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Endothelin and Renal Ion and Water Transport

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Abstract

The renal tubular epithelial cells produce more endothelin-1 (ET-1) than any other cell type in the body. Moving down the nephron, the amount of ET-1 produced appears fairly consistent until reaching the inner medullary collecting duct, which produces at least 10 times more ET-1 than any other segment. ET-1 inhibits Na^+ transport in all parts of the nephron through activation of the ET_B receptor, and to a minor extent, the ET_A receptor. These effects are most prominent in the collecting duct where ET_B receptor activation inhibits activity of the epithelial Na^+ channel. Effects in other parts of the nephron include inhibition of Na^+/H^+ exchange in the proximal tubule and the Na^+, K^+, $2Cl^-$ co-transporter in the thick ascending limb. In general, the renal epithelial ET-1 system is an integral part of the body's response to a high salt intake in order to maintain homeostasis and normal blood pressure. Loss of ET_B receptor function results in salt sensitive hypertension. The goal of this article is to review the role of renal ET-1 and how it affects Na^+ and water transport throughout the nephron.

Keywords

Endothelin; kidney; sodium transport

In 1988, Masashi Yanagisawa published his PhD thesis research in the journal *Nature*.[1] This work created an explosion of research that has contributed to well over 25,000 publications, very successful bi-annual international research conferences, and at least two novel drug therapies for the treatment of pulmonary hypertension, and most likely, several other important drug applications in the not too distant future. The speed at which the pharmaceutical industry moved into this field was quite remarkable and continues to this day, albeit at a very focused level. The complexity and diversity of this field is demonstrated by scientific investigation ranging from basic science areas such as vascular biology, neuroscience, and renal physiology to pathobiology of the gastrointestinal tract, heart

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failure, pain, cancer, hypertension, diabetes and chronic kidney disease just to name a few. All this effort was triggered by Yanagisawa's work related to a small 21 amino acid peptide that he named endothelin (ET).[2]

The ET family of peptides, ET-1, ET-2, and ET-3, has an incredibly diverse range of actions in virtually every organ system in cell types such as endothelium, epithelium, muscle and nerves. The ET system includes specific isoenzymes known as endothelin converting enzymes (ECE) that are responsible for the conversion of relatively inactive precursor peptides, big ET-1, big ET-2, and big-ET-3, to the active peptides. The biological actions of these peptides are mediated through ET_A and ET_B receptors (referred to hereafter as ET_A and ET_B). The kidney contains a very large number of these receptors on both endothelial and epithelial structures.

The actions of the ET peptides depend in large measure on the cell types on which they are located. For example, ET_A on vascular smooth muscle cells mediate most of the vasoconstrictor effects of ET-1, but some vascular tissue also contain ET_B that can result in vasoconstriction. In general, ET_B are primarily located on vascular endothelium and account for endothelial-dependent vasorelaxation that opposes the ET_A mediated effects.

While most of the attention has focused on the vascular actions of the ET system, it is important to recognize that this paracrine system is active within many other cell types throughout the body including neuronal and epithelial cells. Studies over the past decade or more have provided powerful evidence that an important physiological role of ET-1 is to regulate the excretion of Na^+ and water by the kidney. It is somewhat surprising, perhaps, that this powerful vasoconstrictor actually functions to enhance the excretion of dietary Na^+ by reducing renal tubular Na^+ reabsorption through direct effects on ion transport, as well as favorable effects on renal blood flow, glomerular filtration rate, and medullary blood flow. This review will focus on the autocrine function of ET-1 within the renal tubule and its direct effects on Na^+ and water transport along the nephron, while other aspects are reviewed in the accompanying papers.

Proximal tubule

All nephron segments produce ET-1 and also express ET receptors (Figure 1). The proximal tubule (PT) is no exception with synthesis occurring throughout the length of the PT, although expression levels are much lower compared to the thick ascending limb (TAL) and collecting duct (CD). Mechanisms that regulate ET-1 production in the PT under normal physiological conditions are not known. However, a variety of pathophysiological factors such as hypoxia, metabolic acidosis, and inflammation, mediated by tumor necrosis factor alpha (TNFα) and interleukin-1 beta (IL-1β), can increase ET-1 in the PT.

The actions of ET-1 in the PT are not as clear as in other segments of the nephron. ET-1 affects Na^+ transport in the PT through interactions with both the Na^+/K^+ ATPase and the Na^+/H^+ exchanger (NHE3).[3–5] In contrast to other tubular segments, it appears that ET-1 increases reabsorption of Na^+ and water in the PT at very low (sub-picomolar) concentrations, possibly through increasing NHE3 activity. However, higher concentrations (picomolar) appear to reduce reabsorption through inhibition of the Na^+/K^+ ATPase.[6]

Adding to the uncertainty is the observation by Romano et. al. that microinjection of nanomolar ET-1 concentrations into Bowman's capsule increased reabsorption by the proximal tubule.[7] However, this effect may be unrelated to Na^+ transport in the proximal tubule, as glomerular filtration was significantly increased, possibly suggesting that the increase in reabsorption was simply related to the increased filtered load. The mechanism that lead to the hyper-filtration observed by Romano et. al. is not clear. Regardless of these findings, the effects of ET-1 in the PT appear to be mediated primarily by ET_B, although some actions have been ascribed to ET_A. The physiological conditions that lead to the dispirit actions of ET-1 on PT Na^+ transport have yet to be resolved.

