearance) (324). Similarly, inhibition of ω-hydroxylase prevented ET-1 reduction of rat PT Na/K ATPase activity, while ET-1 stimulated PT 20-hydroxyeicosatetraenoic acid (20-HETE) production (103). Thus, it may be that low concentrations of ET-1, sufficient to only activate PKC, lead to augmented PT Na reabsorption; high ET-1 levels may reduce PT Na transport through modulation of arachidonate-dependent pathways. However, the net effect of ET-1 on PT Na reabsorption under physiologic conditions remains an open question.

The mechanisms by which ET-1 exerts biphasic effects of ET-1 on PT Na reabsorption are speculative. One possibility is differential activation of ET receptor isoforms, however this has not been clearly demonstrated. Little data is available with regard to ETA in the PT, however ET-1 stimulation of 20-HETE (which inhibits Na/K ATPase activity) in rat PT has

been reported to be mediated by ETA (103). In contrast, ET-1 and ET-3 were equipotent in decreasing Na/K ATPase activity in rat PT (312), suggesting that ETB activation may also be involved. Similarly, ETB mediated reduced Na/K ATPase activity in PT from WKY rats (517). ETB may also decrease PT Na transport via induction of NO. ETB activation increases cGMP levels in LLC-PK_1 cells (most likely through a Ca^{2+}-dependent pathway) (187, 320); cGMP, in turn, can inhibit PT Na transport (360, 471). Taken together, these data suggest that both ETA and ETB mediate inhibition of PT Na transport, albeit the signaling pathways may differ.

ETB also appear capable of augmenting PT Na transport; this effect occurs largely through activation of Na/H exchange. Initial studies demonstrated that ET-1 increases Na/H exchange in OKP cells transfected with ETB, but not ETA (60). The ETB effect was due to enhanced Na/H exchanger 3 (NHE3) activity, was mediated by the COOH-terminal tail and the second intracellular loop of ETB (248), and was involved tyrosine kinase pathways (61). ETB stimulation of Na/H exchange activity is Ca^{2+}- and Rho kinase-dependent, requires phosphorylation and exocytosis of NHE3 into the apical membrane (339), and may involve G_i-mediated inhibition of cAMP accumulation (144, 320).

It is apparent from the above discussion that the different effects of ET-1 on PT Na transport pathways are not readily explained by differences in receptor isoform-specific responses. While identification of the responsible mechanisms remain elusive, it may be germane to note that ET-1 modulation of NHE3 and Na/K ATPase may serve different purposes. In particular, and as will be discussed in the section on acid/base, ET-1-induced NHE3 activation may be primarily involved in augmenting H^+ secretion in response to metabolic acidosis (339). In contrast, Na/K ATPase regulation may be more involved in responses to alterations in blood pressure or ECFV. Clearly, further elucidation of the factors regulating ET-1 production and ET-1 responsiveness is needed.

C. ET and the thin limb of Henle's loop

The biology of ET in the thin limb of Henle's loop has been minimally investigated. In general, the data on thin limb ET production is conflicting. Some investigators have reported ET-1 protein or mRNA in this nephron segment in the rat (291) and human (314), whereas others have failed to observe ET-1 protein or mRNA in rat (38, 495) or human (341). Even if the thin limb does makes ET-1, it is most likely in very small amounts.

Only one study has examined ET receptors and signaling in thin limbs; in acutely isolated rat thin descending limbs contained ETA and ETB mRNA, while only ETA activation increased $[Ca^{2+}]_i$ (21). The ET-1 stimulated Ca^{2+} signal was reduced in descending limbs from hypertensive rat strains (SHR and Lyon hypertensive) as compared to normotensive WKY and Lyon strains, however the biologic relevance of this is unknown.

D. ET regulation of thick ascending limb NaCl transport

1. ET production and receptor expression by the thick ascending limb—There is not universal agreement on whether or not thick ascending limb (TAL) synthesizes ET-1. Several groups failed to detect ET-1 protein and/or mRNA in rat or human TAL (38, 341, 458, 459, 495). In contrast, ET-1 production was observed in TAL from rabbit and rat (54, 159, 214, 215), while ECE-1 mRNA was observed in rat TAL (84). TAL ET-1 release was greater than PT, but less than collecting duct (214, 215). Taken together, these data suggest that TAL likely do produce ET-1, albeit in relatively low amounts that can make its detection difficult (Figure 6).

Factors regulating TAL ET-1 production are not well known. One study found that increasing osmolarity stimulated cultured rat TAL ET-1 production; since high salt intake raises outer medullary tonicity, this suggests that TAL ET-1 release may be coupled to Na load (159). As will be described below, ET-1 can inhibit TAL Na reabsorption, hence Na intake-induced alterations in TAL ET-1 activity may provide one mechanism for regulating ECFV.

TAL respond to ET-1 via ETB activation (159). However, the available data is contradictory on ET receptor expression. Rat TAL were found to express ETB, but not ETA, protein and mRNA (116, 440). In contrast, no or extremely faint ET receptor expression was detected in rat TAL (78, 431, 481). Thus, TAL appear to contain ETB, although at very low levels.

2. ET actions in the thick ascending limb—ET-1 can inhibit Cl transport in the TAL through NO-, and possibly PKC-, dependent decreases in NKCC2 activity (Figure 6). ET-1 reduced Cl transport in rat cortical TAL through activation of ETB and ensuing increases in $[Ca^{2+}]_i$. and stimulation of NO (the ET-1 effect was abolished by L-NAME) (330). In a similar study, ET-1 inhibited rat medullary and cortical Cl transport vis ETB and PKC, but was independent of prostaglandins, cAMP or alterations increases in $[Ca^{2+}]_I$ (76). ET-1 increases NOS3 expression and NO production by rat MTAL, an effect that is mediated by ETB and PI3K (160). In addition, ET-1 stimulated of MTAL NO production is absent in MTAL from NOS3 deficient mice (161); this effect was Akt-dependent and involved phosphorylation of NOS3 at Ser^{1177}. Since NO can inhibit Na-K-2Cl cotransport in TAL (reviewed in (316)), the above studies paint a convincing picture that ET-1, via ETB activation, stimulates NO and potentially other signaling pathways, to reduced TAL NKCC2 activity. There is evidence that this system is physiologically relevant. As mentioned earlier, high salt intake raises medullary osmolality (159); this was associated with increased TAL NO3 expression which could be prevented by non-selective ET receptor blockade. Further, increased osmolarity stimulated cultured rat TAL NOS3 expression and this could be prevented by ETB blockade (159). Thus, high salt intake increases medullary tonicity, releases ET-1 which, via ETB stimulation of NO, inhibits TAL NaCl reabsorption. The ultimate role of autocrine ET system in controlling BP and ECFV remains uncertain; insights may be gained from studies using mice deficient in TAL ETB and/or ET-1.

In addition to NO, ET may activate other signaling mechanisms that could impact TAL NaCl transport. ET-1 activates the MAPK cascade in rat MTAL, potentially involving non-NO pathways (442). Another interesting possibility is 20-HETE. While not studied in the TAL, ET-1 increases PT 20-HETE, a potent inhibitor of the Na/K ATPase (103). The TAL also produces 20-HETE where it has been shown to inhibit NKCC2 activity, in part by blocking Na/K ATPase as well as a 70 pS apical potassium channel (reviewed in (378, 526)). Thus, studies on ET-1 regulation of TAL 20-HETE, and how this is involved in mediating responses to Na intake, are clearly indicated.

E. ET regulation of collecting duct Na transport

1. Baseline ET production by the collecting duct—The CD is the predominant source of ET-1 in the kidney (212). Within the CD, numerous studies have repeatedly shown that the inner medullary CD (IMCD) produces the most ET-1, at least in the rat and rabbit (54, 214, 458, 459). In addition, porcine and human IMCD produce ET-1 mRNA and protein (19, 213, 341). The outer medullary CD (OMCD) produces the second most amount of ET-1 in the CD (54, 216, 341, 458, 459); both OMCD and IMCD have high ECE-1 content (342). The cortical CD (CCD) synthesizes less ET-1 than elsewhere in the CD, but more than any other nephron segment (214, 291). Similarly, the entire CD expresses relatively high ET-3, albeit much less than ET-1 (214, 441). While specific CD cell types

have not been examined, given that the IMCD produces the most ET-1, it is likely that the principal cell is the major site of ET-1 synthesis in the CD.

Cultured rat IMCD, mouse CCD and MDCK cells secrete 2-10 fold greater ET-1 onto the basolateral as compared to the apical side (218, 386, 447, 457). Since most CD ET receptors are located basolaterally, this suggests that ET-1 potentially functions as an autocrine factor in the CD.

2. Regulation of ET production by the collecting duct (Figure 7)—CD ET synthesis is controlled by ECFV status. Indirect evidence for this comes from studies in which Na loading increases rat medullary ET-1 mRNA, ECE-1 mRNA and protein, and urinary ET-1 excretion (4, 110). More direct evidence comes from studies in which the increase in urinary ET-1 excretion observed following Na loading is substantially blunted in mice with CD-specific knockout of the ET-1 gene (4).

How ECFV expansion stimulated CD ET-1 production is unclear, however it does not appear to relate to circulating hormones. AVP, bradykinin and norepinephrine have no effect on ET-1 release of cultured mouse, rat and/or porcine IMCD cells (OMCD or CCD have not been studied, primarily due to inability to obtain sufficient tissue) (216, 219, 284, 446, 447). Aldosterone increases renal ET-1 mRNA in adrenalectomized rats (499), while DOCA/high Na increases medullary and IMCD ET-1 content (170). Aldosterone enhances cultured mouse IMCD ET-1 gene expression (143); this effect has been ascribed to stimulation of Sgk1 through derepression of ET-1 gene expression by inhibition of Dot1a-Af9-induced histone hypomethylation (525). As will be discussed below, ET-1 has a pronounced natriuretic effect on the CD, hence aldosterone induction of CD ET-1 mitigate the anti-natriuretic effects of aldosterone, but does not explain how ECFV expansion increased CD ET-1 production.

The effect of local factors that respond to ECFV on CD ET-1 production has been examined, however there is as yet no clear consensus. High Na intake increases medullary (at least outer medullary) osmolality (159) and medullary ECE-1 content (110), while renal medullary administration of hypertonic, but not isotonic, NaCl or mannitol into rats increased urinary ET-1 excretion (31). Media made hyperosmolar with betaine or urea enhanced ET-1 production (via p38 MAPK and ERK activation) by MDCK cells, a canine distal nephron cell line (236). In addition, media made hyperosmolar with NaCl or urea stimulated ET-1 synthesis by porcine IMCD cells (284), while hyperosmolar NaCl increased ET-1 protein and/or mRNA content in rat and rabbit IMCD (513). While this makes a nice story, wherein Na loading increases medullary tonicity, leading to increased ET-1 and an ensuing natriuresis, unfortunately there is much conflicting data. For example, hypertonic urea or mannitol have not been consistently found to increase IMCD ET-1 production (513). To make matters even more puzzling, several groups have reported that hyperosmolar media, particularly when due to relatively impermeable solutes like NaCl, raffinose or mannitol, inhibited ET-1 secretion by MDCK or rat IMCD cells (220, 386). The reasons for these disparate results are not readily apparent. The possible of a biphasic ET-1 response to media hyperosmolality was raised by the findings that 6 hr exposure to hypertonic NaCl increased ET-1 release by mouse CD cell lines, while 24 hr exposure reduced ET-1 secretion (447). However, this pattern has not been observed by others. This latter group also noted that AVP was required in order to see CD cell responsiveness to hyperosmolarity, but AVP was not needed for the response in other studies. Thus, there are not obvious differences in study conditions or cell types that explain the varying results. In addition, all of these studies have been conducted on cells in vitro. In essence, it appears that the effect of environmental osmolarity, including the effect of specific solutes, will not be resolved until studies can be conducted using in vivo models. For example, studies examining the effect of

intramedullary infusion of hypertonic saline, or correlation of CD ET-1 mRNA with medullary tonicity, may begin to shed some light on this issue. Finally, from a strictly teological standpoint, while interstitial tonicity can change in the medulla in response to alterations in Na intake, such effects are not likely to occur in the renal cortex; thus, CCD ET-1 production is probably regulated by other factors.

