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Regulation of Sodium Transport in the Proximal Tubule by Endothelin

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Abstract

Human essential hypertension and rodent genetic hypertension are associated with increased sodium transport in the renal proximal tubule and medullary thick ascending limb of Henle. The proximal tubule, which secretes endothelin, expresses the endothelin type B (ETB) receptor. Low (nM) concentrations of endothelin, via the ETB receptor, inhibit sodium and water transport and ATP-driven drug secretion in the proximal tubule. In contrast, very low (pM) and high nM concentrations of endothelin increase renal proximal sodium transport, the receptor involved remains to be determined. The natriuretic effect of ETB receptor stimulation is impaired in spontaneously hypertensive rats, due in part to a defective interaction with D_3 dopamine and angiotensin II type 1 receptors. Impaired ETB receptor function in the renal proximal tubule may be important in the pathogenesis of genetic hypertension.

Introduction

The kidney is important in the long-term regulation of blood pressure and is the major organ involved in the regulation of body sodium homeostasis[1–3]. The proximal tubule and medullary thick ascending limb of Henle are pre-eminent in the overall regulation of sodium balance in essential hypertension[4]. Indeed, several studies have shown that human essential hypertension and rodent genetic hypertension are associated with increased sodium transport in the renal proximal tubule (RPT) and medullary thick ascending limb of Henle[4].

Endothelin (ET) was initially identified as an endothelial cell-derived peptide, with the greatest vasoconstrictor potency of any known endogenous compound[5]. Endothelins are a family of isopeptides (ET-1, ET-2, and ET-3), with at least two receptors subtypes (ETA and ETB). Renal tissue expresses both endothelin receptor subtypes[6], and endothelin is secreted by renal tubules, including the renal proximal tubule[7,8], where it can regulate sodium

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Disclosures

None.

transport in an autocrine/paracrine manner[9]. In the RPTs, ET-1, principally through the ETB receptor, the major ET receptor expressed in the RPT, inhibits ion transport[10], an effect opposite that of the ETA receptor. This review focuses on the regulation of endothelin on sodium transport in the renal proximal tubule and its role in the pathogenesis of essential hypertension.

Endothelin and it metabolism

In 1985, Hickey and co-workers[11] described the existence of a trypsin-sensitive endothelium-derived constricting factor in cultured bovine endothelial cells, which they named as endothelin. Subsequently, more endothelin family members were found. These members include ET-1, ET-2, ET-3 and ET-4 (analogue of human ET-2 in rat and mouse, also named as vasoactive intestinal contractor), and three isoforms of 31-amino-acid ETs (ET-$1^{1–31}$, ET-$2^{1–31}$ and ET-$3^{1–31}$)[12]. Owing to the similarity of actions between ET-$1^{1–31}$ and ET-1 *in vivo*, it is possible that some of the effects of $ET^{1–31}$ result from their partial bioconversion into ETs[13]. Among these isoforms, ET-1 is the principal isoform and is the most potent and long-lasting constrictor of human vessels known to date[5].

ET-1 is produced in many cell types in the renal and cardiovascular systems, such as endothelial cells, smooth muscle cells, cardiomyocytes, leucocytes, macrophages, and renal tubular and mesangial cells[14,15]. Bioactive ETs are the product of post-translational processing of the parent pre-pro-ET peptide. The transcription and translation of *pre-pro-ET* result in the formation of a 203-amino-acid peptide which is subsequently cleaved by a furin convertase to the 38-amino-acid peptide big $ET^{1–38}$. Big ET is processed further into $ET^{1–31}$ by different isoforms of endothelin converting enzymes (ECEs), a group of proteases that belong to the metalloprotease family[16], including ECE-1a, ECE-1b, ECE-1c and ECE-1d, derived from a single gene by the action of alternative promoters.

ET synthesis is regulated by many factors. It is enhanced in response to low-shear stress, turbulent blood flow, hypoxia, cytokines, angiotensin II, epinephrine, and low-density lipoproteins[17]. In contrast, high-shear stress, nitric oxide, vasodilating prostaglandins, and natriuretic peptides suppress ET production[18]. Endothelin synthesis is regulated by sodium diet; a high sodium diet, independent of blood pressure status, increases renal synthesis of endothelin[19]. Distal nephron segments synthesize ET-1 to a greater extent than the proximal tubule[8].