Effects on Na^+/K^+ ATPase

The ability of ET-1 to inhibit the Na^+/K^+ ATPase in the PT has been well documented. The primary receptor mediating this response is ET_B. One of the first demonstrations of this effect showed that ET-1 reduces oxygen consumption and inhibits ouabain sensitive $^{86}Rb^+$ uptake by rabbit PT suspensions, both markers of Na^+/K^+ ATPase activity.[3] Garvin et. al. then reported that ET-1 inhibits fluid and bicarbonate reabsorption in isolated rat PT that was attributed to a 20 percent reduction in Na^+/K^+ ATPase activity. This effect was shown to be mediated by a number of factors including phosphokinase C and enzymes that facilitate arachidonic acid metabolism, such as cyclooxygenase and lipoxygenase.[6] Furthermore, Liu et. al observed that inhibition of Na^+/K^+ ATPase by ET-1 is dependent on increases in intracellular Ca^{2+}.[8]

Effects on NHE3

ET-1 stimulates NHE3 activity in the PT, as evidenced by a number of *in vitro* models. The earliest studies demonstrate activation of NHE3 by ET-1 in rabbit and rat cortical slices and opossum kidney cells through a protein kinase C (PKC) dependent mechanism.[5, 9, 10] *In vivo* evidence suggests that this mechanism is important in acid/base regulation. Laghmani et. al. demonstrated that mice lacking functional ET_B everywhere except dopamine β-hydroxylase expressing cells have a significantly greater reduction in plasma [HCO_3^-] than control mice in response to chronic acid feeding. This was associated with an increase in proximal tubular NHE3 activity in control mice in response to the high acidity diet, while no increase was observed in the ET_B deficient mice. Further, chronic acidosis stimulated ET-1 production by the glomerulus and PT of c57Bl/6 mice, enhancing activity of the NHE3 and the Na^+/citrate co-transporter in the PT, both mediated by ET_B.[11–13] Since these initial observations, the study of endothelin in the regulation of acid/base balance has slowed dramatically. More recently, however, somewhat conflicting data in humans suggest that blockade of ET-1 receptors with the dual ET_A/ET_B blocker, bosentan, stimulates ammonia generation and increases net acid excretion in patients with metabolic acidosis, but only when dietary Na^+ is restricted.[14] Since this study was performed with a dual ET_A/ET_B antagonist, the only FDA approved ET antagonist at the time, further studies are needed to fully understand this pathway and its importance in human physiology.

Work from Jose's laboratory has revealed a number of potentially important regulatory mechanisms that influence ET-1 receptor function in the PT. There appears to be an interaction between the ET_B and dopamine D3 receptors, perhaps heterodimerization, in the

PT.[15] In addition to direct interaction with ET_B, activation of dopamine D3 receptors increases expression of ET_B. Dysfunction of the dopamine D3/ET_B interaction may contribute to hypertension in the spontaneously hypertensive rat (SHR).[16, 17] In addition to dopamine D3 receptors, there is also evidence that the angiotensin type 1 receptor (AT_1R) positively stimulates ET_B function in the proximal tubule. Acute activation of the AT_1R stimulates an increase in cell surface localization of ET_B, while long-term activation increases total ET_B expression.[17, 18] It is thought that this increased expression most likely reduces NHE3 activity, since AT1R/ET_B interaction is absent in SHR rats.

Thin ascending limb

Few studies have been carried out investigating ET-1 action in the thin ascending of the loop of Henle. Conflicting reports suggest that ET-1 may or may not be produced by this portion of the nephron. Autoradiography binding studies have found no ET-1 receptor binding in the thin limb; however one report has suggested a possible physiological role of ET receptors in the thin limb. ET-1 was shown to increase intracellular Ca_{2+} in isolated thin limbs, an ET_B -mediated process.[19] It is still unknown if ET-1 affects water movement in this nephron segment.

Thick ascending limb

The actions of ET peptides in the thick ascending limb (TAL) are generally believed to be physiologically significant in overall fluid-electrolyte balance, due to both the important role the TAL in urine concentration as well as its ability to influence significant Na^+ and water transport. Not only is ET-1 produced by the TAL, expression of both ET_A and ET_B has been observed in rat TAL.[20] Unlike work discussed later for the CD, there are no cell specific knockouts for this nephron segment. However, several lines of evidence suggest that ET-1 has dramatic effects on electrolyte movement in the TAL. The regulation of TAL ET-1 production is closely associated with increased Na^+ intake, which increases tubular flow and medullary tonicity[21]. Both flow and tonicity are believed to be important stimuli for increasing renal tubular ET-1 production.[21]

Effects on $Na^+/K^+/2Cl^-$ cotransporter

De Jesus Ferreira *et al*. first demonstrated that ET-1 reduces Cl^- transport in isolated mouse TAL, an effect that was blocked by PKC inhibitors and was independent of increases in intracellular calcium concentration ($[Ca^+]_i$).[22, 23] Plato *et al*. went on to describe that ET-1 inhibition of $Na^+/K^+/2Cl^-$ co-transporter occurs through the production of nitric oxide (NO), a well-described inhibitor of tubular Na^+ transport.[24] The same group showed that increases in dietary Na^+ increase NOS3 expression in the TAL, which is attenuated by ET_B blockade.[21] In addition, this occurs though activation of phosphatidylinositol 3-kinase, which stimulates protein kinase B (Akt) activity, thus activating NOS3.[25]

Another possible mediator of ET-1 action in the TAL is 20-hydroxyeicosatetraeonic acid (20-HETE), a natriuretic metabolite of arachidonic acid metabolism by CYP-450 enzymes.[26] Outer medullary 20-HETE levels are elevated in rats in response to chronic high

salt feeding. The increase in 20-HETE is abolished in rats treated with an ET_B antagonist directly into the renal outer medulla.[27]

Cortical Collecting Duct

The CD produces significantly more ET-1 than earlier nephron segments. The level of production is particularly high in the inner medullary CD. Synthesis of ET-1 by the CD is stimulated by a number a factors, but most prominently by increased flow and osmolarity that occur as salt intake is elevated.[28] Benzamil blocks flow and high osmolality induced ET-1 production, and thus these mechanisms appear to be related to Na^+ delivery and uptake by ENaC. Interestingly, ET-1 production appears to be suppressed by the circadian transcription factor Period 1, suggesting a role for ET-1 in circadian blood pressure rhythms that may serve as a counter-regulatory system for the salt-retaining effects of aldosterone.[29]

Effects on epithelial Na^+ channel (ENaC)

Patch clamp studies from the Stockand laboratory indicate that ENaC is prominently expressed in the cortical collecting duct (CCD), and ET-1 directly inhibits open probability of the ENaC in isolated CCD of mice (Figure 2). This effect was completely absent in CD ET_B knockout mice, but not CD ET_A knockouts.[30] Furthermore, ENaC open probability was reduced in response to high salt feeding in wild type and CD ET_A knockout mice, but not CD ET_B knockout mice. Collectively, these results suggest that inhibition of ENaC by ET-1 is mediated through ET_B. In contrast to studies by Stockand, a recent finding by Lynch et. al. has suggested that inhibition of ENaC by ET-1 is mediated by both ET_A and ET_B. In isolated perfused CCD from mice, ET-1 significantly inhibited benzamil sensitive Na^+ transport an effect that was abolished by ET_A or ET_B blockade.[31] Since aldosterone stimulates ET-1 production by the cortical CD, ET-1 inhibition of ENaC may be to serve as a negative feedback mechanism for the renal actions of aldosterone.

