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INHIBITION OF ENaC BY ENDOTHELIN-1

Andrey Sorokin[1,*] and **Alexander Staruschenko**[2,*]

[1]Division of Nephrology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

[2]Department of Physiology, Medical College of Wisconsin, Milwaukee, WI, USA

Abstract

The amiloride-sensitive epithelial Na^+ channel (ENaC) is a key player in the regulation of Na^+ homeostasis. Its functional activity is under continuous control by a variety of signaling molecules including bioactive peptides of endothelin family. Since ENaC dysfunction is causative for disturbances in total body Na^+ levels associated with abnormal regulation of blood volume, blood pressure, and lung fluid balance, the uncovering the molecular mechanisms of inhibitory modulation or inappropriate activation of ENaC is crucial for the successful treatment of a variety of human diseases including hypertension. The precise regulation of ENaC is particularly important for normal Na^+ and fluid homeostasis in organs where endothelins are known to act: kidneys, lung and colon. Inhibition of ENaC by endothelin-1 (ET-1) has been established in renal cells and several molecular mechanisms of inhibition of ENaC by ET-1 are proposed and will be reviewed in this chapter.

Keywords

sodium reabsorption; ET-1; blood pressure; collecting duct; signal transduction; ETRA; ETRB; βPix

1. Introduction

The amiloride-sensitive epithelial sodium channel (ENaC) is expressed in the apical membrane of polarized epithelial cells in the distal part of kidney tubule, the lung and the distal colon. These cells are in constant contact with other cells, which is achieved by specific reception and secretion of a number of regulatory molecules, including potent bioactive peptides endothelins. The family of endothelin proteins consists of 3 members: endothelin-1, endothelin-2 and endothelin-3 (ET-1, ET-2 and ET-3, respectively) known to play important roles in renal physiology and pathophysiology due to their involvement into the physiological control of blood pressure and salt homeostasis (Kohan, Inscho, Wesson, & Pollock, 2011; Kohan, Rossi, Inscho, & Pollock, 2011; Simonson & Dunn, 1993; Sorokin & Kohan, 2003). ET-1 is the main isoform which is secreted by renal cells and which also

Correspondence: Dr. Andrey Sorokin, Department of Medicine/Nephrology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA. sorokin@mcw.edu or Dr. Alexander Staruschenko, Department of Physiology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA. staruschenko@mcw.edu.

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operates on a number of renal targets, including its effects in different parts of nephron on top of action as multifunctional bioactive peptides in renal mesangium (Sorokin, 2011). Its production is largely controlled at the level of gene expression (Foschi et al., 2001; Sorokin & Kohan, 2003). ET-1 appears to be an important negative regulator of ENaC *in vivo* and endothelin-dependent regulation of ENaC activity, critical aspect of the functional role of endothelins, will be the subject of this review.

2. Regulation of sodium reabsorption – role of ENaC

Hypertension represents one of the most prevalent chronic health problems of Western nations but the mechanisms responsible for this disease remain poorly understood. Long term control of blood pressure involves Na^+ homeostasis through the precise regulation of the epithelial Na^+ channels (ENaC) in the aldosterone-sensitive distal nephron (ASDN). Although only a small percent of the glomerular filtrate (less than 5–10%) reaches the connecting tubules (CNT) and collecting ducts (CD), these segments are critical for water and electrolyte homeostasis since fine tuning of electrolyte and fluid balance is mediated in these nephron segments through reabsorption and secretion and these processes are under tight control of hormones and non-hormonal factors (Staruschenko, 2012). Na^+ reabsorption in the CNT and CDs is transcellular and is mediated by the connecting tubule cells and the principal cells of CDs. Shown on Figure 1 is a structure of the nephron with segments expressing ENaC. At the basolateral membrane of the principal cells Na^+ extrusion is mediated by the Na^+/K^+-ATPase, which also provides the electrochemical driving force for the apical entry of Na^+ (Feraille & Doucet, 2001). ENaC, which appears to be a trimeric channel comprised of 1 α-, 1 β-, and 1 γ-subunits (Jasti, Furukawa, Gonzales, & Gouaux, 2007; Staruschenko, Adams, Booth, & Stockand, 2005) is responsible for sodium reabsorption in these segments. ENaC dysfunction is causative for disturbances in total body Na^+ levels associated with abnormal regulation of blood volume and blood pressure, as well as alterations in lung fluid balance (Bhalla & Hallows, 2008; Pearce et al., 2014; Soundararajan, Pearce, Hughey, & Kleyman, 2010; Rossier, 2014; Alvarez, Navarro-Gonzalez, & Giraldez, 2013; Warnock et al., 2014). Mutations in genes encoding the ENaC subunits corroborate critical role of this channel in the control of blood pressure. For instance, Liddle Syndrome is an autosomal dominant form of hypertension that results from the C-terminal truncation mutations in the β- or γ-ENaC subunits, which prevents the channel's retrieval from the apical membrane and subsequent degradation, thus leading to increased basal ENaC expression and activity at the apical membrane (Hansson et al., 1995a; Hansson et al., 1995b; Shimkets et al., 1994; Lifton, Gharavi, & Geller, 2001). Loss-of-function mutations in any of the three different ENaC subunits also cause the autosomal recessive form of Pseudohypoaldosteronism type I (PHAI) (Chang et al., 1996; Lifton et al., 2001; Grunder et al., 1997). ENaC-mediated electrogenic sodium entry also provides the driving force for luminal potassium exit via potassium (renal outer medullary K channel (ROMK) and large conductance calcium-activated Maxi-K (BK)) channels (Staruschenko, 2012; Wen, Cornelius, & Sansom, 2014; Welling, 2013). Mutations in ROMK channel result in the Type II Bartter syndrome (Simon et al., 1996; Welling & Ho, 2009; Srivastava et al., 2013).

