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Endothelin-1 and the kidney: new perspectives and recent findings

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Abstract

Purpose of review—The role of endothelin-1 (ET-1) in the kidney has been under study for many years; however, the complex mechanisms by which endothelin controls the physiology/pathophysiology of this organ are not fully resolved. This review aims to summarize recent findings on the field, especially regarding glomerular and tubular damage, Na^+/water homeostasis and sex differences in ET-1 function.

Recent findings—Podocytes have been recently identified as a target of ET-1 in the glomerular filtration barrier *via* ET_A receptor (ET_AR) activation. Activation of ET_AR by ET-1 leads to renal tubular damage by promoting endoplasmic reticulum stress and apoptosis in these cells. In addition, high flow rates in the nephron in response to high salt intake induce ET-1 production by collecting ducts and promote nitric oxide dependent natriuresis through ENaC inhibition. Recent evidence also indicates that sex hormones regulate the renal ET-1 system differently in males and females, with estrogen suppressing renal ET-1 production and testosterone upregulating that production.

Summary—Based on the reports reviewed in here, targeting of the renal ET system is a possible therapeutic approach against the development of glomerular injury. More animal and clinical studies are needed to better understand the dimorphic control of this system by sex hormones.

Keywords

Endothelin; podocyte damage; tubular damage; Na+ homeostasis; sex differences

Introduction

Endothelin-1 (ET-1) is a 21 amino acid peptide that has been described as the most potent vasoconstrictor in the human body. ET-1 is produced by almost every cell type in the kidney. However, evidence demonstrates that most of the production is by endothelial and tubular cells, primarily principal cells of the inner medullary collecting duct. There is a

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Conflict of interest

The authors declare no conflicts of interests

similar distribution of ET_A receptors (ET_AR) and ET_B receptors (ET_BR) that suggest an autocrine function. Over-activation and dysfunction of the renal endothelin-1 (ET-1) system leads to renal disease that seems to result from an imbalance of ET_AR over ET_BR activity. The purpose of this mini-review is to examine the role of the ET system in the kidney with a focus on the most recent evidence on the mechanisms involved.

Endothelin-1 effects on the glomerular filtration barrier

The glomerular capillary wall consists of 3 principal interdependent components: 1) internal layer of endothelial cells, 2) a middle acellular layer of glomerular basement membrane and 3) an external layer of epithelial cells called podocytes. The properties and functions of this complex barrier can be modified by the ET-1 system [1, 2, 3, 4], as summarized in Figure 1. We will focus on the effects of ET-1 on the podocytes, highlighting recent findings on the involvement of ET-1 in podocyte/glomerular impairment and emphasizing promising therapeutic targets.

Podocytes, with their complex cytoarchitecture and interdigitated foot process, are critical determinants of the integrity of the glomerular filtration barrier, and their injury leads to proteinuria, glomerulosclerosis and progression of renal disease [5]. Moreover, podocytes produce, secrete and bind ET-1 [6], thus appearing to function as an autocrine target for this potent peptide [7]. Endothelial cells are considered a principal source of ET-1 within the glomeruli [8]. However, new data underline the importance of endothelium-podocyte cross talk as a major determinant of a healthy filtration barrier [9] and so the cellular location of ET-1 production and function in renal disease is not clear. Autocrine and/or paracrine ET-1 signaling is considered to be crucial in contributing towards the development of albuminuria [10]. Podocytes produce vascular endothelial cell factor (VEGF), which acts on podocytes and neighboring endothelial cells and maintains the health of the endothelium [11]. Loss of VEGF function leads to endothelial dysfunction and proteinuria. Most importantly, loss of VEGF promotes actin cytoskeleton disruption and podocyte impairment by promoting ET-1 release, thereby resulting in severe proteinuria [12]. Moreover, a soluble form of VEGF receptor 1 (fms-like tyrosine kinase 1; sFLT-1) binds podocyte-derived VEGF and neutralizes its effects on endothelial cells, leading to endothelial damage and proteinuria [13]. sFLT-1 also binds to lipid microdomains in podocytes producing structural and functional changes in podocytes and glomerular filtration barrier [12]. On the other hand, increased levels of β-arrestin-1 can activate podocyte motility and sustain glomerular injury. ET-1, *via* upregulated ET_AR, promotes ET_AR/β-arrestin-1/Src kinase complex formation, leading to epidermal growth factor receptor (EGFR) transactivation, β-catenin phosphorylation and increased Snail expression, resulting in podocyte dysfunction and depletion. ET_AR blockade prevented podocyte loss and lesion formation as well as normalized β-arrestin-1 and Snail, suggesting ET_AR antagonism as a potential therapeutic approach in progressive glomerulopathies [14**]. Moreover, recent studies suggest that ET_AR antagonism may partially restore podocyte impairment and prevent podocyte loss [15, 16]; however, the underlying mechanism remains unclear.