There is a much greater appreciation for the physiological role of ET-1 in Na^+ transport in the CD compared to other nephron segments. This is mainly due to a series of studies from Kohan et. al. in which his laboratory knocked out various components of the ET system specifically in the CD of mice, and measured blood pressure in response to changes in dietary salt content.[32–34] Using cre recombinase driven by the aquaporin 2 promoter, they were able to selectively eliminate expression of ET-1 in the CD. These animals displayed an elevated baseline blood pressure as measured by 24hr telemetry and introduction of a high salt diet produced an additional increase in blood pressure. Interestingly, CD specific knockout of ET_B also increased blood pressure in a salt sensitive manner, although to a lesser degree than in the CD ET-1 knockout. CD specific ET_A knockout mice had no difference in blood pressure from controls; however, CD knockout of both ET_A and ET_B fully restored the salt sensitive phenotype observed in CD ET-1 KO mice. Therefore, even though patch clamp studies mentioned earlier suggest that ET_A activation has no effect on Na^+ transport in the CD, *in vivo* physiological observations may suggest otherwise. The cause of these apparent contradictions may be due to which part of the CCD was patch clamped.

Inner Medullary Collecting Duct

The inner medullary collecting duct (IMCD) produces more ET-1 and has more ET_B than any other tissue in the body (Figure 1).[35–39] Even though only a small amount of the filtered load of Na^+ is reabsorbed here, it is the final nephron segment where the "fine tuning" of Na^+ and water homeostasis occurs, potentially impacting overall Na^+ excretion by several fold. Small changes in the amount of Na^+ reabsorbed here can have dramatic effects on Na^+ balance and blood pressure, therefore tight regulation is required.

Similar to other nephron segments, it is thought that ET-1 release by the IMCD is promoted by increases in flow and osmolality, and becomes more important as salt intake is elevated.[40] In fact, similar to the TAL, a high salt diet stimulates both ET-1 mRNA in the inner medulla and increases urinary ET-1 excretion, which is thought to be mainly indicative of IMCD production.[32, 41, 42] Selective knockout of ET-1 expression from the CD severely reduces urinary ET-1 excretion suggesting that urinary ET-1 is derived from intrarenal sources and not due to renal clearance.[32]

Effects on IMCD Na^+ transport

ET-1 inhibits Na^+ reabsorption by the IMCD through activation of ET_B, while very little, if any, ET_A expression has been observed (Figure 3).[43–49] Soon after the discovery of ET-1, Zeidel *et al*. demonstrated that ET-1 inhibits ouabain sensitive $^{86}Rb^+$ uptake and decreases oxygen consumption of intact rabbit IMCD suspensions, suggesting that ET-1 inhibits the Na^+/K^+ ATPase.[3] ET-1 inhibition of transport was blocked by a cyclooxygenase inhibitor and treatment with prostaglandin E2 resulted in inhibition of transport equal to and was not additive to the effects of ET-1.[3].

ET-1 effects on water reabsorption

Water reabsorption by the IMCD is highly dependent on the number of membrane bound aquaporins, and mounting evidence suggests that ET-1 reduces aquaporin expression and promotes water excretion. Early on, it was demonstrated that intravenous infusion of ET-1 in rats increases free water clearance in the absence of changes in renal hemodynamics.[50] Interestingly, ET-1 infusion directly into the renal artery at a dose that reduces renal plasma flow also increased free water clearance in sheep. When treated with an ET_A antagonist, the reduction in plasma flow in response intrarenal ET-1 infusion was abolished, but the diuresis was maintained.[51] Several reports indicate that these results are explained by ET-1 inhibition of vasopressin (AVP) signaling in the CD. For instance, ET-1 inhibits AVP stimulated water permeability and cAMP accumulation in rat isolated perfused IMCD, and IMCD suspensions, a response recapitulated by an ET_B agonist, and blocked by an ET_B antagonist.[52, 53] Further, since increases in $[Ca^{2+}]_i$ are required for AVP signaling in the IMCD and ET-1 simulates an increase in $[Ca^{2+}]_i$ in isolated perfused IMCD, it is possible that ET-1 inhibition of water transport requires a spike in $[Ca^{2+}]_i$.[53] Finally, it was recently demonstrated that increased $[Ca^{2+}]_i$ in response to ET-1 on IMCD is mediated by activation of ET_A and is more prominent in male rats vs. female rats.[1]

Mechanisms of ET-1 induced natriuresis and diuresis

Much of what we know about ET-1 diuretic and natriuretic effects in the IMCD derives from studies in which ET-1 or the ET_B agonist, sarafatoxin 6c (S6c) were infused directly into the renal medulla. In a dose dependent manner, acute intramedullary infusion of S6c increases urine volume and urinary Na^+ excretion in rats. S6c also increased medullary cGMP, and the natriuretic/diuretic response was blunted by a NOS1 and a protein kinase G inhibitor, and was completely absent in rats lacking functional ET_B. These observations suggest that ET-1 inhibition of Na^+ and water reabsorption produce significant natriuresis and diuresis through ET_B dependent increases in NOS1 signaling through PKG and cAMP.[54]