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The expression and activity of ENaCs are regulated by specific hormones and different extra- and intracellular regulatory mechanisms. Considering that ENaC is responsible for the fine-tuning of sodium reabsorption in the last nephron segment, the role of this channel in sodium reabsorption in the kidney in critical and unique. The tight regulation of transcellular Na^+ concentrations is so important that multiple mechanisms work in concert to control them. One of the main mechanisms controlling ENaC activity is activation of the RAAS (Pearce et al., 2014; Rossier, 2014; Quinn, Harvey, & Thomas, 2014; Alvarez et al., 2013). Activation of the RAAS is well known to enhance activity of ENaC. Aldosterone, as well as other corticosteroid hormones, binds to the mineralocorticoid receptor and triggers coordinated changes in the expression of multiple aldosterone-induced genes in a ligand-dependent manner (Stockand, 2002; Kone, 2013). Hyperaldosteronismis results in enhanced sodium reabsorption in the distal nephron, whereas aldosterone insufficiency leads to reduced ENaC activity and urinary sodium wasting. However, substantial experimental data suggest a role for aldosterone-independent mechanisms in regulation of ENaC (Zaika, Mamenko, Staruschenko, & Pochynyuk, 2013). For instance, mice lacking mineralocorticoid receptors still possess ENaC-mediated Na^+ reabsorption in the ASDN (Berger et al., 1998). Besides, it was reported that mice with surgically removed adrenal glands have no detectable circulating aldosterone, but possess robust ENaC activity in the distal nephron (Mironova, Bugaj, Roos, Kohan, & Stockand, 2012). Recent studies further revealed that ENaC activity remained above control levels during maximal mineralocorticoid receptors inhibition with spironolactone (Mamenko et al., 2013). Therefore, other signaling pathways, which modulate ENaC either acutely or at transcription level, work in parallel with the RAAS.

Current chapter is focused on the control of ENaC by ET-1. However, as noticed above, multiple mechanisms are involved in the tight control of ENaC expression and activity in the ASDN. Hormones are key regulators of sodium transport in the kidney and in ASDN specifically. In addition to the RAAS, it was shown that arginine vasopressin (AVP) (Ecelbarger et al., 2000; Mironova et al., 2012; Stockand, 2012; Bankir, Bouby, & Ritz, 2013; Bankir et al., 2013; Sanghi et al., 2014), atrial natriuretic peptide (ANP) (Kudo & Baird, 1984; Wang et al., 2006; Guo, Alli, Eaton, & Bao, 2013) and insulin (alongside with Insulin-like growth factor 1, IGF-1) (Blazer-Yost, Liu, & Helman, 1998; Li et al., 2013; Ilatovskaya, Pavlov, Levchenko, & Staruschenko, 2013; Pavlov et al., 2013a) are critical modulators of ENaC activity. The kallikrein-kinin systems through its peptide bradykinin also play a specific role in blunting ENaC activity, particularly under conditions of elevated sodium intake (Zaika, Mamenko, O'Neil, & Pochynyuk, 2011; Mamenko, Zaika, Doris, & Pochynyuk, 2012; Mamenko, Zaika, & Pochynyuk, 2014). In addition to hormonal regulation of ENaC-mediated sodium transport in the kidney, a number of local autocrine and paracrine factors play critical role in the modulation of ENaC. For instance, recent review article by Stockand and colleagues highlight regulation of ENaC-mediated sodium excretion and blood pressure by purinergic signaling (Mironova, Boiko, Bugaj, Kucher, & Stockand, 2014). Multiple evidence reveal that a robust inhibitory purinergic signaling system intrinsic to the ASDN dynamically regulates ENaC through paracrine ATP signaling via the metabotropic $P2Y_2$ purinergic receptor to properly match urinary Na^+ excretion to dietary Na^+ intake (Pochynyuk et al., 2008; Pochynyuk et al., 2010; Rieg et al., 2007; Rieg, Gerasimova, Boyer, Insel, & Vallon, 2011; Birch, Schwiebert, Peppiatt-Wildman, &