ET-1 has also been implicated in numerous pathophysiological mechanisms within the glomeruli contributing to podocyturia and proteinuria in multiple forms of chronic kidney

disease such as diabetic nephropathy [17], sickle nephropathy [18], hypertensive nephropathy [16] or focal segmental glomerulosclerosis [6]. Blockade of ET receptors protects or delays ET-1 effects in these proteinuric renal diseases, highlighting the therapeutic efficacy of ET-1 antagonists and the importance of further preclinical and clinical studies.

Endothelin and renal tubular damage: new perspectives

The involvement of ET-1 in the development of renal injury is well documented in the literature. Despite many of these reports being centered on the role of this peptide in glomerular diseases, all the components of the ET-1 system are also present in renal tubular cells and their expression is exaggerated during renal injury. Accordingly, several reports document that ET-1 also participates in tubulointerstitial renal disease, as recently reviewed [19]. Human studies using antagonists of ET_AR and studies using transgenic animal models showed that the ET-1 system is involved in renal tubular injury associated with ischemia-reperfusion (I/R) [20] and with radiocontrast-induced or sepsis-induced acute kidney injury (AKI) [21]. Other evidence also indicates involvement of ET-1 in the formation of tubular cysts during polycystic kidney disease (PKD) [19].

Despite many studies linking ET-1 and renal tubular damage, the exact molecular mechanisms by which ET-1 contributes to the pathogenesis of renal disease remain unknown. In recent years, reports have highlighted the induction of endoplasmic reticulum (ER) stress as a possible mechanism promoting ET-1-induced renal apoptosis and renal injury. ER stress is a type of cellular stress caused by accumulation of unfolded proteins in the ER. The cell responds by activating the adaptive unfolded protein response (UPR) that aims to restore cellular homeostasis by decreasing further protein transcription and translation and by increasing expression of ER chaperones to fold the accumulated proteins. However, prolonged and/or severe upregulation of this pathway eventually leads to cell death and organ damage. There is accumulating evidence of a pathophysiological role of ER stress in acute and chronic kidney disease [22**]. Interestingly, both ET-1 and ER stress are upregulated in renal tubules in, among other renal diseases, contrast-induced AKI [23, 24], I/R injury [25, 20], septic shock-induced AKI [26, 27], or diabetic nephropathy [28, 29], suggesting that overactivation of the ET-1 system leads to induction of the ER stress response in renal tubular cells. Further, a very recent report also links stimulation of ER stress pathways in renal proximal cells with the activation of the NLRP3 inflammasome, a key inducer of tubulointerstitial inflammation, a hallmark of renal injury [30*].

Interesting studies performed by Arfian et al. [31] also highlight the importance of ET-1 originating from the vascular endothelium in causing proximal tubular damage during I/R injury. Using a model of mouse lacking ET-1 specifically in vascular endothelial cells (VEET KO mice), these investigators demonstrated that the lack of endothelium-derived ET-1 not only attenuated proximal tubular injury in response to I/R, but also decreased inflammatory and oxidative stress responses. These results suggest that ET-1 produced by the vascular endothelium acts in a paracrine manner on neighboring epithelial cells to induce renal injury [32]. Results from our own laboratory support these observations. Using VEET KO mice, we observed that endothelial ET-1 is critical for the development of outer

medullary tubular apoptosis in response to acute treatment with the AKI-inducer tunicamycin [33] and that ET_AR blockade diminishes tunicamycin- induced tubular apoptosis in the ET_BR deficient rat [34].

All this evidence supports a critical role of ET-1 in the initiation of renal tubular injury (Figure 2) and highlights the ET-1 system as a target against the development of tubular ER stress, apoptosis and renal disease.