Role of salt intake on ET_B function

Altering salt content of the diet has major effects on the natriuretic ability of ET-1. The natriuretic actions of ET_B receptr stimulation can be enhanced by increasing salt intake (unpublished observations). In contrast, reducing salt intake can inhibit ET_B function in male rats.[55] These findings can be attributed to actions of angiotensin II because the reduction in ET_B function is reversed by treatment with an angiotensin receptor blocker. Further, exogenous angiotensin II inhibits ET_B mediated natriuresis.[56, 57]

Sex differences in ET-1 natriuresis and diuresis

Interestingly, interstitial infusion of ET-1 into the renal medulla produces natriuresis in female, but not male rats. This obvious sex difference is due to a marked decrease in medullary blood flow in male rats, but not females, that can be overcome by gonadectomy.[54] These findings further suggest that changes in medullary blood flow have dramatic effects on ET_B function in terms of renal tubular transport function. In the same set of experiments Nakano *et al*. demonstrated that blockade of ET_B in female rats inhibited the natriuretic response to intramedullary infusion of ET-1. They went on to demonstrate that intramedullary infusion of ET-1 into ET_B deficient rats produced natriuresis and diuresis in female, but not male rats, suggesting females have an ET_A contribution to the natriuresis. Further studies indicate that angiotensin II mediated reductions in ET_B function described earlier are attenuated in female rats, thus providing a potential explanation for reduced salt-sensitive blood pressure changes in females.

Role of the ET_A in the CD

The natriuretic effects of ET-1 produced by the IMCD have mostly been attributed to activation of ET_B because early studies found no ET_A on IMCD; however, several functional studies report that ET_A can influence ET-1 actions on Na^+ handling by the IMCD. The most direct indication is from previously mentioned CD knockout studies in mice. Knockout of only ET_B in the CD causes salt sensitive hypertension, but not to the degree of CD ET-1 knockout. While specific ET_A deletion from the CD had no effect on blood pressure, dual CD ET_A/ET_B knockout mice exhibited hypertension similar to what was observed in ET-1 knockout mice, which was more than that observed in CD ET_B knockout mice.

Interstitial infusion of hypertonic saline into the renal medulla produces natriuresis by an ET-1 dependent mechanism. Interestingly, this can only be blocked when the both ET_A and ET_B are blocked.[58] Stuart *et al*. recently provided further evidence that ET_A can influence fluid transport. Knockout of ET_A from the entire nephron of mice resulted in fluid retention, a common side effect of systemic ET_A blockade in humans.[59] Collectively, these findings suggest an ET_A component to the effects of ET-1 on renal tubular transport, although these effects are far less evident compared to the dominant role of ET_B.

Summary and Conclusion

It is clear that ET-1 functions in an autocrine role to regulate renal tubular handling of Na^+ and water (Table 1). Given that 1) increasing dietary Na^+ intake is a powerful stimulus for renal tubular ET-1 production, 2) ET_B is dominant in the CD to inhibit Na^+ reabsorption, and 3) disruption of the ET system in the nephron results in salt-dependent hypertension, it is clear that this system plays a major role in fluid-electrolyte balance and blood pressure regulation. However, a number of important questions remain to be answered. These include the physiological role of the ET system in the PT and the TAL, the nature of ET_A versus ET_B function, and the mechanism by which ET-1 production is regulated.

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References

1. Speed JS, Pollock DM. Endothelin, kidney disease, and hypertension. Hypertension. 2013; 61:1142–1145. [PubMed: 23608655]
2. Yanagisawa M, Kurihara H, Kimura S, Goto K, Masaki T. A novel peptide vasoconstrictor, endothelin, is produced by vascular endothelium and modulates smooth muscle Ca^{2+} channels. J Hypertension. 1988; 6:S188–S191.
3. Zeidel ML, Brady HR, Kone BC, Gullans SR, Brenner BM. Endothelin, a peptide inhibitor of Na^+-K -ATPase in intact renaltubular epithelial cells. Am J Physiol. 1989; 257:C1101–C1107. [PubMed: 2558568]
4. Garvin J, Sanders K. Endothelin inhibits fluid and bicarbonate transport in part by reducing Na^+/K^+ ATPase activity in the rat proximal straight tubule. J Am Soc Nephrol. 1991; 2:976–982. [PubMed: 1662089]
5. Eiam-Ong S, Hilden SA, King AJ, Johns CA, Madias NE. Endothelin-1 stimulates the Na^+/H^+ and Na^+/HCO_3^- transporters in rabbit renal cortex. Kidney Int. 1992; 42:18–24. [PubMed: 1321928]
6. Garcia NH, Garvin JL. Endothelin's biphasic effect on fluid absorption in the proximal straight tubule and its inhibitory cascade. J Clin Invest. 1994; 93:2572–2577. [PubMed: 8200994]
7. Romano G, Giagu P, Favret G, Bartoli E. Effect of endothelin 1 on proximal reabsorption and tubuloglomerular feedback. Kidney Blood Press Res. 2000; 23:360–365. [PubMed: 11070415]
8. Liu Y, Yang J, Ren H, He D, Pascua A, Armando MI, Yang C, Zhou L, Felder RA, Jose PA, Zeng C. Inhibitory effect of ETB receptor on Na^+-K^+ ATPase activity by extracellular Ca^{2+} entry and Ca^{2+} release from the endoplasmic reticulum in renal proximal tubule cells. Hypertension Res. 2009; 32:846–852.
9. Walter R, Helmle-Kolb C, Forgo J, Binswanger U, Murer H. Stimulation of Na^+/H^+ exchange activity by endothelin in opossum kidney cells. Pflugers Archiv. 1995; 430:137–144. [PubMed: 7545278]