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Wildman, 2013; Stockand et al., 2010). This enables blood pressure to be maintained within a normal range despite broad changes in dietary Na^+ consumption. We and others also identified that members of the epidermal growth factors (EGF) are involved in the control of ENaC ((reviewed in (Staruschenko, Palygin, Ilatovskaya, & Pavlov, 2013)). Using the Dahl salt-sensitive rat model, we evaluated the role of EGF and identified that deficiency of renal cortical EGF increases ENaC activity and contributes to salt-sensitive hypertension (Pavlov et al., 2013b). Prostaglandins, cytochrome P450 metabolites, nitric oxide, peroxisome proliferator-activated receptor agonists and other molecules are also among important paracrine and autocrine factors modulating ENaC activity.

3. Endothelin signaling and control of blood pressure

3.1. Endothelin Receptors

Endothelins are multifunctional 21 amino acid vasoactive peptides secreted by numerous cell types (Simonson & Dunn, 1993). All of endothelin's effects are elicited by binding to specific G-protein coupled receptors Endothelin Receptor A (ETRA) (Arai, Hori, Aramori, Ohkubo, & Nakanishi, 1990) and Endothelin Receptor B (ETRB) (Sakurai et al., 1990). ETRA and ETRB demonstrate considerable variability in the distribution between different tissues and among species (Pollock, 1998). Human and rat renal tubular cells, vascular smooth muscle cells, glomerular mesangial cells and many other cell types express substantial levels of both ETRA and ETRB (Orth et al., 2000; Kohan et al., 2011; Bouallegue, Daou, & Srivastava, 2007; Sorokin, 2011). A progressive renal injury like inflammation and fibrosis are mediated via both ETRA and ETRB receptors, while constrictor effects are primarily transduced by ETRA receptors (Neuhofer & Pittrow, 2006). Thus, actions of ET-1 depends on the cell type and physiological situation (Vignon-Zellweger, Heiden, & Emoto, 2011)

3.2. Endothelin Signaling

ET-1 receptors couple to members of the $G\alpha_i$, $G\alpha_q$, $G\alpha_s$ and $G\alpha_{12/13}$ G protein families (Sorokin & Kohan, 2003). Accordingly, when ET-1 binds to its receptor the multiple intracellular pathways are triggered (Sorokin, Foschi, & Dunn, 2002; Sorokin, 2011). Among most important cellular events are activation of phospholipases A, C and D, activation of serine-threonine kinases, increased protein tyrosine phosphorylation and a stimulated influx of Ca^{2+} from outside the cell as well as mobilization of intracellular Ca^{2+} from internal sources.

ET-1 acts via ETRA to induce GTP loading of $G\alpha_q$ and $G\alpha_s$ to stimulate phospholipase C (PLC) and adenylate cyclase respectively. Correspondingly, ETRB stimulates PLC via $G\alpha_q$, and causes the inhibition of adenylate cyclase through $G\alpha_i$. The ET receptors co-localize and interact with caveolin-1 in caveolae and since caveolae integrates different receptor and signaling proteins it adds to the complexity of ET-1 signaling. It is of note, that activation of endothelin receptors leads to the compartmentalization and the binding of $G\alpha_q$ to guanine exchange factor βPix (p21-activated kinase (PAK)-interacting exchange factor β) in caveolae (Chahdi & Sorokin, 2010b). Another important feature of ET-1 signaling is transactivation of growth factor receptors, such as EGF receptor (Chahdi & Sorokin, 2010a; Hua, Munk, &

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Whiteside, 2003; Vacca, Bagnato, Catt, & Tecce, 2000; Iwasaki, Eguchi, Ueno, Marumo, & Hirata, 1999; Kodama et al., 2002) and PDGF receptor (Harada et al., 2014). This ability ET-1 shares with some other ligands of G-protein coupled receptors (Little, 2013; Daub, Weiss, Wallasch, & Ullrich, 1996).