An interesting possibility for local control of CD ET-1 production relates to tubule fluid flow. It is notable that conditions that increase tubule flow, including high intake or administration of salt, salt plus water, or water alone virtually always increase urinary ET-1 excretion in humans and experimental animals (62, 69, 176, 274, 281, 282, 286, 287, 374, 434, 503, 521). Since, as mentioned above, a significant component of urinary ET-1 excretion derives from the CD (2, 4), then tubule fluid flow, which is common to salt and/or water loading, could play a role in increasing CD ET-1 synthesis. This intriguing possibility has not been examined in CD, however there is evidence from other cell types to support this notion. Increasing flow, with resultant increased shear stress, enhances ET- release by endothelial or mesothelial cells (73, 74, 290, 468). In addition, CD cells are capable of sensing and responding to changes in flow. Such regulation includes alterations in K secretion by mouse CCD in response to varying flow (435, 504), while increased tubule fluid flow augments ENaC open channel probability (Po) in rabbit CCD (294). Furthermore, a potential mechanism of flow detection has been indentified in CD whereby flow-induced bending of primary cilia alters $[Ca^{2+}]_I$ (169, 264, 337, 338, 408). Of course, even if flow does regulate CD ET-1 production, in of itself, it would not discriminate between Na and water loading, so other mechanisms must also be involved.

A number of factors have been shown to affect CD (primarily using cultured rat IMCD) ET-1 synthesis, however these are not clearly associated with ECFV. These include inhibitors of cultured rat IMCD ET-1 release (reduced pH (417), interferon-γ (219), and ATP (175)), while stimulatory factors include hypoxia (285), IL-1ß and TGFß (167, 284, 384).

Relatively little is known about the signaling pathways that control ET-1 synthesis in the CD. However, Ca^{2+} appears to play a pivotal role. Increasing $[Ca^{2+}]_I$ with a Ca^{2+} ionophore augmented ET-1 production by IMCD cells (284), while chelation of intracellular Ca^{2+} markedly decreased IMCD ET-1 synthesis (415). Alterations in $[Ca^{2+}]_I$ likely act through calmodulin (CaM) or CaM kinase since inhibition of these pathways also greatly reduced IMCD ET-1 secretion and mRNA content (415). These effects of the Ca/CaM pathway are mediated, at least in part, through changes in ET gene transcription. Inhibition of CaM did not alter ET-1 mRNA stability, however it did greatly reduced activity of a transfected ET-1 promoter-reporter construct in IMCD cells (415). An interesting aspect of these latter studies was that the transfected ET-1 promoter-reporter constructs revealed maximal activity within 1.72 kb 5’ to the transcription start site with only one-third of this activity in the region 0.36 kb 5’ to the transcription start site; this region of the ET-1 promoter has not been typically described as being involved in mediating the known mechanisms for control of ET-1 gene transcription. In addition, CaM inhibition markedly decreased activity of the 1.72 kb, but not 0.36 kb, promoter regions, while it did not affect activity of transfected ET-1 promoter-reporter constructs in aortic endothelial cells. Thus, CD ET-1 synthesis may be under unique regulation involving Ca^{2+}/CaM-dependent pathways. Further exploration of these intracellular signaling pathways controlling ET-1 production by CD should lead to important insights into how not only CD ET-1 synthesis is regulated, but may suggest how ECFV is coupled to this system.

Finally, it is pertinent to note that hypertension has been associated with possible changes in CD ET-1 production. For example, IMCD from hypertensive SHR rats secreted less ET-1

than did IMCD from normotensive WKY rats, while SHR had reduced ET-1 in the outer and/or inner medulla as compared to WKY rats (136, 173, 210). Renal papillary ET-1 content and mRNA are also reduced in Prague hypertensive and Dahl S rats (465). While studies have been quite limited in humans, involving only a small number of patients, individuals with essential hypertension (especially of the salt-sensitive type), have reduced urinary ET-1 excretion (164, 176, 527). Thus, CD ET-1 production may be reduced in the hypertension. As will be discussed below, such an alteration in CD ET-1 could potentially be involved in the pathogenesis and/or maintenance of the hypertensive state.

3. ET receptor expression by the collecting duct—Numerous studies, using binding or autoradiography, have found that the medulla in general, and the CD in particular, is the predominant site of renal ET binding in several species, including man (215, 428, 492, 515) (Figures 3 and 7). Binding, autoradiographic, immunofluorescent, and mRNA studies reveal that the renal medulla and the CD primarily express ETB, with the greatest expression being in the IMCD (19, 58, 199, 217, 239, 431, 440, 481). CD also express ETA, albeit in much smaller amounts than ETB. While some studies have failed to detect ETA message or protein in rat or human CD (58, 198, 431, 440), several other groups, using binding, immunostaining, autoradiography or electron microscopy have found ETA in CD from dog, rat and rabbit IMCD and/or CCD (50, 91, 217, 311, 481, 518). A recent study demonstrated ETA in the basal infoldings of the CD, and particularly in the IMCD (508). Furthermore, as described below, evidence exists for functional ETA in the CD. Finally, as alluded to earlier, the bulk of ET receptors are expressed on the basolateral side of the CD (albeit only IMCD was studied) (218). Thus, given the preferential CD basolateral ET-1 secretion (218, 386, 446, 457), the stage is set for an autocrine ET effect in the CD.

CD ET receptor expression may be subject to regulation. AVP has been shown to downregulate CD ET receptors. AVP, forskolin or dibutyryl cAMP decreased ET-1 binding affinity to rat CCD (430). Interestingly, this effect was prevented by PKA inhibition; ETB, but not ETA, contain a consensus amino acid sequence for PKA-mediated phosphorylation. Similarly, AVP, via cAMP, reduced the B_{max} for ET-1 binding to rat IMCD associated with a decrease in ETB mRNA (498). AII may also downregulate CD ET receptors; AII has been shown to decrease ETA and ETB binding and mRNA content in rat IMCD (via a PKC) (497). It is notable that CD ETB expression is reduced in congestive heart failure models (116, 500), while AII receptor blockade can mitigate this downregulation (500). These findings raise the interesting possibility that AVP and AII, which can stimulate tubule Na reabsorption, reduce ET receptor expression in order to mitigate the natriuretic effects of ET-1 in the CD.

4. Overview of ET regulation of Na transport in the collecting duct—ET-1 can directly reduce Na reabsorption in the CD (Figure 7); the peptide decreases Na transport by rat and rabbit CCD (243, 448). This effect of ET-1 is likely due to inhibition of the major Na reabsorptive pathways in the CCD, namely Na/K ATPase and the epithelial Na channel (ENaC). ET-1 reduces ouabain-sensitive oxygen consumption (which presumably reflects Na/K ATPase activity) in rabbit IMCD cells (520). Beyond this, however, ET effects on Na/K ATPase in the CD have not been investigated. In contrast, much more is known about ET-1 modulation of ENaC in the CD. The peptide decreases amiloride-sensitive Na uptake by amphibian distal nephron A6 cells (via an increase in mean Na channel closed time) (122) and by 3T3 cells stably expressing ENaC (135). Furthermore, ET-1 reduced ENaC open probability in isolated split-open rat CCD (40). The physiologic relevance of CD-derived ET in controlling urinary Na excretion was demonstrated using mice with CD-specific knockout of the ET-1 gene (CD ET-1 KO) (4). These mice lack ET-1 specifically in principal cells of the CD; they are hypertensive by about 15 mmHg systolic BP during normal salt intake, and develop marked hypertension (by about 35 mmHg systolic BP) on a

high Na diet. The hypertension in CD ET-1 KO mice is associated with excessive weight gain and reduced Na excretion when the animals are subjected to Na loading. In addition, increases in renal perfusion pressure were associated with reduced Na excretion in CD ET-1 KO mice (381). Increased ENaC-mediated Na reabsorption may be involved since amiloride largely prevented the elevated BP and Na retention in the CD ET-1 KO mice (4). Thus, CD-derived ET-1 is an important physiologic regulator of Na reabsorption and arterial BP, most likely through, at least in part, inhibition of CD ENaC activity.

5. ET receptor isoforms mediating collecting duct Na transport—ETB appears to be the primary mediator of ET-1 inhibition of CD Na transport (Figure 7). ETB agonism inhibits Na channel activity in A6 cells (122), while ETB, but not ETA, antagonists prevent ET-1 inhibition of ENaC open channel probability in rat CCD (40). Infusion of an ETB antagonist directly into the rat renal medulla infusion decreases volume expansion-induced natriuresis (145), while intramedullary infusion of an ETB agonist increases Na excretion in wild type, but not ETB-deficient, rats (299). These ETB-deficient rats are generated using animals with a null mutation in ETB, while containing a transgene that confers relatively gut-specific ETB expression (the latter prevents intestinal aganglionosis) (126). The rescued ETB deficient rate develop exaggerated hypertension in response to DOCA and high salt intake that is ameliorated by amiloride (125, 126). CD ETB has been most directly implicated in regulation of Na excretion in studies using mice with CD-specific knockout of the ETB gene (CD ETB KO) (129). CD ETB KO mice had about an 8 mmHg elevation in systolic BP during normal salt intake, while systolic BP was increased by about 20 mmHg during high salt intake; the hypertension is associated with impaired ability to excrete a Na load. Note that the magnitude of the hypertension in these CD ETB KO mice is about 50-60% of that seen in CD ET-1 KO animals, suggesting that CD ETB do not account for all of the antihypertensive and natriuretic effects of CD-derived ET-1.

There is conflicting data on the ability of ETA to modulate Na transport in the CD. In A6 cells, ET-1, In the presence of ETB antagonism, enhances Na channel activity (122). In contrast, intramedullary administration of ET-1 causes a natriuresis in ETB-deficient rats that is prevented by ETA blockade (298). Curiously, this latter study found apparent ETA-mediated natriuresis only in female ETB-deficient rats. Only male ETB-deficient animals had ET-1- induced reductions in medullary blood flow, suggesting that ET-1 (presumably via ETA) natriuresis in males is prevented by a concurrent fall in medullary perfusion, thereby mitigating any direct tubular effect of the peptide. Perhaps of greatest direct relevance is the finding that mice with CD-specific knockout of ETA (CD ETA KO) have no detectable alterations in arterial BP or urinary Na excretion on a normal or high salt diet (132). Thus, taken together, the above studies do not provide convincing evidence that ETA plays a role in the physiologic regulation of CD Na reabsorption. However, a subsequent study indicates that the simple paradigm of CD ETA and ETB operating as individual receptors with well-defined agonists and signaling pathways may not be valid. In this study, mice with CD-specific knockout of both ETA and ETB (CD ETA/B KO) were found to hypertension and Na retention that was similar to that seen in CD ET-1 KO mice on a normal or high Na diet, and substantially greater than that in CD ETB KO animals (381). These results were unexpected since CD ETA KO mice had no phenotype. One possible explanation is that both ETA and ETB can exert natriuretic effects, but that ETB are more effective (since ETB are much more prevalent in CD). In this scenario, absence of CD ETA may be obscured by abundant ETB, while absence of ETB may be particularly compensated for by upregulation of ETA (this has not been specifically investigated). Another possibility is that CD ET receptors may undergo homo- and hetero-dimerization with potential functional implications. For example, one might envision that ETB homodimers and ETA/B heterodimers normally exist since the ETB isoform predominates, however in CD ETB KO, ETA homodimers may form and exert a natriuretic effect. Resolution of these possibilities

will be quite challenging, but represents an exciting new avenue for investigation into how ET receptors operate.