10. Guntupalli J, DuBose TD Jr. Effects of endothelin on rat renal proximal tubule Na^+-P_i cotransport and Na^+/H^+ exchange. Am J Physiol. 1994; 266:F658–F666. [PubMed: 8184900]
11. Licht C, Laghmani K, Yanagisawa M, Preisig PA, Alpern RJ. An autocrine role for endothelin-1 in the regulation of proximal tubule NHE3. Kidney Int. 2004; 65:1320–1326. [PubMed: 15086471]
12. Laghmani K, Preisig PA, Moe OW, Yanagisawa M, Alpern RJ. Endothelin-1/endothelin-B receptor-mediated increases in NHE3 activity in chronic metabolic acidosis. J Clin Invest. 2001; 107:1563–1569. [PubMed: 11413164]
13. Liu L, Zacchia M, Tian X, Wan L, Sakamoto A, Yanagisawa M, Alpern RJ, Preisig PA. Acid regulation of NaDC-1 requires a functional endothelin B receptor. Kidney Int. 2010; 78:895–904. [PubMed: 20703215]
14. Pallini A, Hulter HN, Muser J, Krapf R. Role of endothelin-1 in renal regulation of acid-base equilibrium in acidotic humans. Am J Physiol Renal Physiol. 2012; 303:F991–F999. [PubMed: 22859405]
15. Zeng C, Asico LD, Yu C, Villar VA, Shi W, Luo Y, Wang Z, He D, Liu Y, Huang L, Yang C, Wang X, Hopfer U, Eisner GM, Jose PA. Renal D3 dopamine receptor stimulation induces natriuresis by endothelin B receptor interactions. Kidney Int. 2008; 74:750–759. [PubMed: 18547994]
16. Yu C, Yang Z, Ren H, Zhang Y, Han Y, He D, Lu Q, Wang X, Wang X, Yang C, Asico LD, Hopfer U, Eisner GM, Jose PA, Zeng C. D3 dopamine receptor regulation of ETB receptors in renal proximal tubule cells from WKY and SHRs. Am J Hyper. 2009; 22:877–883.
17. Zeng C, Wang Z, Asico LD, Hopfer U, Eisner GM, Felder RA, Jose PA. Aberrant ET_B receptor regulation of AT receptors in immortalized renal proximal tubule cells of spontaneously hypertensive rats. Kidney Int. 2005; 68:623–631. [PubMed: 16014039]
18. Zeng C, Hopfer U, Asico LD, Eisner GM, Felder RA, Jose PA. Altered AT1 receptor regulation of ETB receptors in renal proximal tubule cells of spontaneously hypertensive rats. Hypertension. 2005; 46:926–931. [PubMed: 16144989]
19. Bailey MA, Haton C, Orea V, Sassard J, Bailly C, Unwin RJ, Imbert-Teboul M. ET_A receptor-mediated Ca^{2+} signaling in thin descending limbs of Henle's loop: impairment in genetic hypertension. Kidney Int. 2003; 63:1276–1284. [PubMed: 12631344]
20. Dean R, Zhuo J, Alcorn D, Casley D, Mendelsohn FA. Cellular distribution of ^{125}I-endothelin-1 binding in rat kidney following in vivo labeling. Am J Physiol. 1994; 267:F845–F852. [PubMed: 7977789]
21. Herrera M, Garvin JL. A high-salt diet stimulates thick ascending limb eNOS expression by raising medullary osmolality and increasing release of endothelin-1. Am J Physiol Renal Physiol. 2005; 288:F58–F64. [PubMed: 15353403]
22. de Jesus Ferreira MC, Bailly C. Luminal and basolateral endothelin inhibit chloride reabsorption in the mouse thick ascending limb via a Ca^{2+}-independent pathway. J Physiol. 1997; 505(Pt 3):749–758. [PubMed: 9457649]
23. Bailly C. Effect of luminal atrial natriuretic peptide on chloride reabsorption in mouse cortical thick ascending limb: inhibition by endothelin. J Am Soc Nephrol. 2000; 11:1791–1797. [PubMed: 11004208]
24. Plato CF, Pollock DM, Garvin JL. Endothelin inhibits thick ascending limb chloride flux via ET_B receptor-mediated NO release. Am J Physiol Renal Physiol. 2000; 279:F326–F333. [PubMed: 10919853]
25. Herrera M, Hong NJ, Ortiz PA, Garvin JL. Endothelin-1 inhibits thick ascending limb transport via Akt-stimulated nitric oxide production. The J Biol Chem. 2009; 284:1454–1460.
26. Ito O, Roman RJ. Role of 20-HETE in elevating chloride transport in the thick ascending limb of Dahl SS/Jr rats. Hypertension. 1999; 33:419–423. [PubMed: 9931140]
27. Speed JS, George EM, Arany M, Cockrell K, Granger JP. Role of 20-hydroxyeicosatetraenoic acid in mediating hypertension in response to chronic renal medullary endothelin type B receptor blockade. PloS one. 2011; 6:e26063. [PubMed: 22016812]
28. Pandit MM, Strait KA, Matsuda T, Kohan DE. Na delivery and ENaC mediate flow regulation of collecting duct endothelin-1 production. Am J Physiol Renal Physiol. 2012; 302:F1325–F1330. [PubMed: 22357920]