The contraction of smooth muscle and glomerular mesangial cells induced by ET-1 depends upon stimulation of inositol triphosphate (IP_3) generation and elevation of cytosolic free Ca^{2+} concentration ($[Ca^{2+}]_i$) (Badr et al., 1989; Bouallegue et al., 2007). The calcium influx and mobilization pathways activated by ET-1 vary immensely and are cell-type-specific with regard to which ET receptor subtypes are involved (Tykocki & Watts, 2010). Initial transient increase in ($[Ca^{2+}]_i$) after ET-1 treatment is followed by a sustained lesser increase. It has been shown that early transient peak reflects IP_3-mediated release of Ca^{2+} from intracellular sources, which is associated with cell alkalinization through augmented Na^+/H^+ exchange (Simonson et al., 1989; Simonson & Dunn, 1991; Simonson & Dunn, 1993). The continued plateau of $[Ca^{2+}]_i$ which over time decreases towards the initial level is due to the increased influx of Ca^{2+} across the plasma membrane. This pattern of initial increase followed by sustained influx is induced by ET-1 in both vascular and non-vascular cells (Tykocki & Watts, 2010). Vascular smooth muscle cells and glomerular mesangial cells express L-type Ca^{2+} channels (McDermott, Hurst, & Whiteside, 1993; Sonkusare et al., 2006) as well as transient receptor potential canonical (TRPC) proteins, a family of nonselective Ca^{2+}-permeable cation channels (Du et al., 2007; Gonzalez-Cobos & Trebak, 2010). Members of TRPC family which were shown to be activated by stimulation of endothelin receptors in various cells or tissues include TRPC1, TRPC3, TRPC6 and TRPC7 (Horinouchi, Terada, Higashi, & Miwa, 2013). Low concentrations of ET-1 added to mesangial cells induced slow sustained increase in $[Ca^{2+}]_i$ through a voltage-channel-independent mechanism, whereas higher than 100 pM concentrations caused a transient increase of $[Ca^{2+}]_i$, which was dependent on Ca^{2+} release from intracellular stores and required activation of PLC and Protein kinase C (PKC) (Simonson et al., 1989).

Endothelin-mediated increase of $[Ca^{2+}]_i$ causes the activation of calcium-dependent intracellular tyrosine kinase Pyk2 (Sorokin, Kozlowski, Graves, & Philip, 2001; Park, Bose, Leszyk, & Czech, 2001; Kawanabe, Hashimoto, & Masaki, 2003) providing therefore the link between G-protein coupled endothelin receptors and the induction of tyrosine phosphorylation via mobilization of intracellular calcium. Activation of Pyk2 in ET-1-treated cells requires not only Ca^{2+} mobilization, but also an increased activity of Src kinases (Sorokin et al., 2001). ET-1 was shown to activate Src kinases (Simonson & Herman, 1993) and it appears that at least some members of Src family are recruited to the complex of β-arrestin 1 with ETRA in an agonist-dependent manner (Imamura et al., 2001). Pyk2/p130Cas/BCAR3/Rap1 signaling cascade activated via ETRA receptors is involved in regulation of adhesion and spreading of mesangial cells (Rufanova, Alexanian, Wakatsuki, Lerner, & Sorokin, 2009). Pyk2 also mediates ET-1 signaling to GLUT4 glucose transporters in 3T3-L1 adipocytes (Park et al., 2001).

The ability of ET-1 to act as a mitogen is well established (Bouallegue et al., 2007; Fukuda et al., 1996; Sorokin, 2011). Since GTP-loading of the small GTPase Ras, which is followed by activation of the Raf-MEK-ERK signaling pathway, is indispensable for cell

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proliferation, it is not surprising that ET-1 is not only a potent inducer of Ras activation, but also is an effective stimulator of ERK signaling cascade (Wang, Simonson, Pouyssegur, & Dunn, 1992; Foschi, Chari, Dunn, & Sorokin, 1997). Remarkably, other mitogen-activated protein kinases (MAPK) cascades: JNK/SAPK (Araki, Haneda, Togawa, & Kikkawa, 1997), p38 MAP kinase (Sorokin et al., 2001) and ERK5 (Dorado et al., 2008) are also induced by ET-1. The significance of activation of these MAPKs by ET-1 has been investigated in different cellular systems and is partially responsible for multifunctional activity of endothelins.

3.3. Targeting Endothelins

The increase of ET-1 production accompanies the wide variety of renal diseases and since the most efficient way to interfere with excessive ET-1 action is to block its specific reception by ETR receptors, the pharmacological blockade of ETR received unprecedented attention from multiple pharmaceutical companies. Quite a few nonselective (targeting both ETRA and ETRB) and selective (targeting either ETRA or ETRB) antagonists were created and evaluated for their efficiency (Motte, McEntee, & Naeije, 2005). This class of compounds showed noteworthy promise in different animal models of renal and cardiovascular diseases and sufficient rationale for testing them for treatment of human pathologies was obtained (Benigni et al., 1993; Kohan & Pollock, 2013; Boffa, Tharaux, Dussaule, & Chatziantoniou, 2001; Dhein et al., 2000; Fukuda et al., 1996; Gomez-Garre et al., 1996; Neuhofer & Pittrow, 2006). Numerous clinical trials addressing the benefits of blockade of ETR receptors in the treatment of cardiovascular and renal diseases has been initiated. It was reported that ETR antagonists can reverse proteinuric renal disease and glomerulosclerosis, and their remarkable antiproteinuric effects are additive to those of standard antiproteinuric therapy (Barton, 2008). There are two ETRA antagonists approved in the United States for the treatment of pulmonary hypertension: Ambrisentan and Bosentan. Sitaxsentan, the most selective ETRA antagonist clinically available, has been approved for use in Europe, Canada, and Australia but not in the USA. It was however recently voluntarily withdrawn by Pfizer driven by a review of evolving safety information from clinical trials regarding concerns about idiosyncratic, fatal hepatic failure (Raja & Raja, 2011). Nevertheless, experimental data and recent clinical studies suggest that, despite limitations connected with side effects and relatively poor antagonist selectivity, the antagonists of ETRA, hold promise in the treatment of hypertension and diabetic nephropathy (Meyers & Sethna, 2013). Antagonists of the ETRB are not usually beneficial since they might cause vasoconstriction along with salt and water retention. The blockade of ET-1 actions reduces the progression of chronic kidney disease and might even be beneficial in dialysis patients, even though the potential therapeutic effect of ETR antagonists for treatment of end-stage kidney disease still requires the verification by clinical trials (Kohan & Pollock, 2013).