6. Mechanism of ET regulation of collecting duct Na transport—Several kinases have been implicated in ET-1 inhibition of CD NaCl transport (Figure 7). PKC may play a role in ET-1 inhibition of AVP-stimulated chloride transport in the rat CCD (448), however is does not appear to mediate ET-1 effects on ENaC in this nephron segment (40). ET-1 inhibition of ENaC was dependent upon Src kinase activity in 3T3 cells transfected with the three ENaC isoforms (135). In addition, ETB-mediated inhibition of ENaC open channel probability in isolated split-open CCD required Src kinase and MAPK1/2 (40), while ET-1 increases MAPK activity in rat OMCD and IMCD (442). Thus, ET-1 inhibition of CD ENaC is due, at least partly, to ETB activation with resultant involvement of Src and MAP kinases. In this regard, it is relevant to note that MAPK-mediated ENaC phosphorylation reduces both ENaC activity and number (32, 56, 109, 395). Recent studies using cultured CD cells led credence to the notion that ET-1 can reduced ENaC apical membrane expression in that long-term ET-1 exposure reduced ENaC channel number through enhanced ß1Pix binding to 14-3-3ß, preventing 14-3-3ß interaction with the ubiquitin ligase Nedd4-2, and thus enhancing ENaC internalization and degradation (323).

Nitric oxide also mediates, at least in part, ET-1 inhibition of CD Na reabsorption. Nitric oxide has been demonstrated to inhibit Cl transport in TAL (330), reduce Na flux in CCD (316), and decrease ENaC activity in cultured CD cells (154). IMCD from ETB-deficient rats have decreased NOS activity (436), while ETB activation increases NOS1-dependent NO production and cGMP accumulation in rat IMCD cells (416). Further, ET-1 increased NOS1 protein expression in IMCD3 cells (possibly via ETA) (421), while ETA or ETB blockade reduces NOS3 mRNA and protein expression in rat IMCD cells (515). The most direct evidence for a role for NO in mediating ET-1 natriuretic actions comes from studies using CD ET-1 KO mice (381). These animals had reduced NO metabolite excretion during normal or high Na intake as well as during graded increases in renal perfusion pressure; this was associated with reduced inner medullary NOS1 and NOS3 activities. Importantly, inhibition of NO formation greatly increased BP in control animals, but had a minimal effect on BP in CD ET-1 KO mice; in essence, the difference in BP between the two groups was eliminated. In agreement with these findings, the natriuretic response to intramedullary infusion of an ETB agonist was reduced by NOS1 inhibition (299). Thus, these studies strongly indicate that NO is a key mediator of ET-1-induced natriuresis; how this occurs remains to be determined.

Initial studies suggested that prostaglandins might be involved in the natriuretic response to ET-1, however subsequent studies have not supported this notion. Cyclooxygenase blockade was originally shown to abolish ET-1 inhibition of Na/K ATPase activity in rabbit IMCD (520), while ET-1 was found to stimulate rabbit and mouse IMCD PGE_2 production (via ETB and COX2) (221, 520). In contrast, generalized COX or COX2-specific inhibition did not alter Na retention or BP in CD ET-1 KO mice (131). In addition, CD ET-1 KO actually had increased IMCD PGE_2 levels, i.e., COX activity appears to be upregulated. Hence, eicosanoids do not appear to be central in mediating the natriuretic effects of ET in the CD.

7. Paracrine effects of collecting duct-derived ET—Since the CD produces very large amounts of ET-1, the potential exists for CD-derived ET-1 to exert paracrine effects. While a number of obvious possibilities exist, including modulation of regional blood flow or transport functions in neighboring tubules, this has not been definitively shown. However, there is some data to suggest the interesting possibility that CD-derived ET-1 may modulate renin production. CD ET-1 KO mice, despite being volume expanded and hypertensive, have plasma renin activity and aldosterone levels that are not different from controls (4).

These mice have renal renin contents similar to controls, while their hypertension is significantly abrogated by either AII or aldosterone blockade (130). Thus, the hypertension in CD ET-1 KO animals may be partly due to failure to suppress renin production. Since ET-1 is well described to inhibit renal renin production (3, 100, 244, 263, 288, 297, 358, 359, 373, 385, 388, 427), and since CCD and connecting segment are adjacent to the juxtaglomerular apparatus and afferent arteriole (355, 464), the possibility exists that CD-derived ET-1 exerts a paracrine inhibitory effect on renal renin production.

V. ET regulation of water transport

A. Overview of ET and water transport

Intravascularly administered ET increases urinary water excretion, even if given at doses that reduce RBF (137, 197, 364, 383). ETB-specific agonists also increase urine flow, although interpretation of these studies is confounded by the renal vasodilatory effects of these agents (65, 281, 519). In addition, water loading increases human and experimental animal urinary ET-1 excretion (220, 282, 503, 521). Thus, the renal response to water loading is increased ET-1 synthesis which, in turn, can exert a diuretic effect.

The evidence is compelling that ET inhibits water reabsorption in the CD. ET-1 dose-dependently decreases AVP-stimulated water (but not urea) transport in rat CCD and IMCD (90, 296, 309, 448). Mice lacking ET-1 in the CD have altered water metabolism, including reduced diuresis after acute water loading, decreased plasma AVP concentration under euvolemic conditions, and exaggerated responsiveness to exogenous administered AVP (increased urine osmolality, AQP2 mRNA and AQP2 phosphorylation) (128). Thus, absence of CD ET-1 augments AVP responsiveness, indicating that endogenous CD ET-1 functions as a physiologic inhibitor of AVP-induced water retention.

B. Signaling pathways in ET regulation of water transport

ET inhibition of AVP-stimulated water transport in the CD is partly due to reduced adenylyl cyclase activity; ET inhibits AVP-stimulated adenylyl cyclase-dependent cAMP accumulation in rat and/or porcine CCD, OMCD and IMCD (90, 221, 284, 296, 309, 431, 448, 449) (Figure 7). ET-1 may exert this cAMP-inhibiting effect in an autocrine manner since anti-ET-1 antibodies enhanced AVP-stimulated cAMP accumulation in IMCD cells (218). Further, ET-1 does not inhibit dibutyryl cAMP-stimulated water transport in the IMCD (309), indicating that the peptide's effect depends upon adenylyl cyclase activity. CD isolated from CD ET-1 KO mice have increased cAMP accumulation in response to AVP or forskolin (128) and this is associated with increased expression of adenylyl cyclases 5 and/or 6 (414). Thus, there is compelling evidence that CD ET-1 acts as a physiologic inhibitor of AVP-stimulated adenylyl cyclase activity in the CD.

The diuretic effect of ET-1 on the CD is primarily due to activation of ETB; ETB-specific agonists inhibit AVP-induced cAMP accumulation in rat IMCD, while ETB-, but not ETA-, specific antagonists, block ET-1's effect (90, 221, 502). Notably, mice with CD-specific ETA deletion have increased plasma AVP levels, increased ability to eliminate a water load, and reduced AVP- and forskolin-stimulated cAMP accumulation (the latter in acutely isolated IMCD) (132). Since these mice express only ETB in the CD, this raises the possibility that enhanced ETB binding by ET-1 (since ETA are absent) promotes a diuresis. In addition, these mouse studies suggest that CD ETA may exert an antidiuretic effect, however more direct evidence of this is needed. Finally, the diuretic effect of ET-1 on the CD may be mitigated by AVP itself; AVP reduces ETB affinity for ET-1 in rat CCD (via a PKA) (430).

The inhibitory effect of ET-1 on cAMP accumulation is due, at least in part, to inhibitory G proteins, PKC and changes in intracellular Ca^{2+}(Figure 7). Pertussis toxin prevents the inhibitory effect of ET-1 on AVP-induced cAMP and water transport in the IMCD, implicating G_i in this process (221, 296). These effects of ET-1 on AVP responsiveness are dependent upon PKC and are associated with increased inositol phosphates in CD cells (221, 296, 449, 450, 501, 502). In turn, ET-induced increases in $[Ca^{2+}]_i$ are likely involved in this process. The data on ET-1 actions on intracellular Ca^{2+} in CD cells is somewhat conflicted, however this likely reflects ET-1 modulation of multiple regulatory pathways. In general, ET-1 seems to cause an initial rapid rise, follow by a sustained elevation, in CD $[Ca^{2+}]_I$ (284, 302). The initial increase in $[Ca^{2+}]_I$ is probably related, at least in part, to release of Ca^{2+} from cell stores. While initial studies showed that the rapid and transient increase in $[Ca^{2+}]_I$ depended upon extracellular Ca^{2+} entry (302), subsequent studies found that extracellular Ca^{2+} entry was uninvolved (235, 296). In contrast, the prolonged ET-1-induced increase in $[Ca^{2+}]_I$ most likely depends upon extracellular Ca^{2+} entry which is partly mediated by dihydropyridine-sensitive Ca^{2+} channels (235, 243). Initial studies found no evidence for dependence upon dihydropyridine-sensitive Ca^{2+} channels (302), however subsequent studies indicated that the sustained increase in $[Ca^{2+}]_I$ was blocked by nifedipine or similar agents (235, 243, 296). These increases in $[Ca^{2+}]_I$ may play a role in ET-1 inhibition of water transport since increased $[Ca^{2+}]_I$ has been demonstrated to reduce AVP-stimulated adenylyl cyclase activity in rat IMCD (via PLC-induced activation of PKC) (437). However, the component of ET-1-augmented $[Ca^{2+}]_I$ that involves dihydropyridine-sensitive Ca^{2+} entry may not be involved in regulation of water transport since inhibition of these channels did not change AVP-induced cAMP accumulation in rat CD (449, 450).

While ET-1 can stimulate CD production of prostaglandins and NO, and these substances have been shown to modify AVP actions, there is no evidence to date that they are involved in ET-1 regulation of water transport. Inhibition of COX does not change ET-1 effects on AVP-stimulated cAMP content in cortical through inner medullary CD (221, 449, 450). In addition, neither NOS blockade nor factors that augment NO production (NO donors, L-arginine, NADPH, or tetahydrobiopterin) altered ET-1 inhibition of AVP-stimulated cAMP accumulation in the IMCD (416).

VI. ET and acid/base transport

A. Overview of ET and acid/base transport

Published data to date support the notion that renal ET-1 helps mediate increased kidney acid (H^+) excretion in response to a systemic H^+ challenge, but does not measurably contribute to H^+ excretion under “control” conditions. Because diets in industrialized societies are typically acid inducing (353), “control” conditions typical of humans in industrialized societies might be one in which ET-mediated kidney H^+ excretion *is* the basal state. Additionally, ET-1 mediates increased kidney acidification in experimental models of chronic kidney disease with reduced GFR (488), a syndrome with a significant and increasing prevalence. Furthermore, data from animal (327) and more recently from human (328) studies suggest that increased kidney ET-1 action induced by metabolic acidosis associated with reduced GFR contributes to progressive GFR decline in some types of progressive nephropathies. Hence, understanding the ET-mediated contribution to kidney acidification has important physiologic, pathophysiologic, and possibly clinical relevance.