29. Stow LR, Voren GE, Gumz ML, Wingo CS, Cain BD. Dexamethasone stimulates endothelin-1 gene expression in renal collecting duct cells. Steroids. 2012; 77:360–366. [PubMed: 22209709]
30. Bugaj V, Mironova E, Kohan DE, Stockand JD. Collecting duct-specific endothelin B receptor knockout increases ENaC activity. Am J Physiol Cell Physiol. 2012; 302:C188–C194. [PubMed: 21918182]
31. Lynch IJ, Welch AK, Kohan DE, Cain BD, Wingo CS. Endothelin-1 inhibits sodium reabsorption by ET_A and ET_B receptors in the mouse cortical collecting duct. Am J Physiol Renal Physiol. 2013; 305:F568–F573. [PubMed: 23698114]
32. Ahn D, Ge Y, Stricklett PK, Gill P, Taylor D, Hughes AK, Yanagisawa M, Miller L, Nelson RD, Kohan DE. Collecting duct-specific knockout of endothelin-1 causes hypertension and sodium retention. J Clin Invest. 2004; 114:504–511. [PubMed: 15314687]
33. Ge Y, Stricklett PK, Hughes AK, Yanagisawa M, Kohan DE. Collecting duct-specific knockout of the endothelin A receptor alters renal vasopressin responsiveness, but not sodium excretion or blood pressure. Am J Physiol Renal Physiol. 2005; 289:F692–F698. [PubMed: 15928212]
34. Ge Y, Bagnall A, Stricklett PK, Strait K, Webb DJ, Kotelevtsev Y, Kohan DE. Collecting duct-specific knockout of the endothelin B receptor causes hypertension and sodium retention. Am J Physiol Renal Physiol. 2006; 291:F1274–F1280. [PubMed: 16868309]
35. Kohan D. Endothelins in the normal and diseased kidney. Am J Kid Dis. 1997; 29:2–26. [PubMed: 9002526]
36. Chen M, Todd-Turla K, Wang W-H, Cao X, Smart A, Brosius FC, Killen PD, Keiser JA, Briggs JP, Schnermann J. Endothlein-1 mRNA in glomerular and epithelial cells of kidney. Am J Physiol. 1993; 265:F542–F550. [PubMed: 8238383]
37. Kohan DE. Endothelin synthesis by rabbit renal tubule cells. Am J Physiol. 1991; 261:F221–F226. [PubMed: 1877647]
38. Uchida S, Takemoto F, Ogata E, Kurokawa K. Detection of endothelin-1 mRNA by RT-PCR in isolated rat renal tubules. Biochem Biophys Res Commun. 1992; 188:108–113. [PubMed: 1384475]
39. Ujiie K, Terada Y, Nonoguchi H, Shinohara M, Tomita K, Marumo F. Messenger RNA expression and synthesis of endothelin-1 along rat nephron segments. J Clin Invest. 1992; 90:1043–1048. [PubMed: 1522212]
40. Lyon-Roberts B, Strait KA, van Peursem E, Kittikulsuth W, Pollock JS, Pollock DM, Kohan DE. Flow regulation of collecting duct endothelin-1 production. Am J Physiol Renal Physiol. 2011; 300:F650–F656. [PubMed: 21177779]
41. Speed JS, LaMarca B, Berry H, Cockrell K, George EM, Granger JP. Renal medullary endothelin-1 is decreased in Dahl salt-sensitive rats. Am J Physiol Regu Integr Comp Physiol. 2011; 301:R519–R523.
42. Fattal I, Abassi Z, Ovcharenko E, Shimada K, Takahashi M, Hoffman A, Winaver J. Effect of dietary sodium intake on the expression of endothelin-converting enzyme in the renal medulla. Nephron Physiol. 2004; 98:89–96.
43. Cernacek P, Legault L, Stewart DJ, Levy M. Specific endothelin binding sites in renal medullary collecting duct cells: lack of interaction with ANP binding and cGMP signalling. Can J Physiol Pharmacol. 1992; 70:1167–1174. [PubMed: 1282083]
44. Omatsu S, Tomoyoshi T. Immunohistochemical study on endothelin in rat kidney. Hinyokika Kiyo. 1997; 43:109–114. [PubMed: 9086345]
45. Edwards RM, Trizna W. Characterization of 125I-endothelin-1 binding to rat and rabbit renal microvasculature. J Pharmacol Exp Ther. 1995; 274:1064–1089.
46. Yukimura T, Notoya M, Mizojiri K, Mizuhira V, Matsuura T, Ebara T, Miura K, Kim S, Iwao H, Song K. High resolution localization of endothelin receptors in rat renal medulla. Kidney Int. 1996; 50:135–147. [PubMed: 8807582]
47. Kohan DE, Hughes AK, Perkins SP. Characterization of endothelin receptors in the inner medullary collecting duct of the rat. J Biol Chem. 1992; 267:12336–12340. [PubMed: 1318315]
48. Wendel M, Knels L, Kummer W, Koch T. Distribution of endothelin receptor subtypes ET_A and ET_B in the rat kidney. J Histochem Cytochem. 2006; 54:1193–1203. [PubMed: 16835394]

49. Yamamoto T, Suzuki H, Kubo Y, Matsumoto A, Uemura H. Endothelin A receptor-like immunoreactivity on the basal infoldings of rat renal tubules and collecting ducts. Arch Histol Cytol. 2008; 71:77–87. [PubMed: 18974600]
50. Schnermann J, Lorenz JN, Briggs JP, Keiser JA. Induction of water diuresis by endothelin in rats. Am J Physiol. 1992; 263:F516–F526. [PubMed: 1415580]
51. Kamphuis C, Yates NA, McDougall JG. Differential blockade of the renal vasoconstrictor and diuretic responses to endothelin-1 by endothelin antagonist. Clin Exptl Pharmacol Physiol. 1994; 21:329–333. [PubMed: 7923901]
52. Edwards RM, Stack EJ, Pullen M, Nambi P. Endothelin inhibits vasopressin action in rat inner medullary collecting duct via the ET_B receptor. J Pharmacol Exptl Therap. 1993; 267:1028–1033. [PubMed: 8263761]
53. Nadler SP, Zimpelmann JA, Hebert RL. Endothelin inhibits vasopressin-stimulated water permeability in rat terminal inner medullary collecting duct. J Clin Invest. 1992; 90:1458–1466. [PubMed: 1328300]
54. Nakano D, Pollock JS, Pollock DM. Renal medullary ET_B receptors produce diuresis and natriuresis via NOS1. Am J Physiol Renal Physiol. 2008; 294:F1205–F1211. [PubMed: 18305094]
55. Kittikulsuth W, Pollock JS, Pollock DM. Loss of renal medullary endothelin B receptor function during salt deprivation is regulated by angiotensin II. Am J Physiol Renal Physiol. 2012; 303:F659–F666. [PubMed: 22674027]
56. Kittikulsuth W, Pollock JS, Pollock DM. Sex differences in renal medullary endothelin receptor function in angiotensin II hypertensive rats. Hypertension. 2011; 58:212–218. [PubMed: 21646601]
57. Kittikulsuth W, Looney SW, Pollock DM. Endothelin ET_B receptors contribute to sex differences in blood pressure elevation in angiotensin II hypertensive rats on a high-salt diet. Clin Exptl Pharmacol Physiol. 2013; 40:362–370. [PubMed: 23713708]
58. Boesen EI, Pollock DM. Acute increases of renal medullary osmolality stimulate endothelin release from the kidney. Am J Physiol Renal Physiol. 2007; 292:F185–F191. [PubMed: 16912066]
59. Stuart D, Rees S, Woodward SK, Koesters R, Strait KA, Kohan DE. Disruption of the endothelin A receptor in the nephron causes mild fluid volume expansion. BMC Nephrol. 2012; 13:166. [PubMed: 23217151]
60. Bugaj V, Pochynyuk O, Mironova E, Vandewalle A, Medina JL, Stockand JD. Regulation of the epithelial Na^+ channel by endothelin-1 in rat collecting duct. Am J Physiol Renal Physiol. 2008; 295:F1063–F1070. [PubMed: 18667482]