3.4. Endothelin-mediated control of blood pressure

Regulation of blood pressure by endothelin is a result of complex interweaving of endothelin's effects upon vasculature, humoral systems, nervous system, heart function and specialized kidney cells (Kohan et al., 2011). It is generally accepted that effects of endothelin upon blood pressure and Na^+ homeostasis are the consequences of vasodilation

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caused by stimulated nitric oxide (NO) production by endothelial cells, attenuation of water reabsorption in the CD, decrease of Na^+ transport in several segments of nephron, impairment of afferent nerve inputs and inhibition of renin release (Kohan et al., 2011).

ET-1 is among the most potent vasoconstrictors. In terms of contractility, the net effect of ETRA activation is contraction, whereas the net effect of activation of ETRB tends to be vasorelaxation (Sorokin & Kohan, 2003). Renal microvascular smooth muscle cells which express both ETRA and ETRB react to ET-1 by vasoconstriction, whereas ETRB microvascular endothelial cells promote vasodilator responses (Guan & Inscho, 2011; Pollock, Keith, & Highsmith, 1995). The vasorelaxant effect of ET-1 is due to stimulated secretion of endothelium-derived relaxing factor NO (Levin, 1996). The ability of ETRB to induce NO release is linked to nitric oxide synthase (NOS) activation which is markedly increased when intracellular Ca^{2+} rises (Forstermann & Sessa, 2012). In turn, NO can modulate ET-1 activity via inhibiting ET-1 formation/secretion (Bourque, Davidge, & Adams, 2011). Since NO and ET-1 continuously interfere with each other actions, the pressure regulation by ET-1 and NO is more complex than simply their individual pressor and depressor action (Rapoport, 2014). Nonetheless, it is widely recognized that endothelial NOS keeps all types of blood vessels dilated, making NO/ET-1 interferences an important factor of endothelin-mediated control of blood pressure (Forstermann & Sessa, 2012).

The role of ET-1 in regulation of water reabsorption became evident from studies utilizing either *in vivo* administration of ET-1 or analysis of mice with CD specific knockouts of ET-1. Administration of ET-1 inhibits vasopressin-stimulated osmotic water permeability in CDs (Oishi, Nonoguchi, Tomita, & Marumo, 1991; Nadler, Zimpelmann, & Hebert, 1992). Mice lacking ET-1 production in CD, the major renal site of ET-1 production, have impaired excretion of an acute, but not a chronic, water load suggesting that ET-1 functions as a physiological autocrine regulator of vasopressin-mediated water permeability in the CDs (Ge et al., 2005; Kohan, 2013). These effects seem to be mediated by ETRB, since blockade of ETRA was inefficient, while agonists of ETRB had inhibitory effect (Kohan, 2013). The data obtained with ETRB CD specific knockout indicates however that ETRB of CD only partially mediates the antihypertensive and natriuretic effects of ET-1 (Ge et al., 2006). It is likely, that ET-1 effects are associated with via inhibition of vasopressin-stimulated cAMP accumulation, which is achieved by ET-1 triggered elevation of intracellular Ca^{2+} and PLC-mediated activation of PKC (Teitelbaum & Berl, 1994; Kohan, 2013).

The overall action of ET-1 to increase blood pressure and vascular tone is partially due to ET-1-mediated stimulation of the sympathetic nervous system (Agapitov & Haynes, 2002; Kohan et al., 2011). The renal tissues are densely innervated by sympathetic nerves and increases in renal sympathetic activity, to which ET-1 contributes importantly, decreases urinary sodium excretion (Kopp, 2011). Endothelins are significantly involved in modulation of the activation of the afferent renal nerves and can induce the release of neurotransmitters, promote the development of postganglionic neurons and influence the generation of action potentials (Kopp, 2011; Kohan et al., 2011). Even though the mechanisms responsible for effects of ET-1 in ganglia, peripheral nerves and central nervous system resulting in blood regulation are not sufficiently studied, ET-1 and its receptors have been implicated in the

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enhanced sympathetic excitability associated with salt-sensitive hypertension, regulation of baroreflex activity and systemic hemodynamics (Kohan et al., 2011).