Renal Endothelin and Sodium/Water Homeostasis: recent findings

The physiological role of ET-1 is to inhibit Na^+ and water reabsorption by the nephron, which is especially important as salt intake is increased [35]. Release of ET-1, mainly by principal cells of the inner medullary collecting duct (CD), is thought to occur in response to increased tubular flow and shear stress, and possibly to increased osmolality associated with high salt intake [36–40]. Until recently, it was thought that inhibition of Na^+ reabsorption was primarily through activation of type B receptors (ET_BR); however, recent findings suggest an integral role of ET_AR. Recent reviews discussed mechanisms by which ET-1 regulates Na^+ balance by each portion of the nephron [35, 41], therefore, we will only focus on new findings related to mechanisms of ET-1 release and the potential “hidden” role of tubular ET_AR.

Increased salt intake induces renal tubular production of ET-1, which in turn, inhibits epithelial Na^+ channels (ENaC) to reduced tubular reabsorption and contributes to natriuresis [41]. Recently, Pandit et al. [39] demonstrated that increased shear stress significantly increases ET-1 production by mouse inner medullary CD cells (mIMCD3) through polycystin-2 and intracellular Ca^{2+} spikes. Interestingly, blockade of ENaC did not affect flow-mediated increases in ET-1 [40]. However, a recent study [42**] suggests that higher flow rates (3–10 fold higher than Pandit et al.) increase NO production by mIMCD3 cells, a response that is dependent on activation of ET_BR. Further, benzamil, an ENaC blocker, prevents the NO increase in response to shear stress, suggesting an ENaC dependent mechanism [42**]. In addition, ET-1 inhibits ENaC open probability, or fraction of time that the channel is in the open conformation, in collecting ducts from control mice, but not from collecting duct NOS1 knockout mice [42**]. These studies suggest that high Na^+ intake leads to increased renal medullary osmolality and increased tubular flow: excess Na^+ is sensed by ENaC channels leading to increased ET-1 production and elevated NO, which most likely inhibits ENaC and promotes excretion of excess Na^+.

Several *in vitro* studies implicate ET_BR in the inhibition of Na^+ and water reabsorption throughout the nephron, while inhibition of ET_AR typically has no effects [43]. However, the use of several CD specific knockout models showed that knockout of ET-1 production by the CD causes salt sensitive hypertension [44]. Knockout of ET_BR produced hypertension, but not to the extent of ET-1 KO, while CD ET_AR KO mice had no blood pressure phenotype. Interestingly, dual CD ET_AR/ET_BR KO mice had a similar blood pressure phenotype as CD ET-1 KO, indicating that ET_AR are necessary for normal tubular function, but their absence can be compensated by a functional ET_BR [45] (Figure 3). These are important findings because human trials of chronic kidney disease demonstrated that ET_AR specific inhibitors increased fluid retention in treatment group [46]; unfortunately, the

high doses of antagonist used in these trials could possibly be a result of non-specific inhibition of ET_BR. However, another study recently demonstrated that the fluid retention associated with systemic ET_AR inhibitors is mediated at the level of the nephron, because whole nephron ET_AR KO mice have significantly less fluid retention in response to ET_AR antagonism than controls [47]. If ET_BR compensates for loss of ET_AR, further studies are needed to determine if dual ET_A/ET_B nephron KO mice have fluid retention during chronic treatment with ET_AR antagonists.

Two recent clinical trials studying the effects of ET_AR inhibition on diabetic nephropathy have been undertaken with the idea that using lower doses of an ET_A selective antagonist compared to previous clinical trials would extend benefit with less incidence of fluid retention. The recently completed phase 2 trial, “Reducing Residual Albuminuria in Subjects with Diabetes and Nephropathy with Atrasentan (RADAR)” showed that patients given 0.75 mg of Atrasentan had significantly lower 24 hr blood pressure and albuminuria with a similar number of adverse events as the placebo group. On the other hand, volunteers given 1.25 mg had similar reductions in pressure and albuminuria as the 0.75 mg group, but had a significant rise in adverse events suggesting that lower doses of atrasentan are optimal to provide renal protection with less incidence of fluid retention in diabetic patients [48]. Recently, an exciting phase 3 trial, “Study of Diabetic Nephropathy with Atrasentan (SONAR)” was designed [49]. Using the optimal dose of 0.75 mg of atrasentan, the SONAR trial will enroll over 4000 volunteers with the primary endpoint being time to doubling of serum creatinine or end stage renal disease. This study will certainly provide the most comprehensive, well-controlled study for the chronic used of ET_A receptor antagonist in renal disease.