B. Overview of the renal response to a systemic H^+ challenge

The routine H^+ challenge to systemic acid-base homeostasis for most humans is H^+ derived from liver metabolism of dietary protein (252, 353). Metabolism of sulfur- and phosphate-containing amino acids yields H^+ and most diets in industrialized societies include dietary

protein with a high proportion of such amino acids (353). This metabolically produced, "fixed" H^+ might increase body fluid [H^+] and induce a physiologic response designed to restore optimum [H^+]. Two responses designed to maintain and/or restore optimal body fluid [H^+] are 1) H^+ buffering (251) in which body buffers bind added H^+ to minimize the [H^+] increase that would otherwise occur, and; 2) "fixed" H^+ excretion, predominantly by kidneys (146, 252). Because H^+-titrated buffers less effectively buffer subsequently added H^+, buffer-bound H^+ must eventually be excreted to regenerate body buffers and restore buffering capacity. Consequently, all added H^+ must be excreted to restore acid-base homeostasis. Thus, ET-mediated kidney H^+ excretion might routinely contribute to the H^+ challenge induced by our industrialized society diets.

Most experimental models exploring the effect of an H^+ challenge on systemic acid-base balance use H^+ challenges that are in excess of that routinely encountered by animals or humans. Such studies show an important role for enhanced proximal tubule acidification in mediating kidney H^+ excretion (39). The Na^+/H^+ exchanger type 3 (NHE3) is the major luminal H^+ transporter in the proximal tubule, while more modest contributions are made by the H^+-ATPase (340). Large H^+ loads lead to increased activity of both NHE3 (340) and H^+-ATPase (52) in the proximal tubule. Similarly, these large H^+ loads increase acidification in the thick ascending limb of the loop of Henle (42). Because NHE is the major luminal H^+ transporter in the loop of Henle with smaller contributions by H^+-ATPase (42), the acidification increase in response to this large H^+ challenge presumably includes stimulated NHE activity. Finally, these large H^+ loads administered systemically enhance distal nephron acidification (18, 256, 275) that is mediated by enhanced activity of NHE2 (275), H^+-ATPase (276), and H^+, K^+-ATPase (400). In short, large systemic H^+ loads lead to increased acidification in most acidifying nephron segments that have been studied.

Animals and humans rarely face H^+ challenges of the magnitude used in most experimental models. The more routine H^+ challenge faced by humans is much more modest and is associated with little to no measurable changes in plasma acid-base parameters (245). More modest H^+ challenges that substantially increase urine net H^+ excretion do so without measurable changes in plasma acid-base parameters or proximal nephron acidification, but do increase distal nephron acidification (487, 488, 490). Furthermore, unlike the mineral salts typically used to induce H^+ challenges in experimental models, the H^+ challenge faced by humans is typically provided by H^+-producing dietary protein. Increased H^+-producing dietary protein increases distal nephron acidification (203, 204, 242, 494) that is clearly evident with comparable HCO_3 delivered loads (203). Enhanced distal nephron acidification in response to a more physiologic H^+ challenge is mediated by both decreased HCO_3 secretion and increased H^+ secretion whether the challenge is induced by modest NH_4Cl ingestion (487, 488, 490) or by H^+-producing dietary protein (203, 204, 242, 494). Nevertheless, increased intake of H^+-producing dietary protein also increases proximal tubule acidification as indicated by overall recovery of increased filtered HCO_3 load mediated by increased whole kidney and single nephron GFR induced by high protein diet (494).

In vivo studies show that a modest and chronic dietary H^+ challenge can increase kidney net H^+ excretion and distal nephron acidification without measurable changes in plasma acid-base parameters, but with detectable increases in H^+ content of the kidney interstitium (487). Such a systemic H^+ challenge also increases renal ET-1 protein (262, 488) and its mRNA (203, 262). This increase in kidney ET-1 is detectable within the interstitium (203), however the cellular source of this ET is not clear. As has been discussed previously, virtually every cell type within the kidney can synthesize and release ET-1. Furthermore, endothelial and epithelial cells likely release the majority of their ET-1 abluminally, thereby facilitating autocrine and paracrine effects within the kidney (467).

C. Adrenal cortex ET production and its role in kidney acidification

Acid-stimulated ET secretion from non-kidney tissue might directly or indirectly enhance kidney acidification in response to an H^+ challenge. ET-stimulated aldosterone secretion (14, 79, 307) enhances distal nephron acidification induced by H^+-producing dietary protein (204). In addition, dietary mineral H^+ (379) and H^+-producing dietary protein (393) increase plasma aldosterone. Furthermore, an H^+ extracellular environment increases aldosterone secretion by adrenocortical cells in vitro (237). The adrenal cortex synthesizes ET (14) that stimulates secretion of mineralocorticoids (14, 79) and glucocorticoids (79). Because glucocorticoids (9, 26) and mineralocorticoids (94) stimulate H^+ secretion in kidney tubule epithelium, adrenal cortical ET might indirectly increase kidney acidification through increased mineralocorticoid and glucocorticoid secretion.

D. ET effects on acidification

1. Cells—ET increases intracellular pH of many cell types in vitro including skin fibroblasts (124), platelets (451), vascular smooth muscle (172), glomerular mesangial (407), cardiac myocyte (470) and kidney epithelial cells (469). ET increases Na^+/H^+ antiporter activity in kidney epithelial membrane vesicles (93) and cortical slices (144) and is the cell membrane H^+ transporter that is most consistently influenced by ET in these indicated cell types.

2. Renal tubules—In addition to enhancing cell membrane H^+ transport, ET enhances acidification across kidney tubule epithelia. ET mediates enhanced proximal tubule acidification in chronic metabolic acidosis induced by NH_4Cl loading through stimulation of ETB but appears not to mediate proximal tubule acidification in non-H^+-loaded animals (246, 247). ET, via ETB activation, mediates enhanced distal nephron acidification induced by dietary H^+ loading with NH_4^+ salts (488) and H^+-producing dietary protein (203, 204, 242, 494). ET also stimulates H^+ secretion in alpha intercalated cells and decreases HCO_3 secretion in beta-intercalated cells of the rabbit cortical collecting duct in an in vitro model of metabolic acidosis (455). The latter studies support that these effects of ET are direct rather than acting through other mediators. In addition, exogenous ET stimulates distal nephron acidification in vivo (484). As observed in the proximal tubule, ET appears not to mediate basal distal nephron acidification in control animals (203, 204, 488). In the loop of Henle, ET stimulates local NO release (329) and NO inhibits thick ascending limb Na^+/H^+ exchange (127), suggesting that ET indirectly inhibits acidification in this segment. Because ET-induced NO action on thick ascending limb Na^+/H^+ exchange activity might more importantly inhibit NaCl reabsorption in this nephron segment (330), this indirect action of ET action in the thick ascending limb would increase distal nephron Na^+ delivery with an anticipated increase in distal nephron Na^+/H^+ exchange activity (479), enhancing distal nephron acidification. Consequently, the net effect of ET is increased proximal and distal nephron acidification.

E. Direct mechanisms by which H^+-induced ET activity increases kidney acidification

ET increases proximal tubule acidification in H^+-challenged animals and cells primarily if not exclusively through enhanced activity of NHE3 (59, 246, 247), the major H^+ transporter in the proximal tubule (340). ET-1-mediated stimulated NHE3 activity in opossum kidney cells (a proximal tubule cell line) appears to act through ETB, but not ETA (60). The ETB effect was mediated by the COOH-terminal tail and the second intracellular loop of ETB (248), and involved tyrosine kinase pathways (59). ETB stimulation of NHE3 activity is Ca2+- and Rho kinase-dependent, requires phosphorylation and exocytosis of NHE3 into the apical membrane (339), and might involve Gi-mediated inhibition of cAMP accumulation (320). Because ET increases Na^+/H^+ exchange in the distal tubule and NHE2 appears to be

the major apical NHE isoform responsible for luminal H^+ secretion in this segment (472), ET appears to increase NHE2 activity. As noted, ET stimulates H^+ secretion in alpha intercalated cells (455) whose luminal acidification is mediated predominantly by H^+-ATPase (453, 478). These in vitro studies (455) suggest that ET can stimulate H^+-ATPase activity without acting through other mediators. On the other hand, ET might indirectly stimulate distal nephron H^+-ATPase in vivo (203, 204) through ET-induced stimulation of aldosterone secretion that in turn increases distal nephron H^+-ATPase activity (204). Whether ET stimulates H^+-ATPase activity in vivo directly and/or through other mediators awaits clarification.

F. Indirect mechanisms by which H^+-induced ET activity increases kidney acidification

Because many cytokines influence distal nephron acidification and ET influences levels of many of these cytokines, ET might affect kidney acidification indirectly as well as directly. As discussed earlier, ET increases distal nephron H^+-ATPase activity in vivo through stimulated aldosterone secretion (204). Of the three major distal nephron H^+ transporters (Na^+/H^+ exchanger, H^+-ATPase, and H^+, K^+-ATPase) (113), dietary H^+ leads to ET-mediated stimulated activity of Na^+/H^+ exchange (246, 247) and H^+-ATPase (203, 204). Dietary H^+-induced, ETmediated distal nephron acidification appears not to be mediated by stimulated H^+, K^+-ATPase activity (204). Although K^+ depletion increases H^+, K^+-ATPase activity (94, 489), stimulated H^+, K^+-ATPase in chronic metabolic alkalosis associated with K^+ depletion appears not to be mediated by ET (489). In addition, ET might indirectly enhance kidney acidification through ET-stimulated secretion of mineralocorticoids and glucocorticoids by the adrenal cortex (26, 79) that stimulates H^+-ATPase (26) and Na^+/H^+ exchange (9, 26), respectively, in kidney tubules as discussed earlier.

Reduced HCO_3 secretion contributes importantly to enhanced acidification induced by chronic dietary ingestion of mineral H^+ (488, 490) and H^+-producing dietary protein (203, 204, 494). The phenomenon of reduced HCO_3 delivery to the terminal distal nephron leads to increased net H^+ excretion (113) but this phenomenon also enhances NH_4^+ secretion (211) and permits secreted H^+ to titrate non-HCO_3 buffers and thereby constitute net H^+ excretion rather than HCO_3 recovery (39). ET reduces distal nephron HCO_3 secretion (that reduces distal nephron acidification) (203, 204, 494) and does so indirectly through stimulated NO production (494). Other studies show that NO stimulates overall acidification in both the proximal (471) and distal (454) nephron in other settings.

G. ET interaction with other mediators of kidney tubule acidification

Other hormones/cytokines modify kidney tubule acidification but few if any have been studied to determine if and/or how any of them interrelate with ET to modify kidney tubule acidification. AII stimulates luminal Na^+/H^+ exchange and basolateral Na^+/HCO_3 co-transport (133) as well as stimulates H^+-ATPase (466) in the proximal tubule, increasing acidification in this nephron segment. Whether stimulation of Na^+/H^+ exchange by AII and ET-1 is additive has not been reported in kidney epithelia. Furthermore, AII stimulates distal nephron H^+-ATPase (258, 259) thereby increasing acidification in this nephron segment as well. Because AII stimulates ET-1 secretion in kidney mesangial cells (222), some AII effects on acidification might be mediated through ET-1. On the other hand, cAMP stimulates cortical collecting duct HCO_3 secretion, thereby decreasing acidification in this nephron segment (390). Because cAMP inhibits cytokine-stimulated ET-1 secretion in kidney mesangial cells (223), cAMP might decrease this effect of ET to decrease distal nephron HCO_3 secretion (494). The net cAMP effect would be reduced distal nephron acidification.