The synthesized ET-1 is released in two ways. One way is via a constitutive pathway, producing intense constriction of the underlying smooth muscle, which contributes to the maintenance of endogenous vascular tone. The other way is via release from endothelial cell-specific storage granules (Weibel-Palade bodies) in response to external physiological stimuli, producing further vasoconstriction[20]. Although plasma ET-1 is present in the highest concentration in blood/plasma, compared with ET-2 and ET-3, ET-1 concentrations are still lower in plasma than in endothelial and other cells. It is accepted that ET-1 functions as a locally released, rather than a circulating, hormone.

Endothelin receptors

Endothelin receptor classification—ET receptors are classified as ETA and ETB by the International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification[21]. Both ETA and ETB receptors belong to the seven-transmembrane domain or G-protein-coupled rhodopsin-type receptor superfamily. Pharmacologically heterogeneous responses seem to be related to the existence of alternatively spliced variants of ETA and ETB receptors. A third receptor, named ETC, which is specific for ET-3 binding, was cloned from dermal melanophores from the amphibian *Xenopus laevis*, but a mammalian homologue has yet to be identified[21] (see below).

The three ET receptors have different affinities to the three isoforms of ET (ET-1, ET-2 and ET-3). ET receptors can bind all endothelin isoforms, but the ETA receptor has a much higher affinity for ET-1, the most abundant ET in human plasma, than for ET-3, while the ETC receptor has a higher affinity for ET-3 than ET-1. In contrast, the ETB receptor binds to all three ET isoforms with equal affinity.

Localization of endothelin receptors—In all species studied, including humans, endothelin binding is greater in the renal inner medulla than in the inner cortex[8,22,,23].

In the rat, there is faint immunostaining of the ETA receptor in the proximal convoluted and straight tubules, restricted to the basal side and intense staining in distal tubule collecting duct[24,25]; ETA receptor is also expressed in mesangial cells, pericytes of descending vasa recta and vascular smooth muscle cells (VSMCs) of veins and arteries, specifically the interlobar, arcuate, and interlobular arteries, as well as efferent and afferent arterioles[25]. The ETB receptor is the major endothelin receptor in the kidney; 70–80% of endothelin receptors in kidney are ETB receptors[6,8], which in the rat are expressed in proximal tubule, inner medullary collecting duct, glomerular capillaries, vasa recta endothelial cells, and VSMCs of interlobular, efferent and afferent arteries[25–28].

In the mouse, the ETA receptor has been shown to be expressed in some proximal tubules and vessels, but not in glomeruli. In agreement with the rat studies, the ETB receptor is expressed in the proximal tubule and collecting duct[29]. Faint staining of ETA and ETB receptors has also been reported in human glomeruli, and proximal and distal tubules. In agreement with the rat studies, the distal nephron expresses more ET receptors that the proximal nephron[30,31].

Signal transduction of ET receptors in the RPTs

Both ETA and ETB receptors are linked to Gq/11, $G\alpha_S$ and $G\alpha_{i/O}$[32,33]. In some cells (e.g., Chinese hamster ovary cells), the ETA receptor is linked to $G\alpha_S$ while the ETB receptor is linked to $G\alpha_i$ [34]. However, in hepatocytes, the ETB receptor is also linked to $G\alpha_S$[35]. The ETB, but not the ETA receptor, also activates $G\alpha_{13}$[36].

In rat renal brush border membranes, the endothelin-mediated increase in phospholipase C activity and protein kinase C translocation to the brush border membrane are mediated by the ETB but not by the ETA receptor. In contrast, the ETC receptor is involved in endothelin-mediated signaling in basolateral membranes[37]. Both ETA and ETB receptors

belong to the Class A receptors of the GPCR family because they bind to β arrestin 1 with a higher affinity than β arrestin 2 and do not bind to visual arrestin[38,39].