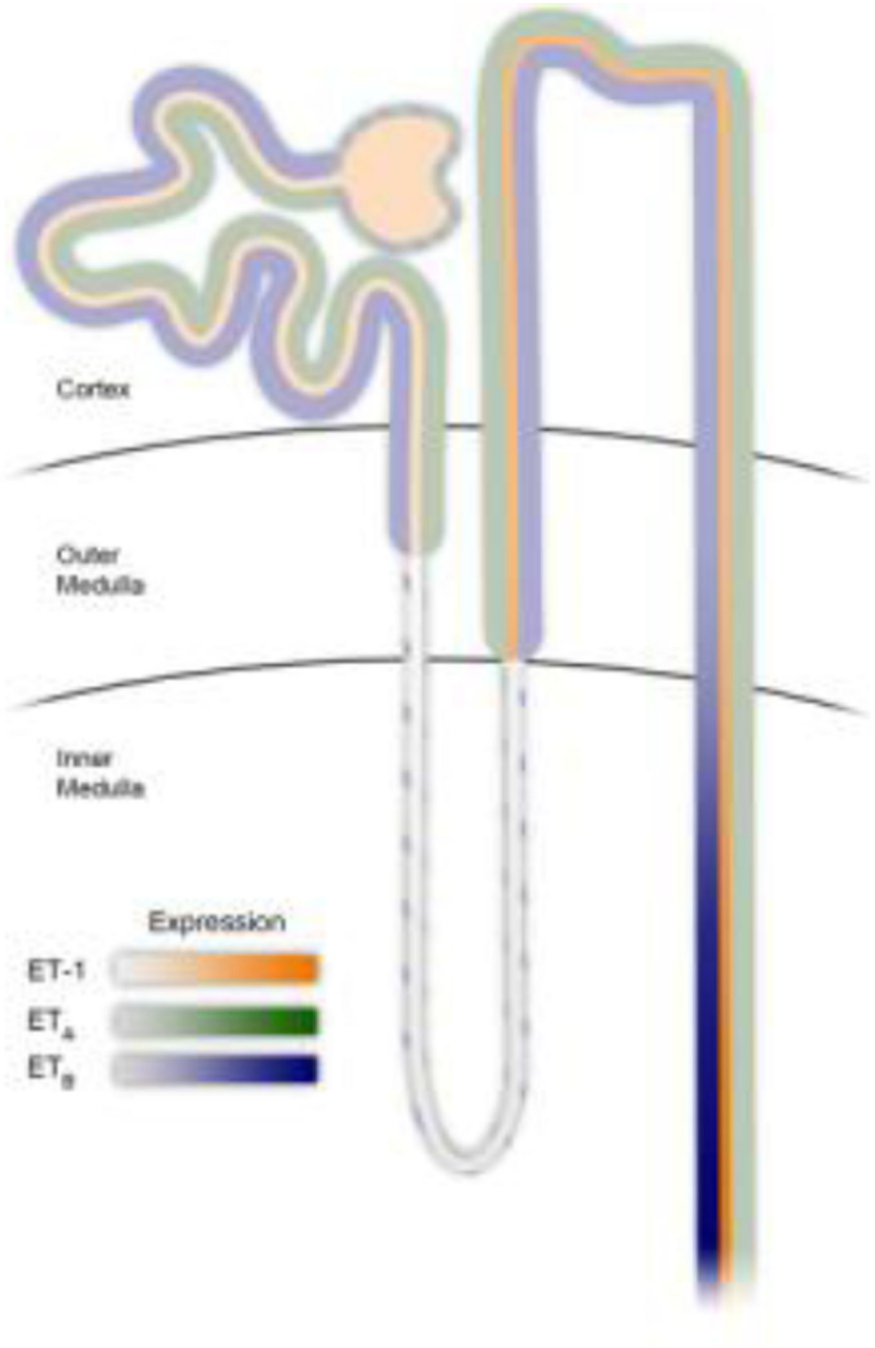

Figure 1.
Relative ET-1 production and receptor density along the nephron.