Figure 8 outlines a proposed cascade by which ET increases kidney acidification in response to an H^+ challenge:

H. ET role in enhanced kidney acidification associated with pathophysiologic conditions

Enhanced distal nephron H^+ secretion that "maintains" chronic metabolic alkalosis is mediated by kidney ET (485, 486, 491). Conversely, it is reduction of this enhanced distal nephron H^+ secretion (rather than an induced increase in distal nephron HCO_3 secretion) that "corrects" this disturbed distal nephron acidification in this setting (486). Because K^+ depletion is important in the maintenance of chronic metabolic alkalosis (486) and because ET mediates enhanced NHE3 activity in an autocrine fashion in proximal tubule epithelium exposed to an acid environment in vitro (10), K^+ depletion appears to be an important component of this effect. Indeed, K^+ repletion in chronic alkalosis reduces the associated increased urine ET-1 excretion (486), a surrogate of kidney ET-1 production (483), which is characteristic of this disorder (489).

The reduced functioning nephron mass of CKD challenges remaining functioning nephrons to excrete metabolically produced H^+ despite their reduced number. Animals with reduced kidney mass have increased proximal (271) and distal (241, 259, 488) nephron acidification in vivo. Animals with CKD due to reduced nephron mass also have increased urine ET-1 excretion (28, 488), consistent with increased endogenous kidney ET-1 production (483, 488). ET mediates enhanced distal nephron acidification in remnant kidneys (488), an experimental model of CKD.

I. Possible pathophysiologic role of ET in syndromes with enhanced kidney acidification

Animals with chronic metabolic alkalosis develop fibrosis with subsequent calcium deposition in kidney parenchyma (257). In addition, experimental animals with reduced kidney mass develop glomerulosclerosis with tubulo-interstitial fibrosis (141). ET increases kidney matrix production and fibrosis in vitro (369) and might mediate glomerulosclerosis in vivo (354). Consequently, increased ET activity in these and possibly other settings might contribute to associated progressive kidney injury through ET-mediated glomerulosclerosis and fibrosis. Indeed, ET mediates 1) tubulo-interstitial injury in animals with intact nephron that ingest an H^+-inducing diet (492), 2) GFR decline induced by metabolic acidosis in animals with reduced nephron mass (327); and 3) GFR decline in animals with less severely reduced nephron mass without metabolic acidosis but with H^+ retention (493). Consistent with these animal studies, amelioration of the metabolic acidosis of humans with low GFR using dietary alkali reduced parameters of kidney injury, slowed GFR decline, and reduced kidney ET production (328). These recent studies suggest strategies designed to prevent or ameliorate the untoward actions of increased kidney ET activity induced by chronic metabolic acidosis and/or by chronic dietary H^+ will help to slow or stop the associated progressive kidney injury.

VII. ET and the renin-angiotensin system

Renin Release

In vitro studies have shown that ET-1 can inhibit renin release from juxtaglomerular cells through a Ca^{2+} dependent mechanism (280, 348, 426). Consistent with these observations are studies in anesthetized dogs showing that intravenous infusion of ET-1 reduces renin release (263, 317). It appears as though the intrarenal baroreceptor dominates over the direct actions of ET-1 given that higher doses of ET-1 that increase renal vascular resistance, and thus reduce glomerular pressure, actually increase renin release.

ET-1 may also attenuate renin release stimulated by other factors such as isoproterenol and cAMP (244, 288), most likely through ETB-dependent NO release (3, 359, 385). However, the physiological interplay between ET-1 and NO to control renin release has yet to be clarified. This may be due to the conflicting roles proposed for NO more than anything. NO directly stimulates renin release from isolated juxtaglomerular preparations, although NO-dependent vascular relaxation may effectively increase pressure reaching the glomerulus, which would inhibit renin release via the intrarenal baroreceptor (391). In isolated afferent arterioles, inhibition of NO synthase reduces renin release (445). Addition of the ET receptor antagonist, bosentan, reversed the effect of NOS inhibition suggesting that NO functions to inhibit the effects of ET-1 on renin secretion.

The influence of ET-1 on juxtaglomerular cells to attenuate renin secretion is consistent with the general function of ET-1 and ETB to promote sodium excretion, although as described above, ETA appears to function in opposition. Since renin secretion is influenced by many factors, including renal perfusion pressure, sodium intake, and sympathetic nerve activity, the physiological role of ET-1 on renin secretion has yet to be resolved.

Based on current knowledge, we hypothesize that endogenous ET-1 stimulated during high salt intake will attenuate renin release stimulated by other factors such as sympathetic nerve activity. This hypothesis is supported by long-term studies in rats and humans demonstrating increased plasma renin activity following ET receptor blockade (238, 388).

Angiotensin II and ET-1

These vasoactive peptides share many common features in that both are small peptides that activate G-protein coupled receptors, they exert dominant vasoconstrictor effects, and their activities are modulated by changes in dietary salt intake. In addition, there are a number of direct interactions between these systems. AII stimulates release of ET-1 and increases mRNA expression in a variety of cell types, including endothelial cells (97, 98, 180), vascular smooth muscle cells (356) and cardiomyocytes (188). ETA blockade attenuates the vasoconstrictor effects of AII in isolated vascular preparations (53, 475).

Blockade of ET receptors in vivo also inhibits the acute vasoconstrictor response to AII in several vascular beds including the kidney (22, 357, 482). The ability of ET antagonists, either ETA selective or combined ETA/ETB, to inhibit the in vivo actions of AII is most likely attributable to the AII-dependent release of ET-1 from vascular endothelium that in turn activates ETA to produce vasoconstriction. However, AII-induced constriction is much more rapid and shorter-lived compared to ET-1-dependent effects and so a more complicated relationship is likely. Indeed, there have been suggestions that ETA and AT1 receptors may heterodimerize to create an interplay in post-receptor signaling. ET-1 also appears to contribute to the hypertension produced by chronic elevations in AII as again evidenced by the ability of ET antagonists to lower blood pressure in these models (24, 72, 157, 346). The degree of hypertension produced by chronic AII infusion is salt-dependent. Although we know that the ET system is activated by a high salt diet, the potential interaction between AII and ET-1 to influence sodium excretion has yet to be resolved.

VIII. ET and renal nerves

The renorenal reflex involves increased renal pelvic pressure activating nerves in the renal pelvic wall which cause a reflex fall in efferent renal sympathetic nerve activity, stimulating a diuresis and natriuresis (232, 234). ETB activation in Schwann cells surrounding renal afferent nerves can stimulate noradrenergic mediated release of PGE_2, which in turn induces the release of substance P, leading to increased renal afferent nerve activity (231, 233). ETB blockade in the renal pelvis in rats fed a high Na diet reduced renal afferent nerve activity in

response to increased pelvic pressure (231). Hence, at least during high Na intake, ET-1, via ETB, may augment renal mechanosensory nerve activity, thereby increasing the renorenal reflex response and stimulating Na excretion.

While ETB has been clearly implicated in modulating the renorenal reflex, the role of renal pelvis ETA is less clear. In contrast to ETB, ETA are found in smooth muscle of the pelvic wall and not on nerve tissue (233). ETA can enhance smooth muscle contraction, an effect that should increase renal afferent nerve activity (233). However, during low Na intake, ETA, via unclear mechanisms, suppresses renal afferent nerve activity in response to increased pelvic pressure (229, 233). One way ETA may act is through interaction with AII. Similar to ETA activation, AII inhibits the renorenal reflex; the AII effect may be mediated by ETA since: 1) AII effects are not additive with ETA; and 2) ETA blockade prevents AII inhibition of renal nerve activity as well as AII suppression of PGE_2-induced cAMP accumulation and substance P release (229-231). How ETA and AII interact is unclear as well as whether this has physiological relevance.

IX. Renal ET and hypertension

The powerful vasoconstrictor actions of ET-1 make it easy to propose this system as an important contributor to hypertension. Indeed, there are numerous reports that ET-1 production is elevated in animal models and humans (previously reviewed in (177)). The role for ET-1 is complicated by the opposing actions of ETA and ETB and the difficulty of studying a peptide that functions as an autocrine and paracrine factor. Soon after the development of ETA and ETA/ETB antagonists, it became evident that blood pressure lowering actions were observed only in salt-dependent models such as in mineralocorticoid and AII-dependent models as well as the Dahl salt-sensitive rat (177, 331). ET receptor blockade has no effect in other models such as the SHR and the 2-kidney, 1-clip Goldblatt hypertensive rat (260, 261).

Initial studies examining the influence of chronic ET-1 infusion in an attempt to duplicate a model of hypertension also yielded a less than simplistic mechanism of vasoconstriction dependent hypertension. Intravenous infusion of ET-1 for 7 days in Sprague-Dawley rats results in hypertension only when rats are maintained on a high salt intake (95, 295). Similarly, mice expressing a transgene for preproET-1 targeted to the endothelium have normal blood pressures (12), but become hypertensive when maintained on a high salt diet (11).

Pharmacological blockade of ETB or genetic mutation of ETB increases endogenous ET-1 levels, and therefore, increases ETA activation (126, 336). The resulting hypertension can be inhibited with an ETA antagonist and produces a consistent level of hypertension even in animals on a normal salt diet. These findings suggest that ETB normally functions to prevent ETA-dependent hypertension. However, hypertension produced by reduced ETB activity is not simply due to reduced ET-1 clearance since the elevation in blood pressure is highly dependent upon salt intake consistent with salt-dependent increases in ET-1 production and/or activity (126, 336).

Intrarenal production of ET-1 has been difficult to use to assess the role of ET-1 in hypertension due to the contrasting actions of ETA and ETB in the vascular versus tubular system. Increased ET-1 or ET receptor expression may occur in hypertension, but could represent an effort to increase ETB activity, increase sodium and water excretion, and thus lower arterial pressure. On the other hand, increased ETA activity in hypertension could reduce renal blood flow and GFR, and potentially lead to retention of extracellular fluid volume and thus hypertension. Likewise, we know that urinary ET-1 arises from intrarenal sources and can be increased in hypertension, but whether this is spill-over from

overproduction of vascular ET-1, or a consequence of renal tubular ET-1 contributing to the natriuretic actions of the peptide, remains to be determined.

In human hypertension, there are reports of increased or no change in plasma ET-1 (7, 34, 165, 195, 253, 254, 310, 418). As in animal studies, it is not known whether increases in plasma ET-1 represent increased production or reduced clearance of the peptide. The variability in findings could be attributable to several reasons, including the antibody used in the assay, the genetic heterogeneity of the subject population, the level of dietary salt intake, the degree of stress during blood sampling, and any number of other factors. One aspect that appears fairly clear is that plasma ET-1 is elevated in African Americans compared to age-matched Caucasians (102, 108, 452). It is uncertain whether this is related to earlier observations that African Americans have a higher incidence of salt-dependent hypertension (149, 477).

Both ETA and ETA/B antagonists can lower systemic arterial pressure in a wide range of subjects with hypertension (82, 177, 206). Their use has been approved specifically for pulmonary hypertension. To date, there has been only one published phase III study for resistant hypertension (476). Although this initial study demonstrated clear efficacy, the company terminated their development of this compound for apparent lack of efficacy in a second unpublished trial. The reasons for the disparate results in the two trials have not been adequately explained. For a more thorough presentation or discussion of the use of ET antagonists in human hypertension, the reader is referred to other excellent reviews (1, 82, 83, 206, 331).