Effect of endothelin on RPT transport

***In-vivo* studies—**Low-dose infusion of endothelin in anesthetized rats has been reported to decrease sodium transport in proximal and distal nephron segments, assessed by lithium clearance, which is associated with an increase in renal blood flow but not glomerular filtration rate[40]. At a dose that does not alter renal plasma flow, endothelin also decreases proximal but not distal tubule sodium reabsorption, also assessed by lithium clearance[8,41,42], showing that endothelin infusion causes natriuresis without altering glomerular filtration rate or renal blood flow, and suggesting a direct inhibitory effect of endothelin-1 on Na^+ transport along the nephron. However, the endothelin-mediated natriuresis has not been consistently observed[43,44]. One group reported that the natriuretic effect of exogenous ET-1 is due solely to an increase in blood pressure since renal decapsulation or maintaining renal perfusion pressure at baseline values (ET agonists often increase arterial pressure) with an aortic clamp prevents ET-1-induced natriuresis[43]. The possible explanation for the inconsistent findings on endothelin agonist-induced natriuresis may be due, at least partly, to differential activation of ETA and ETB receptors. For example, when the ETA receptor, but not the ETB receptor, is blocked, a natriuretic effect of ET-1 is detected[45]. One study showed that low doses of ET causes a natriuresis by decreasing renal proximal tubular reabsorption that is not due to ETB receptors [46].

In contrast to the studies on sodium excretion, there is unanimous agreement that systemically administered endothelin increases urinary water excretion. Even when given at doses that markedly decreased renal blood flow, the renal arterial infusion of ET-1 increased urine volume and free water clearance[47]. This effect may be mediated by the ETB receptor, because the infusion of ETB-specific agonists (IRL1620 or sarafotoxin 6c) increases urine flow[10,46].

The ETB receptor also works as a clearance receptor. The ETB receptor in endothelial cells removes ET-1 from the circulation[48,49]. Blockade of the ETB receptor increases circulating immunoreactive ETs (ET-1 and ET-3), and mice with genetic ablation of the ETB receptor in endothelial cells have elevated plasma concentrations of ET-1[48,49].

***In-vitro* studies—**Endothelin has diverse effects throughout the nephron. In the rat proximal tubule, endothelin has a biphasic effect on ion and fluid transport[50]. Low concentrations (pM) increase whereas a high concentration (low nM) of ET-1, decreases fluid transport through protein kinase C-, cyclooxygenase- and lipoxygenase-dependent mechanisms[42,50]. However, higher concentrations (high nM) of endothelin also increase renal proximal tubule transport[7]. In agreement with the data on sodium transport, low nM concentrations of endothelin, via the ETB receptor, have also been shown to inhibit the secretion of fluorescent substrates in renal proximal tubules of the killifish[51].

Endothelin-1 inhibits fluid and bicarbonate absorption in the isolated-perfused rat proximal straight tubule[52] and fluid transport in the mid-proximal convoluted tubule measured by the split-drop micropuncture method[53]. A preliminary report also indicates that endothelin

decreases sodium-phosphate cotransport in rat renal brush border membranes[53]. Garvin and Sanders showed that the ability of endothelin to inhibit fluid and bicarbonate transport in the rat proximal straight tubule is mediated by a reduction in Na^+-K^+ ATPase activity[52]. These effects are probably mediated by the ETB receptor because stimulation of the ETB receptor also inhibits Na^+-K^+ ATPase activity in immortalized rat S1 renal proximal tubule cells[55], similar to that observed in proximal tubules, about 20–40% reduction[52,53]. The inhibitory effect of endothelin, via the ETB receptor, on Na^+-K^+ ATPase activity in human and rat renal proximal tubule cells is mediated by an increase in intracellular calcium via phosphatidyl inositol-3 kinase[55]. However, in suspensions of rabbit proximal tubule cells endothelin was not found to reduce oxygen consumption, used as an index of Na^+-K^+ ATPase activity[56]. It remains to be determined whether or not the differential effect of endothelin on Na^+-K^+ ATPase activity between rats and rabbits is related to species differences.

The effect of endothelin on NHE3 activity in renal proximal tubule cells is still controversial. Short-term (<1 hr) incubation of rat renal cortical cortical slices with endothelin increases NHE3 activity that is mediated by protein kinase C and inhibition of cAMP production[57]. Short-term (< 1hr) stimulation with endothelin of opossum kidney cells which express ETB but not ETA receptors, also increases NHE3 that is mediated equally by Ca^{2+}-dependent and tyrosine kinase-dependent pathways[58,59]. However, long-term (≥6 hr) stimulation of the ETB receptor in the same opossum kidney cells leads to inhibition of NHE3 activity and expression[60]. One may conclude from these studies that in the renal proximal tubule, endothelin, via the ETB receptor, inhibits sodium transport by decreasing Na^+-K^+ ATPase activity. In contrast, endothelin, via the ETB receptor, acutely stimulates but chronically inhibits NHE3 activity. However, the end-result of ETB receptor stimulation should still be a decrease in renal proximal tubule transport because of the inhibition of Na^+-K^+ ATPase activity.