Sexual Dimorphism in the renal endothelin system

Sex differences in cardiovascular and kidney diseases are widely reported for pre-menopausal women and ET-1 is a potential mediator of this sexual dimorphism. Male-female differences in the actions of ET-1 in the kidney were reviewed before [50]; accordingly, our review here will focus on recent aspects of sexual dimorphism in the renal ET-1 system and the potential regulatory effects of sex-steroids on this signaling system.

Sex-related differences in ET receptor expression and function are a potential contributor to male-female differences in renal medullary ET-1 system signaling. Our group demonstrated increased ET_AR expression in male IMCDs compared to female [51], thus, enhanced ET_AR function in male rats could limit ET_BR-dependent natriuresis (Figure 3). Additionally, females are protected from the decrease in medullary blood flow observed in males in response to intramedullary infusion of ET-1 [52]. Moreover, Nakano et al. demonstrated that renal medullary ET_AR contribute to Na excretion in ET_BR-deficient female rats. Inner medullary ET_BR expression did not appear to be sex-dependent [50] in these studies; however, others showed that ET_BR play a significantly greater beneficial role in protecting female rats against angiotensin II-induced hypertension [53].

Few studies have investigated the regulatory role of sex hormones on the renal ET-1 system. Estradiol suppresses renal ET-1 overproduction and the consequent renal damage in I/R AKI [54]. Additionally, progesterone appears to regulate the renal ET-1 system. Zhang et al. [55]

showed that pregnancy and progesterone treatment in ovariectomized mice enhance renal ET_AR expression. Recent studies support the role of renal ET-1 in the pathophysiology of preeclampsia [56, 57]. Investigating the connection between progesterone and ET_AR in preeclampsia may lead to preventive interventions for this condition.

On the other hand, the possibility that testosterone modulates the renal ET-1 system is also postulated, but available data are insufficient to draw a clear picture. Androgens may up-regulate ET-1 production directly or interfere with the renin-angiotensin system, thus promoting renal damage by causing renal vasoconstriction and mitogenesis that can contribute to kidney fibrosis [58*]. These detrimental changes associated with renal ET-1 overexpression were attenuated by orchiectomy, suggesting an interaction of male sex hormones with the ET-1 system [59]. Collectively, male and female sex hormones are likely to be modulating the renal ET-1 system; however, more studies are needed to understand their impact on vascular and tubular components of the ET-1 system in the kidney.

The renal effects of ET-1 through ET_AR activation render ET_AR antagonism an attractive option for the treatment of chronic kidney disease [60**, 61]. Studies analyzing the protective effects of ET receptor blockers specifically in the female population are very rare. Jokar et al. [62] evaluated the effect of bosentan (dual ET_A and ET_B receptor antagonist) on cisplatin-induced nephrotoxicity in male and female rats. The renoprotective effect of bosentan was not observed in either sex in this setting; however, it promoted the severity of renal injuries only in females [62]. This observation may be related to blockade of ET_BR, which exerts a central renoprotective role in females. A recent study suggests that ET receptor antagonists have estrogen-like vasculoprotective effects in ovariectomized rats. Thus, ET receptor antagonists may be an alternative therapy to prevent vascular disease in postmenopausal women [63]. Further research on the protective mechanisms of ET receptor antagonists after menopause and future clinical studies are needed.

Conclusion

The reviewed studies demonstrate and clarify new mechanisms involved in the role of ET-1 in renal dysfunction, and that the use of different kinds of ET receptor antagonism appears to be a valid therapeutic approach to prevent or attenuate the development or progression of renal disease.

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Key points

- ET-1 leads to podocyte damage by promoting actin cytoskeleton disruption *via* ET_AR activation in these cells.
- Vascular ET-1 induces tubular ER stress and apoptosis in a paracrine manner.
- In response to high salt intake, high tubular flow activates ET_AR in IMCD to increase ENaC-dependent NO production.
- ET_BR is renoprotective in females, not males; however, more research in the sex dimorphism in the renal ET-1 system will ensure better therapies.