X. Summary and Conclusion

ET-1 is produced by, and acts upon, virtually every cell type in the kidney. It is not surprising, therefore, that ET-1 exerts multiple effects on the kidney. The major physiologic effects of renal ET-1 are regulation of renal hemodynamics and control of urinary Na, water and acid excretion. In this final section, we provide an overview of the importance of the renal ET system with regard to each of the above physiologic functions.

ET-1 regulation of water transport is the least complex renal physiologic regulatory pathway involving this peptide. High water intake increases renal (probably mainly CD) ET-1 production. ET-1 inhibits, most likely through an autocrine pathway involving ETB, AVP-stimulated cAMP accumulation, leading to reduced AQP2 water channel insertion into the apical membrane and inhibition of water reabsorption. Elimination of CD ET-1 causes impaired excretion of an acute water load, implicating this system in the physiologic regulation of the renal response to enhanced water intake.

ET-1 modulation of renal Na handling involves multiple cells types and includes tubular and vascular elements (Figure 9). Within the nephron, high Na intake increases TAL and CD ET-1 production. TAL-derived ET-1 activates autocrine ETB leading to increased NO production and inhibition of Cl^- transport. CD-derived ET-1 activates ETB, which, through a variety of signaling mechanisms, decreases both ENaC open probability and number. ET-1 from both TAL and CD may act in a paracrine manner to increase medullary blood flow through dilation of vasa recta. The effects of high Na intake on PT ET-1 production are uncertain, however it is possible that autocrine inhibition of Na/K ATPase activity by ET-1 in the PT could contribute to the natriuretic response. High Na intake-stimulated renal ET-1 production is also likely to reduce juxtaglomerular apparatus renin production, although the cellular source of such ET-1 is uncertain. Finally, renal ET-1 may affect renal pelvis mechanosensory nerve activity during high Na intake leading to enhancement of the renorenal reflex. Taken together, these effects of renal ET-1 are of fundamental importance in reducing blood pressure and promoting a natriuresis in response to elevated Na intake.

From the above discussion, it is apparent that, in general, ETB activation has a net antihypertensive and natriuretic effect through renal vasodilation, reduction of renin release, and direct inhibition of nephron Na reabsorptive mechanisms. In addition, collecting duct ETB activation inhibits AVP-stimulated water reabsorption. In contrast, ETA activation leads to reductions in RBF and GFR associated with increases in arterial pressure; tubule ETA modulation of Na and water transport requires clarification. Alterations in renal ET-1 production and/or ET receptor activity may be involved in the pathogenesis of salt-sensitive hypertension. Further studies on how the renal ET-1 system is regulated, and exerts its effects on renal hemodynamics and tubular Na and water transport processes, will likely shed substantial light on normal and disordered regulation of arterial pressure.

Renal ET-1 is also involved in the control of acid/base balance. Acidemia stimulates renal ET-1 production, although the precise cellular sources are uncertain, ET-1 than acts upon the proximal tubule (via ETB) to increase NHE activity, while it stimulates distal nephron proton secretion and bicarbonate reabsorption. While this effect of academia on renal ET-1 production helps maintain acid/base homeostasis, it may also contribute to acidosis-associated progression of chronic kidney disease.

In conclusion, the renal ET-1 is fundamentally important in normal and disordered regulation of renal hemodynamics and multiple tubule transport processes. Continued studies are needed to not only better define how renal ET-1 and its receptors function in health and disease, but to potentially direct future therapies that target specific components in the renal ET system.

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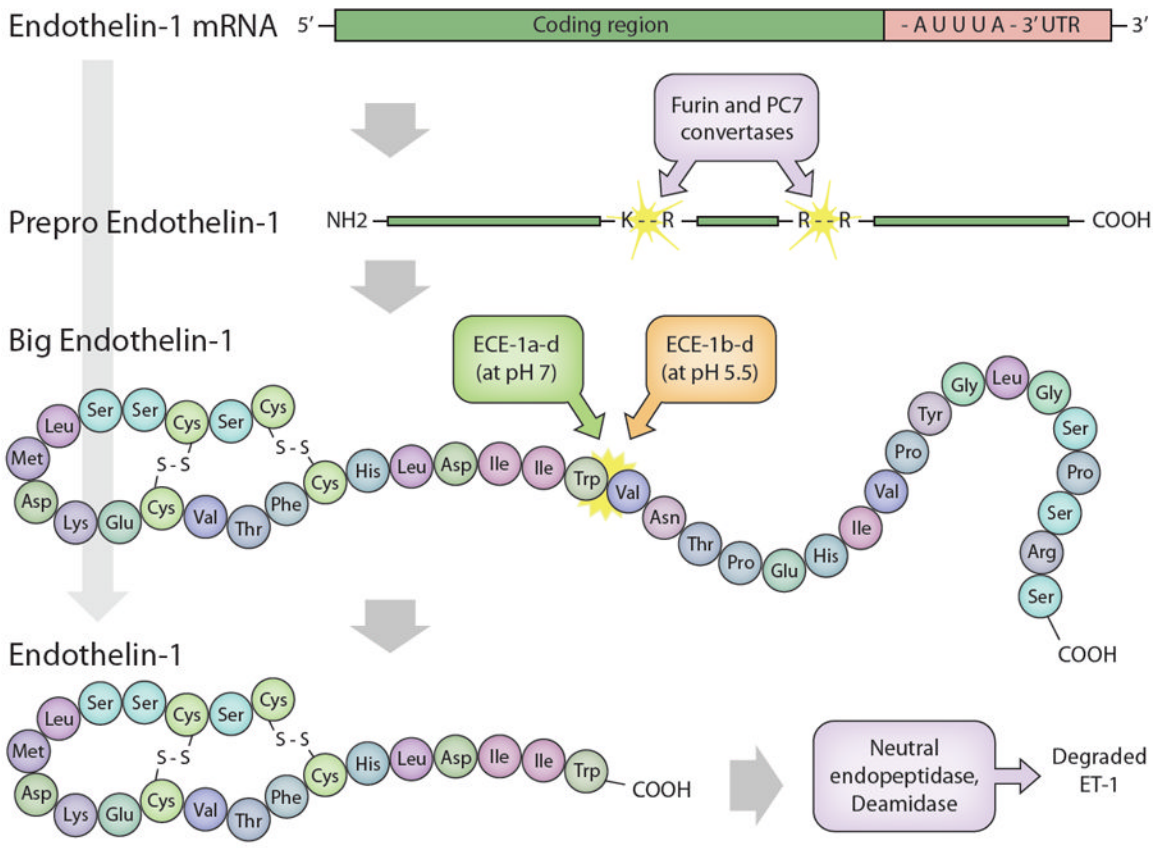

Figure 1.

Biosynthetic and degradation pathways for ET-1. ET-1 mRNA encodes preproET-1. The short signal peptide is cleaved to yield proET-1 which, in turn, is cleaved by furin or PC7 convertases at dibasic amino acids to yield Big ET-1. Big ET-1 is cleaved by different ET converting enzymes (ECE) to mature ET-1. ET-1 is degraded by neutral endopeptidase and deamidase.

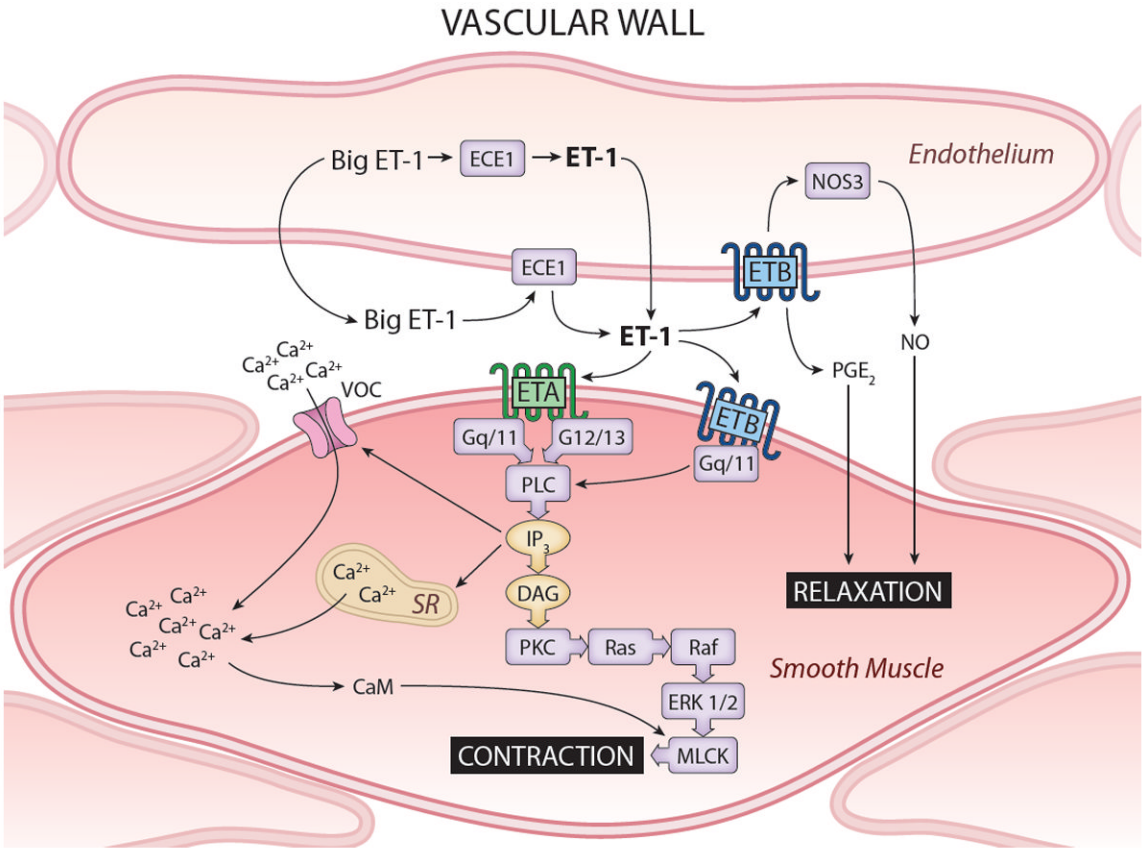

Figure 2.

Schema of ET in vasculature. Endothelial cells express ETB exclusively and are the predominant vascular source of ET-1. ET-1 and nitric oxide synthase 3 (NOS3) can increase ETB activity or amount, respectively, leading to NO and PGE_2 production with resulting vasolaxation. Activation of vascular smooth muscle ETA or ETB leads to a signaling cascade involving G-proteins, phospholipase C (PLC) and inositol triphosphate (IP3) that activate voltage-operated Ca^{2+} channel (VOC) and sarcoplasmic reticulum (SR)-mediated increases in $[Ca^{2+}]_i$ and calmodulin (CaM) activation. CaM, together with activation of protein kinase C (PKC) by diacylglycerol (DAG) and Ras/Raf/ERK1/2 activation, causes myosin light chain kinase (MLCK) activation and cell contraction.