ET-1 was shown to inhibit renin release from rat kidney cortical slices and isolated juxtaglomerular cells (Moe, Tejedor, Campbell, Alpern, & Henrich, 1991; Kramer et al., 1994). Studies utilizing administration of ET-1 intravenously suggest that endothelin inhibits renin release *in vivo* (Otsuka et al., 1989). Even though inhibition of renin release by ET-1 *in vitro* and *in vivo* has been documented a long time ago, there is no consensus on what is the physiological significance of this effect. It has been hypothesized that high salt diet induces ET-1 production which promotes Na excretion by attenuating the renal baroreceptor responsible for renin release (Kohan et al., 2011). It has been reported that ET-1 generation is increased by Ang II and that vasoconstrictor effects of Ang II are partially mediated by ET-1 (Imai et al., 1992). Furthermore, synergistic effect of ET-1 and Ang II on blood pressure has been observed in rats and enhancement of ET-1-induced vasoconstriction by Ang II was shown through upregulation of ETRA (Lin et al., 2014). The crosstalk between the angiotensin and endothelin system is complex and is observed in a number of cellular systems including cells of cerebrovasculature, hepatic stellate cells, renal mesangial and endothelial cells (Lopez-Ongil, Diez-Marques, Griera, Rodriguez-Puyol, & Rodriguez-Puyol, 2005; Konczalla et al., 2013; He, Miao, Li, & Qi, 2013) .

4. Collecting duct: ET-1 and ENaC

4.1. ET receptors expression and endothelin production in CDs

Renal ET-1 production is facilitated by shear stress, inflammation, oxidative stress, the Renin-Angiotensin-Aldosterone System (RAAS) and other systems and mechanisms (for review see (Kohan et al., 2011)). Changes in extracellular fluid volume also increase ET-1 levels. Importantly, most of these mechanisms result in activation of ENaC in ASDN. Thus, endothelin system might represent feedback mechanism, which plays protective role in the maintenance of ENaC-mediated sodium absorption in the kidney and blood pressure, respectively. As summarized in excellent reviews by Kohan and colleagues (Kohan et al., 2011; Kohan et al., 2011)), the CDs are the major source of ET-1 in the kidney and may produce and release more ET-1 than any other cell type in the body. Consistent with this conclusion is that mice with the CD specific ET-1 knock out have markedly reduced urinary ET-1 excretion in response to salt loading (Ahn et al., 2004). A numerous *in vitro* and *ex vivo* studies suggested that ET-1 inhibits Na^+ and water reabsorption in the CDs (Takemoto, Uchida, Ogata, & Kurokawa, 1993; Tomita, Nonoguchi, Terada, & Marumo, 1993; Kohan, Padilla, & Hughes, 1993; Edwards, Stack, Pullen, & Nambi, 1993; Nadler, Zimpelmann, & Hebert, 1992). However, central evidence of ET-1 in CDs was published only ten years ago when Ahn et al. demonstrated that the absence of CD principal cell ET-1 causes hypertension and sodium retention (Ahn et al., 2004). Mice with CD-specific knockout of ET-1 (under control of the AQP2 promoter) were hypertensive and had reduced sodium excretion in response to sodium loading. Systolic blood pressure was increased by approximately 15 and 35 mmHg during normal and high Na^+ intake, respectively (Ahn et al., 2004).

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As discussed above, effects of endothelins are mediated by activation of ETRA and ETRB receptors. Both receptors are expressed in the CNT and entire CDs, where ENaC is involved in sodium transport (see Figure 1). Importantly, ET receptors are localized at the basolateral membranes with no evidence of their expression at the luminal side. A numerous studies identified expression of the ETRA receptor in these nephron segments (Kohan, Hughes, & Perkins, 1992; Wendel, Knels, Kummer, & Koch, 2006; Yukimura et al., 1996; Yamamoto, Suzuki, Kubo, Matsumoto, & Uemura, 2008). While some studies suggest that ETRA receptor is expressed in the distal tubules, majority of work identified that the greatest levels of these receptors are localized in the inner medullary collecting ducts (IMCD). Functional studies using genetic deletion of ETRA receptor in the principal cell of CDs (Ge, Stricklett, Hughes, Yanagisawa, & Kohan, 2005) or entire nephron (Stuart et al., 2012) revealed that renal ETRA receptor, at least under normal physiological conditions, does not play a major role in the regulation of blood pressure, sodium excretion or systemic hemodynamics. In following study using tissue specific promoters to target ETRA receptors in heart, smooth muscles, nephron and collecting duct, the authors demonstrated that fluid retention is due to a direct effect on the CDs and partially to a vascular effect but not related to cardiac function (Stuart, Chapman, Rees, Woodward, & Kohan, 2013). Recent studies tested the effects of ET-1 on ENaC-mediated (benzamil-sensitive) Na^+ transport by measuring lumen-to-bath isotopic ^{22}Na reabsorption (J_{Na}) using *in vitro* microperfusion and identified that ET-1 regulation of Na^+ reabsorption in the CDs involves both ETRA and ETRB receptors (Lynch, Welch, Kohan, Cain, & Wingo, 2013). However, despite the data demonstrating expression ETRA receptor and some evidence of its functional role, it appears that the ETRB receptor is predominant isoform in the CDs and in the renal medulla and most effects on ENaC involved activation of the ETRB receptor.