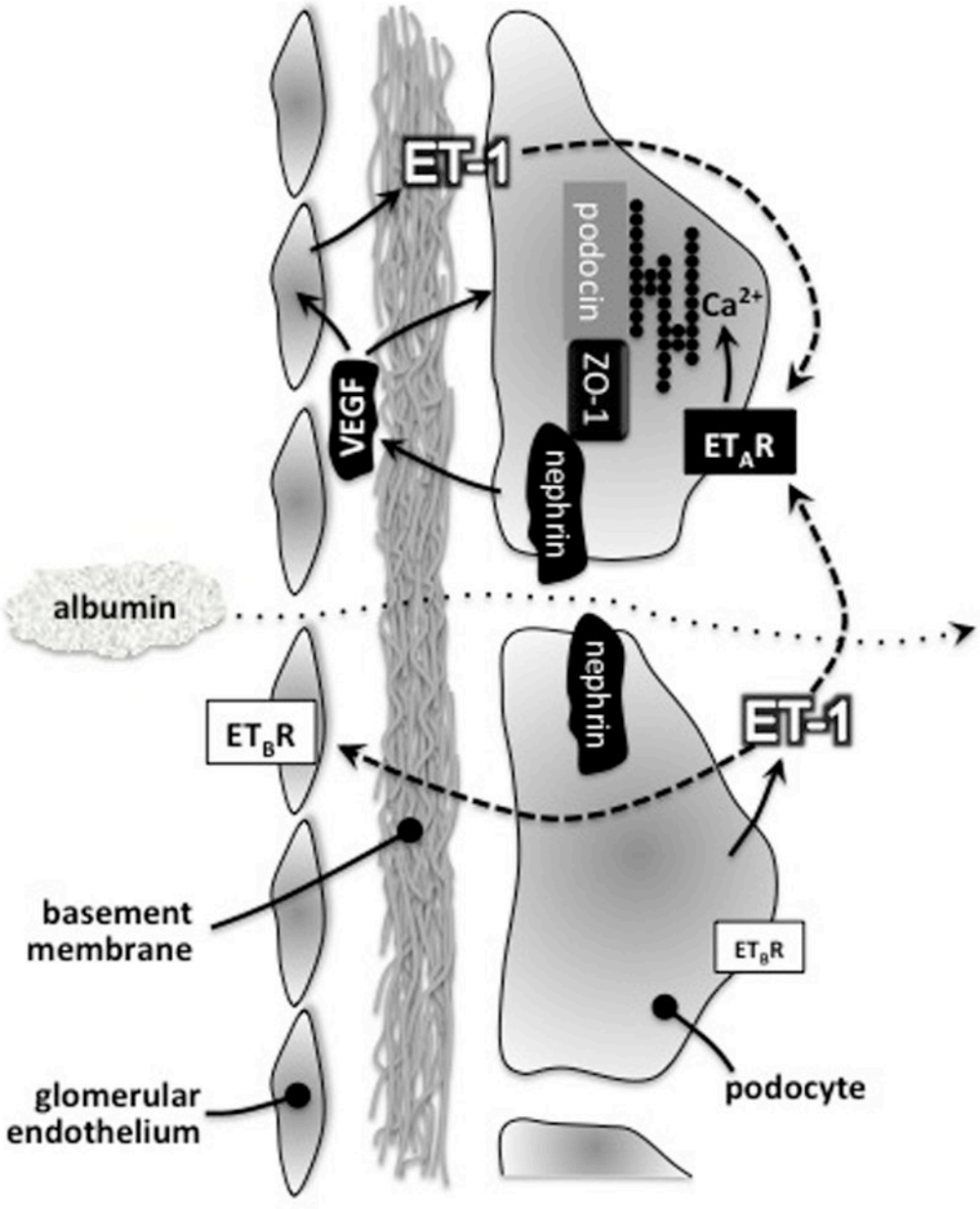

Figure 1.