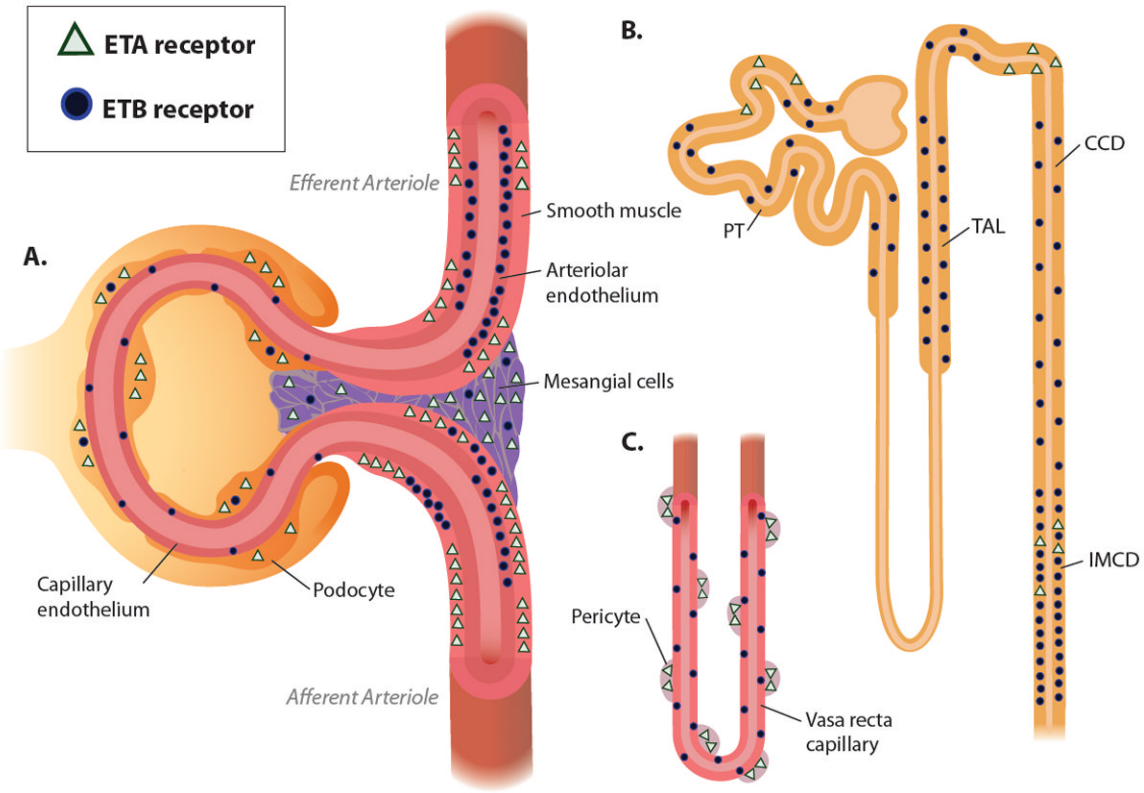

Figure 3.

Schema of functional ET receptors in the glomerulus and renal arterioles (Panel A), nephron (Panel B) and vasa recta (Panel C). A = contractile ETA; B = contractile ETB; white B with shadow: relaxant or natriuretic ETB that stimulates NO production; white A with shadow: natriuretic ETA. The amount of ET receptor shown in a given area is representative of the level of ET receptor activity in that region. Afferent arteriolar smooth muscle has more vasoconstrictive ET receptors than do efferent arterioles, while efferent arteriole endothelium has more vasodilatory ETB than does afferent arteriole (Panel A). Podocytes and mesangial cells contain primarily contractile ETA (Panel A). The inner medullary collecting duct (IMCD) has the greatest density of natriuretic ET receptors, although natriuretic ET receptors exist in the cortical collecting duct (CCD), thick ascending limb (TAL) and proximal tubule (PT) (Panel B). Vasa recta express contractile ETA on pericytes and vasodilatory ETB on endothelial cells (Panel C).

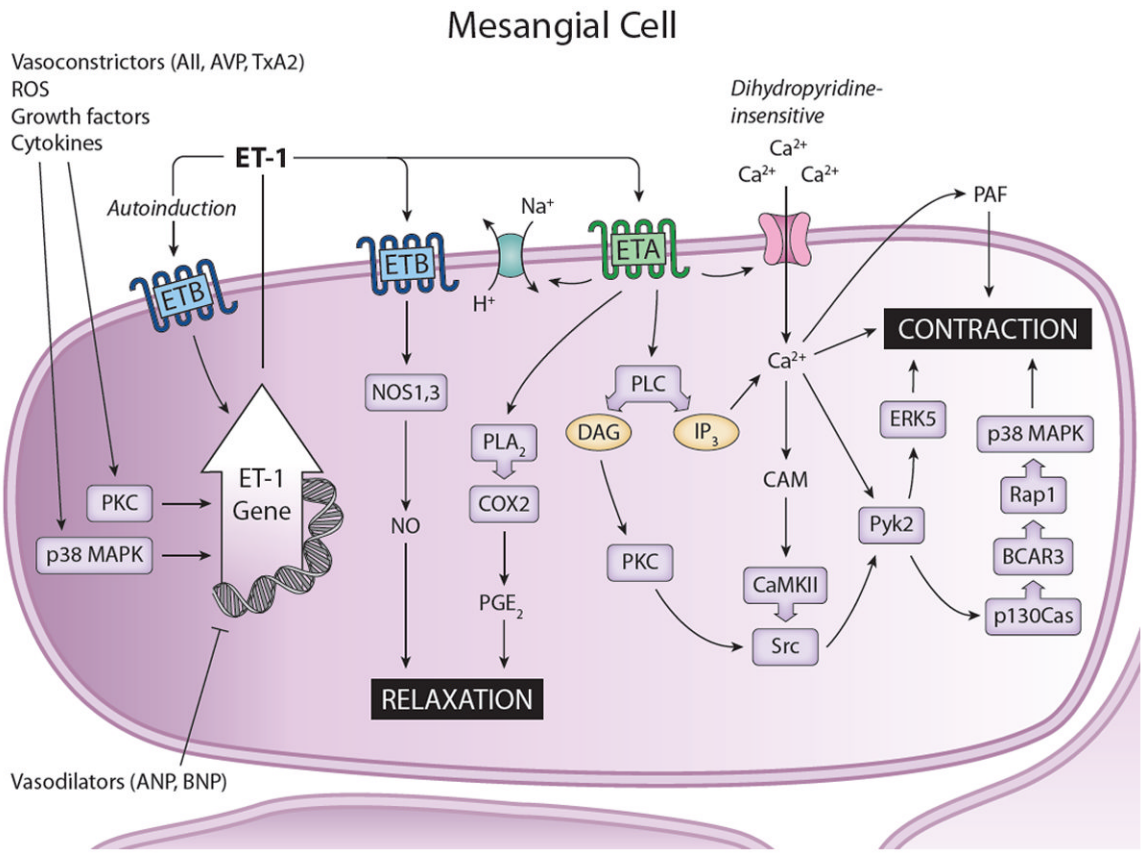

Figure 4.

Synthesis and actions of ET-1 in mesangial cells. A large variety of substances stimulate ET-1 production, including ET-1 itself. Vasodilators tend to inhibit mesangial cell ET-1 synthesis. ET-1 likely acts in an autocrine manner. In general, ETA activation leads to cell contraction, while ETB activation causes relaxation. Please see text for definitions of abbreviations.

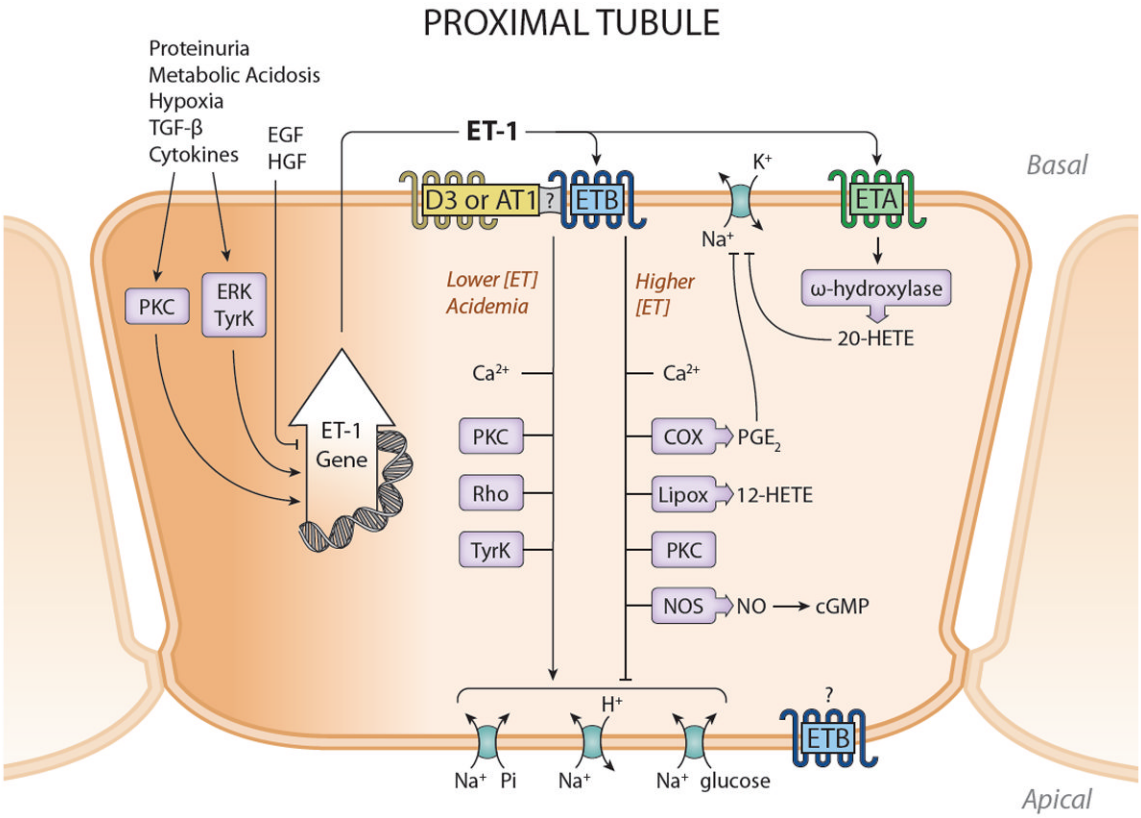

Figure 5.

Synthesis and actions of ET-1 in the proximal tubule. ET-1 production is enhanced during inflammation, hypoxia, glomerular injury and acidemia. Most studies implicate ETB in mediating ET effects on the proximal tubule, although ETA activation may result in inhibition of Na reabsorption. ETB effects appear to depend upon the concentration of ET-1, with lower concentrations stimulating Na transport processes and higher concentrations having the opposite effect. It is likely that ET-1 exerts primary a natriuretic effect on the proximal tubule under physiologic conditions. Please see text for definitions of abbreviations.