Expression of the ETRB receptor in CDs was shown by multiple techniques in different species. While mice with CD-specific (or entire nephron) knockouts of ETRA receptor did not have altered blood pressure or sodium excretion (Ge et al., 2005; Stuart et al., 2012), CD-specific knockout of the ETRB receptor causes hypertension and sodium retention. However, CD-specific knockout of the ETRB receptor increases blood pressure to a lesser extent than CD ET-1 knockout (Ge et al., 2006). Combined knockout of both ETA and ETB receptors in CDs had increased blood pressure, which increased further with high salt intake. The degree of blood pressure elevation during normal Na^+ intake was similar to CD-specific ET-1 knockout mice and higher than in CD ETRB knockout animals.

4.2. ET-1 regulation of ENaC in CDs

Kurokawa et al. reported more than twenty years ago that in rabbit CCDs perfused *in vitro*, low concentrations of ET-1 gradually increased total cellular membrane resistance because of inhibition of the luminal Na^+ channel (Kurokawa et al., 1993). Another evidence of the key role of ENaC in ET-1 mediated processes was provided by Gariepy et al. who demonstrated that ETRB knockout rats develop hypertension on a high salt diet and that normal blood pressure in these salt-sensitive, hypertensive rats restores after amiloride treatment (Gariepy, Ohuchi, Williams, Richardson, & Yanagisawa, 2000). Moreover, electrophysiological study showed that picomolar concentrations of ET-1 attenuate ENaC open probability (P_o) in an amphibian distal nephron cell line and this effect is prevented by

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ETRB antagonist but not ETRA antagonist (Gallego & Ling, 1996). Similar results were demonstrated in mammalian fibroblast cells by stably expressing genes for the three ENaC subunits (Gilmore, Stutts, & Milgram, 2001). Patch clamp studies of ENaC activity in isolated split-opened tubules provided compelling support for ET-1 acutely regulating ENaC activity and helped to identify signaling pathways and time-line of these effects. Bugaj et al. demonstrated in native rat CD principal cells that ET-1 dynamically decreases ENaC P_o via ETRB receptors by about three-fold within 5 min. Authors demonstrated that subsequent intracellular pathways involved Src tyrosine kinase activity and MAPK1/2 signaling (Bugaj et al., 2008). Following electrophysiological studies in CDs isolated from CD-specific ET-1, ETRA, ETRB, and ETRA/ETRB knockout mice further confirmed that ENaC regulation by ET-1 via ETB receptors contributes to the antihypertensive and natriuretic effects of the local endothelin system in the mammalian CDs (Bugaj, Mironova, Kohan, & Stockand, 2012). Shown on Figure 2 is a basic scheme of ENaC regulation by ET-1.

5. Lung, smooth muscle and distal colon: ET-1 and ENaC

Pulmonary arterial hypertension (PAH) is one of human pathologies for which ET-1 is clearly a key mediator (Shao, Park, & Wort, 2011). The pathobiology of PAH is associated with increased pulmonary vascular resistance resulting from hyperplasia of vascular cells within vascular wall. ET-1 contributes to vascular remodeling by having direct effects on all three layers of vessel wall: endothelial cells, smooth muscle cells and fibroblasts. Excessive local pulmonary ET-1 production in patients with pulmonary hypertension has been established (Cacoub et al., 1997) and increased circulative levels of ET-1 are in correlation with increased mortality in PAH patients (Cacoub, Dorent, Nataf, & Carayon, 1993). Remarkably, PAH is one of a very short list of human diseases for which treatment with ET receptors antagonists have been approved. Endothelin-receptor antagonism with Bosentan, which is a dual ETRA and ETRB antagonist, was beneficial for the therapy for PAH (Rubin et al., 2002; Sitbon et al., 2003). Currently, two orally active antagonists: dual antagonist Bosentan and ETRA selective antagonist Ambrisentan are approved as a treatment for PAH (Rubin, 2012).