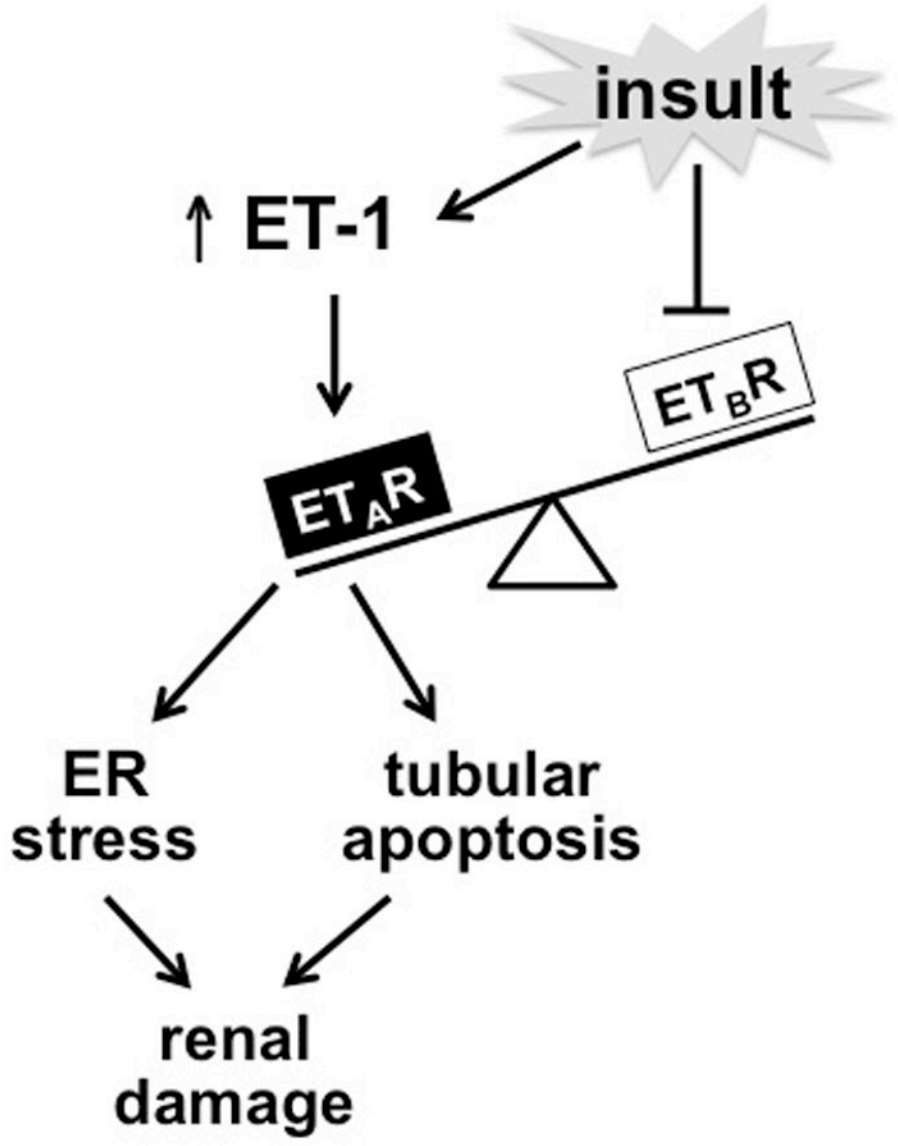

Figure 2.

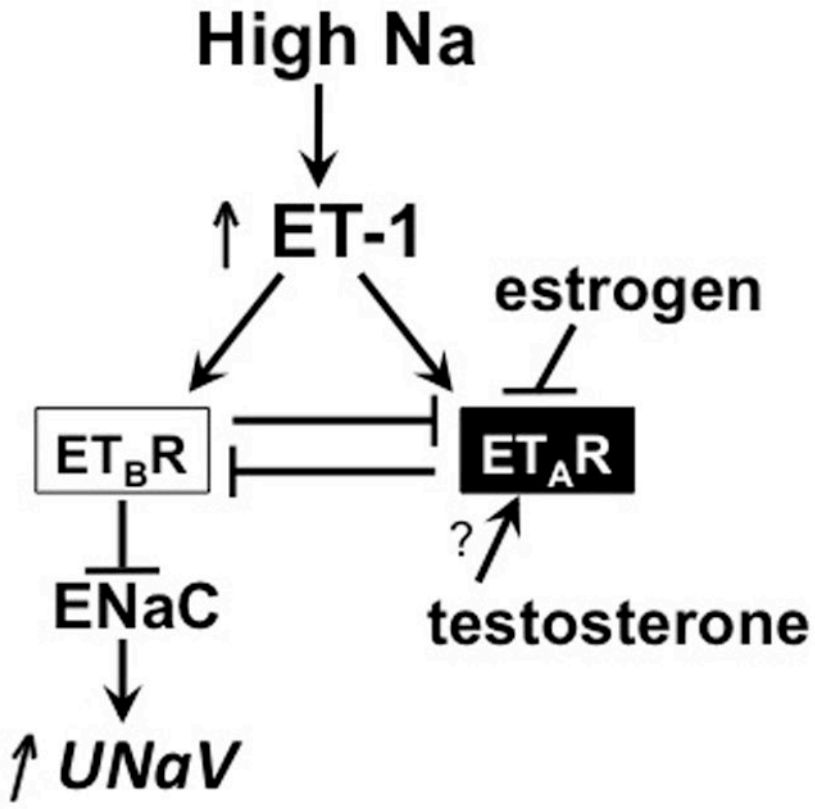

Figure 3.