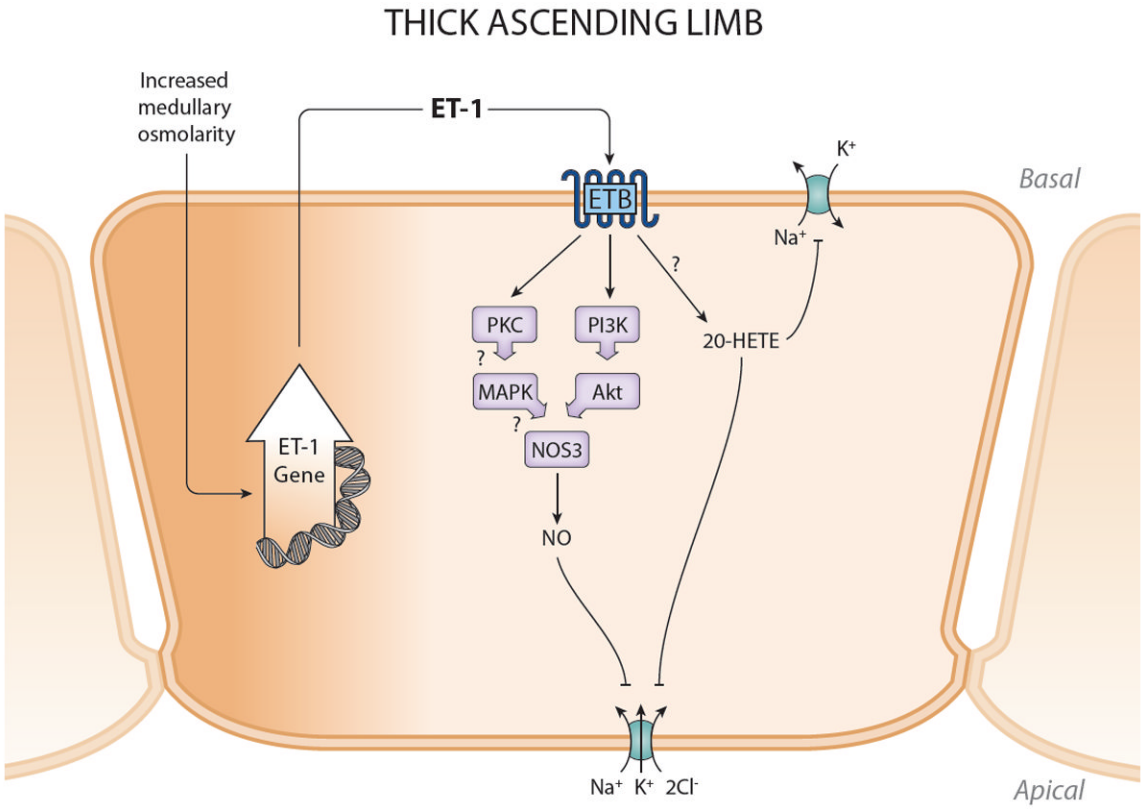

Figure 6.

Synthesis and actions of ET-1 in the thick ascending limb. ET-1 production is stimulated by increased medullary osmolality which occurs during high Na intake. ET-1 can then act in an autocrine manner, via ETB, to stimulate NOS3 activity and inhibit NKCC2. ETB may also increased 20-HETE with possible inhibition of Na/K ATPase activity, although this is unproven. Please see text for definitions of abbreviations.

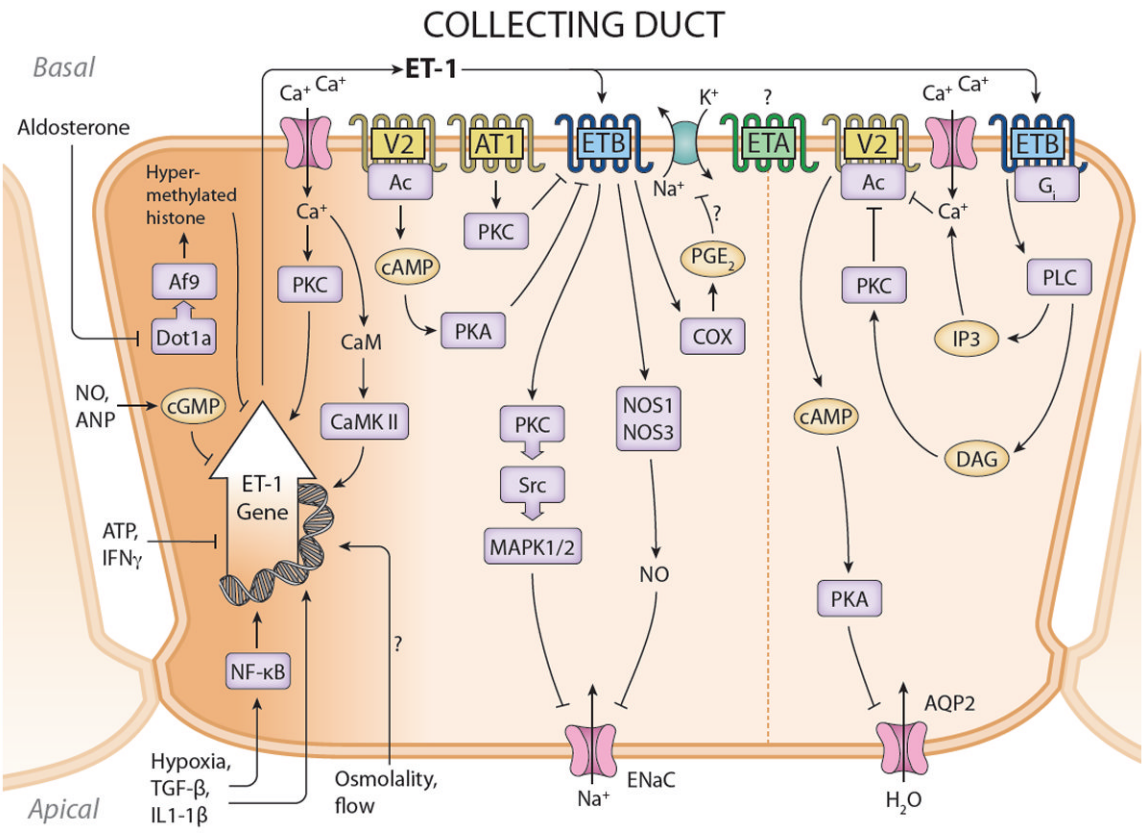

Figure 7.

Synthesis and actions of ET-1 in the collecting duct. ET-1 gene transcription is under complex control, involving transactivators binding to cis elements in the ET-1 promoter, as well as histone methylation. The latter effect mediates aldosterone stimulation of collecting duct ET-1 production; this may serve as a negative feedback regulator of aldosterone-stimulated Na transport in this nephron segment. ETB mediates ET-1 inhibition of water transport, primarily through inhibition of AVP-stimulated adenylyl cyclase (AC) activity. ETB also mediates ET-1 inhibition of ENaC activity; this involves both NO and MAPK. V2 and AT1 receptors have been reported to inhibit ETB expression in this nephron segment. The role of ETA in regulating collecting duct Na and water transport is uncertain. Please see text for definitions of abbreviations.

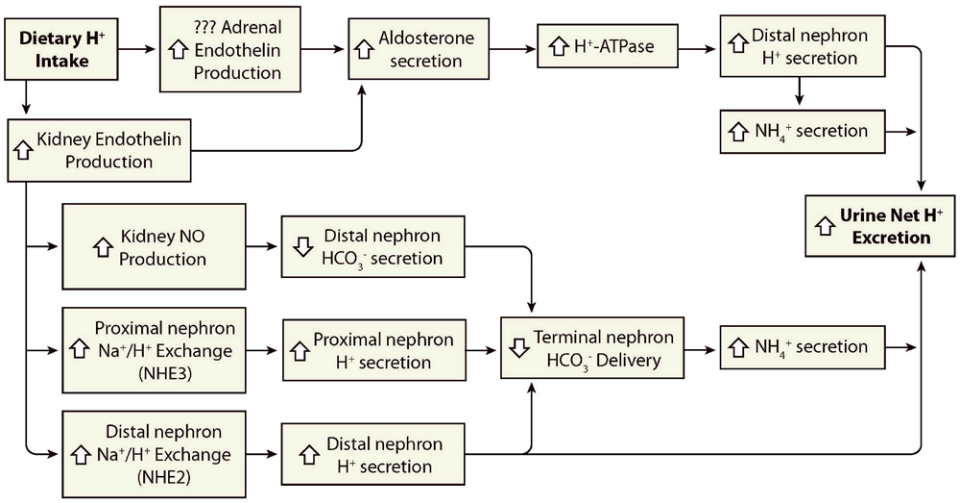

Figure 8.

Role of the renal ET system in control of urinary acid excretion. Dietary acid intake stimulates renal and possibly adrenal ET-1 production. Renal ET-1 increases proximal tubule H+ secretion and distal nephron H+ secretion and bicarbonate reabsorption. Adrenal ET-1 increases aldosterone which stimulates distal nephron H+ secretion. Please see text for definitions of abbreviations.

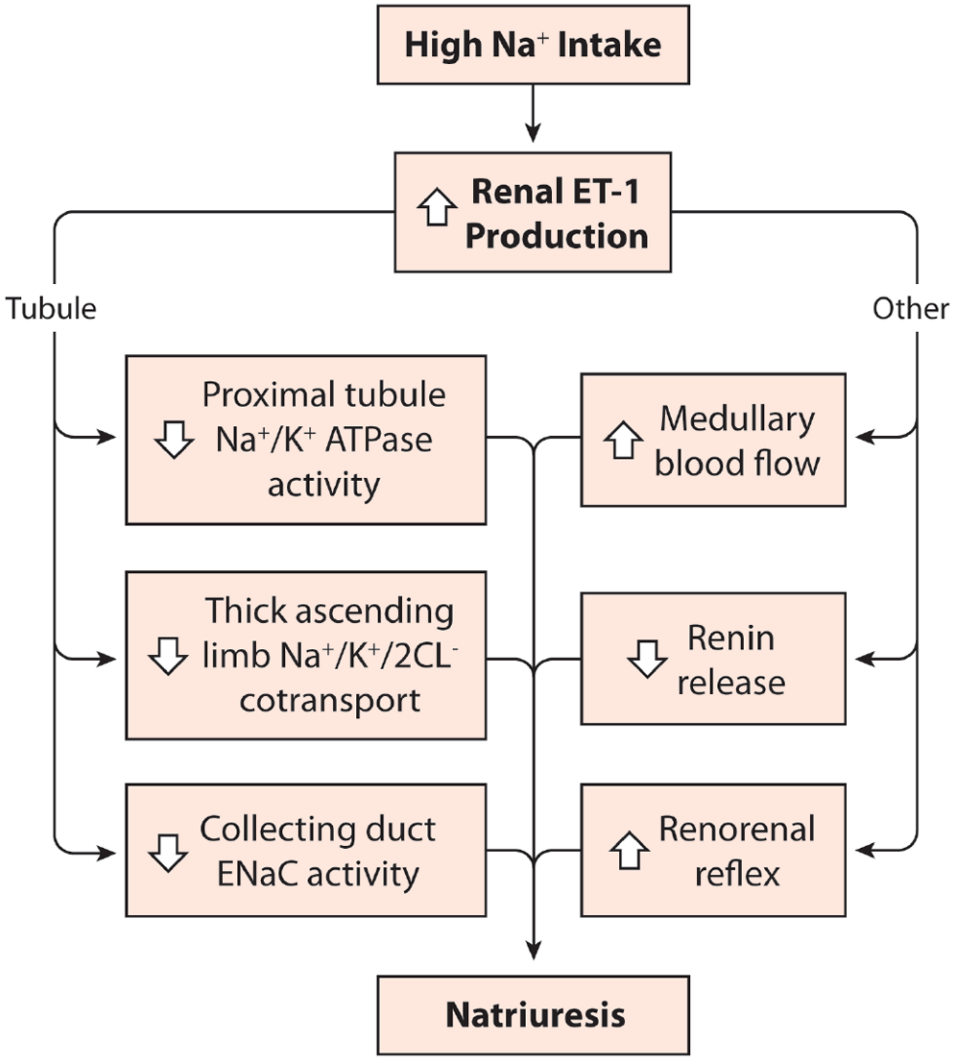

Figure 9.

Integrated renal response to high Na intake. High Na intake increases renal ET-1 synthesis, particularly in the nephron. This can reduced tubule Na reabsorption by inhibiting Na transport mechanisms in the proximal tubule, thick ascending limb and collecting duct. ET-1, most likely derived from the medullary collecting duct and/or medullary thick ascending limb, may also increase medullary blood flow through vasodilation of vasa recta.