Interaction with other GPCRs

Interaction between ETA and ETB receptors—ETA and ETB receptors may exist as constitutive homodimers[61]. They may also exist as constitutive heterodimers[62] and therefore, there may be a “cross-talk” between these two ET receptors. The ETB receptor may be essential in regulating the development or expression of the ETA receptor because ETA receptor expression is decreased in central or peripheral tissues of ETB receptor deficient mice[63]. ETA and ETB receptor heterodimers may be responsible for a sustained Ca^{2+} signaling by delaying their internalization[64]. Both the ETA and ETB receptors are required for the full diuretic and natriuretic actions of endothelin associated with the intramedulary hyperosmotic saline infusion[65]. An increased ratio of ETA and ETB receptor activity is important in the development and progression of DOCA-salt-induced hypertension and organ damage[66]. Indeed, blockade of ETB receptors in this model of hypertension increases the severity of vascular and renal proximal tubular damage[66].

Interaction with the D_3 dopamine receptor—Dopamine, an endogenous catecholamine, is an important regulator of sodium balance and blood pressure via renal and non-renal mechanisms, including the regulation of appetite centers in the brain, secretion/

release of hormones and humoral agents and interaction with hormones that regulate renal ion transport. Dopamine receptors are divided into D_1- and D_2-like subtypes based on their interaction with the effector enzyme, adenylyl cyclase. Among D_2-like receptor subtypes, the D_3 receptor, along with the D_4 receptor, has the highest affinity for dopamine. Stimulation of the D_3 receptor increases sodium and water excretion in normotensive rats[67,68]. The natriuresis caused by D_3 receptor stimulation is due, in part, to inhibition of Na^+-K^+ ATPase activity, via a cooperative interaction with ETB receptors[28]. The D_3 and ETB receptors co-localize and physically interact in rat renal proximal tubules and increase each other's expression (Figure 1). In immortalized renal proximal tubule cells, D_3 receptor stimulation increases ETB receptor expression by a calcium-mediated process which is absent in renal proximal tubule cells from spontaneously hypertensive rats[69,70].

Interaction with the AT_1 receptor—In the basal state on normal sodium intake and especially during sodium deficit, angiotensin II, via the AT_1 receptor, is pre-eminent in renal sodium conservation. The AT_1 and ETB receptors physically interact and regulate each other's expression (Figure 1). Long-term activation of the AT_1 receptor increases ETB receptor expression whereas short-term activation increases cell surface ETB receptor expression in rat renal proximal tubule cells, effects that are not observed in renal proximal tubule cells from spontaneously hypertensive rats[71,72].

Endothelin and hypertension

Increased ET-1 plasma levels, relative to normotensive subjects, regardless of renal function, have been reported in hypertensive patients in some studies[73–75]. Most studies, however, have found no differences in circulating endothelin levels between hypertensive and normotensive subjects[76]. However, the ETB receptor may be involved in the pathogenesis of hypertension. High-sodium diet or deoxycorticosterone-salt-treatment increases the blood pressure of ETB receptor-deficient rats. The increased renal sodium transport in these rats probably occurs at a distal tubular level because the increased blood pressure caused by increased sodium diet is normalized by blockade of the epithelial sodium channel with amiloride[77]. ETB receptor blockade produces hypertension that is exaggerated by salt intake or deoxycorticosterone[78,79]. Systemic ETB receptor blockade also produces hypertension in mice that is maintained by the ETA receptor[80]. These findings strongly suggest that the ETB receptor, by itself, or in conjunction with the ETA receptor, can regulate blood pressure and decreased expression or activity of ETB receptors increases blood pressure. However, these studies have not determined the involvement of the ETB receptor expressed in the proximal tubule. As indicated above, the natriuretic effect of ETB receptor agonists is impaired in spontaneously hypertensive rats. Although ETB receptor expression is not different in renal proximal tubules between normotensive and spontaneously hypertensive rats, angiotensin II increases total ETB receptor expression or plasma membrane expression in cells from normotensive but not from hypertensive rats[71]. The physical interaction between ETB and AT_1 receptors is also impaired in renal proximal tubule cells from spontaneously hypertensive rats[72]. The blunted natriuretic effect of dopamine in spontaneously hypertensive rats may also be due to an impaired physical interaction between D_3 and ETB receptors in the proximal tubule[28], resulting in the impaired inhibition of Na^+-K^+ ATPase activity[70].