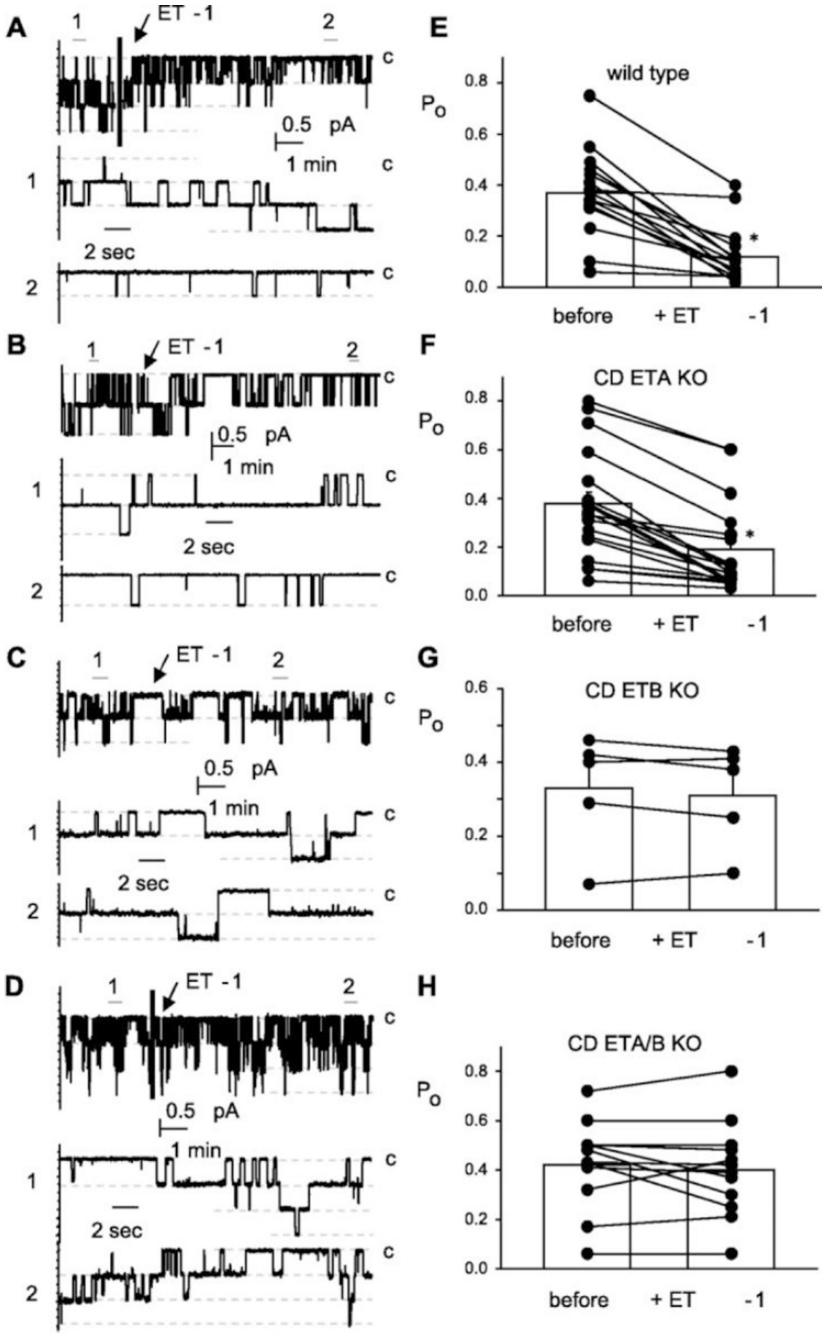

Figure 2.

ENaC activity in isolated split open cortical CD using patch clamp techniques. Exogenous ET-1 reduces ENaC open probability in CD from floxed control mice and CD specific ET_A KO mice. ET-1 induced reductions in ENaC activity was absent in tubules from CD ET_B KO mice (used with permission ref. 28)

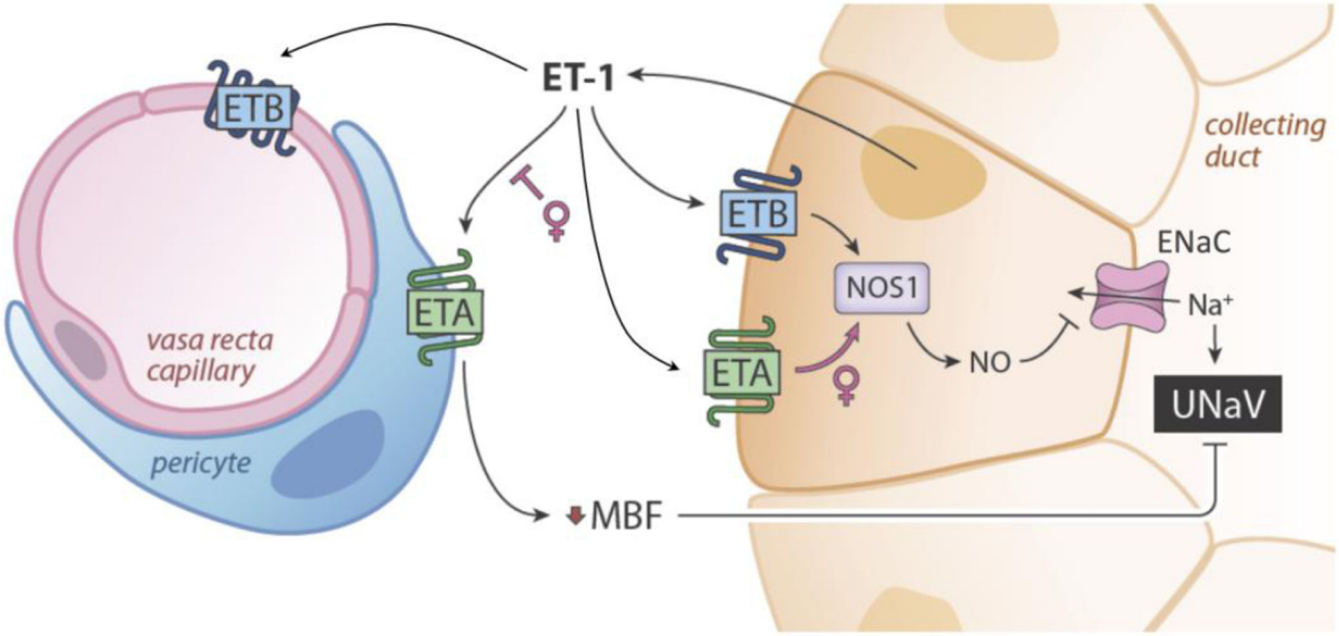

Figure 3.
Autocrine and paracrine effects of inner medullary collecting duct derived ET-1.

Table 1

ET-1 inhibition of Na^+ transporters along the nephron.

Proximal Tubule	**NHE3, Na^+/K^+ ATPase,**	**ET_B, ET_A?**	**3, 4, 6, 10**
Thin Limb			
Thick ascending Loop	$Na^+/K^+/2Cl^-$, Na^+/K^+ ATPase	ET_B	22, 24
Cortical Collecting Duct	Na^+/K^+ ATPase, ENaC	ET_A, ET_B	30, 60
Inner Medullary CD	Na^+/K^+ ATPase, ENaC?	ET_A, ET_B	3