Conclusion

The renal proximal tubule in all studied species expresses the ETB receptor. Endothelin has a U-shaped effect on ion and fluid absorption in the renal proximal tubule. The natriuretic effect of ETB receptor agonists and low nM concentrations of endothelin is, in part, due to inhibition of sodium and water transport in the proximal tubule. This is due mainly to inhibition of Na^+-K^+ ATPase activity and NHE3 activity, the latter occurring only in the long-term, as acute stimulation of ETB receptors increases NHE3 activity. The inhibition of Na^+-K^+ ATPase activity in renal proximal tubules by stimulation of the ETB receptor that results in natriuresis is probably abetted by increased positive interaction with the D_3 receptor and negative interaction with the AT_1 receptor. The impaired natriuretic effect of ETB receptor stimulation in spontaneously hypertensive rats may be caused by impaired ETB receptor function that may be related to impaired interaction with D_3 and AT_1 receptors.

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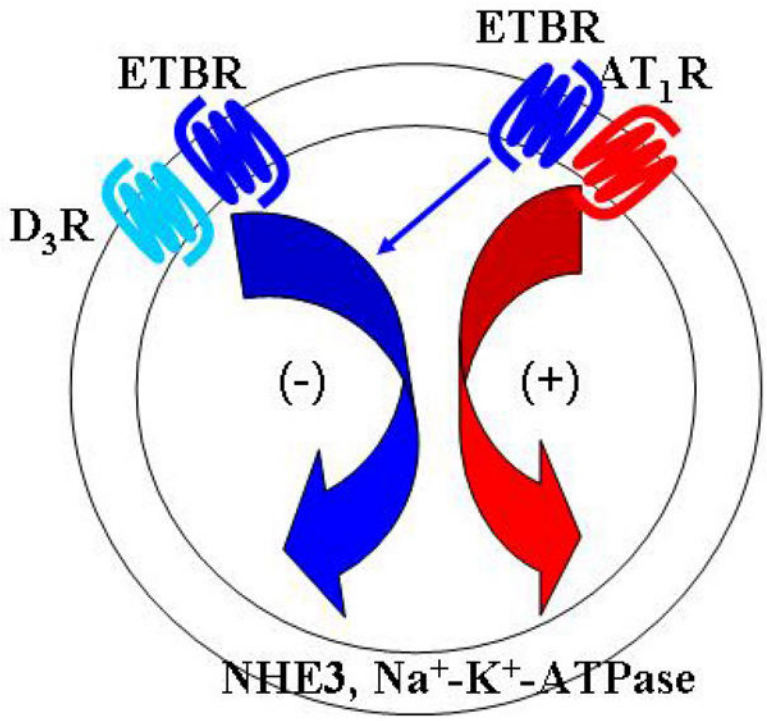

Figure 1. Interactions among ETB (ETBR), D_3 dopamine (D_3R), and AT_1 (AT_1R) receptors in the regulation of sodium transport in the renal proximal tubule

Stimulation of the AT_1R increases the activity of sodium transporters, sodium exchangers, and the sodium pump (e.g., $NaHCO_3$ cotransporter, Na^+H^+exchanger, and Na^+-K^+-ATPase), while their activity is decreased by the stimulation of ETBR and dopamine receptors (e.g., D_1R and D_3R). The ETBR, D_3R, and AT_1R physically interact with each other. Stimulation of the ETBR increases D_3R expression and function but the opposite effect occurs with AT_1R expression and function. The D_3R also negatively regulates AT_1R expression. In contrast, stimulation of the AT_1R increases ETBR expression, in the long-term, and ETBR cell surface expression, in the short-term. Thus, the ETBR synergistically interacts with the D_3R to counterbalance the stimulatory effect of the AT_1R on sodium transport in the renal proximal tubule.