The lung is the site in human body where fluid content is tightly controlled within certain limits and, accordingly, treatment of pulmonary edema by ENaC activators/stimulators has been in a focus of scientific interest of multiple laboratories (Fronius, 2013). TGF-β, a key mediator of acute kidney injury, was shown to drive the internalization of the ENaC from the alveolar epithelial cell surface, leading to the persistence of alveolar flooding (Peters et al., 2014). In addition, these channels are potential contributors to cystic fibrosis lung disease (Hobbs, Da, & Tarran, 2013; Donaldson & Galietta, 2013). Thus, multiple lung pathologies are associated with ET-1 signaling and regulation of ENaC, but it appears that there is little overlap between the diseases linked with either endothelin system or ENaC complex. ENaC abnormal function is described in the context of disintegrating fluid homeostasis control, whereas endothelin system is primarily involved in lung pathologies accompanying vascular remodeling. Hence, the interaction between increased pulmonary production of ET-1 and activity of ENaC has not been sufficiently investigated yet. It is tempting to suggest that since ENaC mediated pulmonary pathologies are generally explicated by increased ENaC activity, the excessive ET-1 production is supposed to attenuate ENaC action and

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correspondently should contribute to prevention of pulmonary channelopathies. Nonetheless, multiple mechanisms have been described to be relevant for the regulation of ENaC in pulmonary epithelial cells (Eaton, Helms, Koval, Bao, & Jain, 2009). ENaC in the lung is under control of β-Adrenergic agents, puinergic agonists, steroids, inflammatory chemokines, reactive oxygen and nitrogen species and low oxygen tension (Eaton et al., 2009). Epithelial pulmonary cells of alveolar surface are exposed to air-filled compartment and ENaCs were reported to be directly activated by shear stress (Fronius, Bogdan, Althaus, Morty, & Clauss, 2010). The receptor for advanced glycation end-products (RAGE) regulated lung fluid balance via PKC-gp91^{phox} signaling to ENaC (Downs, Kreiner, Johnson, Brown, & Helms, 2014). Kinases SGK, PKC and PKA up-regulate ENaC activity in a variety of epithelial cell systems (Baines, 2013; Eaton, Yue, Eaton, & Bao, 2014). Some of these signaling molecules and pathways are well known components of signal transduction by ET-1.

ET-1 system contributes to the pathogenesis of vascular diseases and is known to activate at least three major signaling pathways in vascular smooth muscle cells: phosphoinoisitide cascade, MAPK signaling cascades and Phosphoinositide 3-kinase (PI-3 kinase) pathway (Bouallegue et al., 2007). It is of note that β-ENaC subunit is expressed in smooth muscle cells where they are supposed to act as mechanotransducers to regulate myogenic response and hypertension (Drummond, 2012).

Abnormal activation of endothelin system is widely accepted as a common mechanism which is engaged in the progression of solid tumors (Rosano, Spinella, & Bagnato, 2013). The cancers where ET-1 signaling was shown to be an active player include colon cancer. Accordingly, the majority of information with regard to ET-1 action in the colon is related to its cancer-promoting effect. The signaling via ETRA is involved in colon cancer progression and metastasis (Nie et al., 2014; Sorby, Kleiveland, Andersen, Bukholm, & Jacobsen, 2011). On the contrary, not only the connection between ENaC activity and colon cancer progression has not been revealed, but even the concept of ENaC system playing significant role in cancer progression is unproven.

The involvement of distal colon ENaC in regulation of sodium reabsorption and regulation of blood pressure has been proposed (Rossier, 2014). The ENaC-β and ENaC-γ expression was shown to be diminished by high salt intake in colonic epithelial cells (Lienhard, Lauterburg, Escher, Frey, & Frey, 2012). Whether ET-1 mediated inhibition of ENaC underlies the ability of colonic epithelial cells to contribute to the protection of the mammalian body against salt overload remains to be determined. It must be taken into consideration that whereas ET-1 and ETRA, but not ETRB, were expressed at a high level in primary and cultured colon carcinoma cells, in normal colon tissues ET-1 level was very low or undetectable (Liakou et al., 2012). Whether high salt diets triggers increased production of ET-1 in colon tissues, as it does in kidney, has not been established and, accordingly, the connection between ET-1 signaling and inhibition of ENaC function in colon cells, although probable, cannot be postulated.

Preeclampsia (PE), a systemic disorder which is one of the leading cause of maternal mortality worldwide, is characterized by hypertension, proteinuria and edema (Al-Jameil,

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Aziz, Fareed, & Tabassum, 2014). It is instigated by abnormal insufficient placenta which releases in the blood stream tumor necrosis factor alpha (TNFα) and soluble fms-like tyrosine kinase (sFlt-1) causing the subsequent overexpression of vascular and renal ET-1 (Speed & Pollock, 2013). Multiple experimental models of PE are associated with elevated tissue levels of ET-1 and it appears that ET-1 serves as a final common pathway linking factor produced during placental ischemia to cause elevation of blood pressure (Palei, Spradley, Warrington, George, & Granger, 2013).

There is sufficient evidence indicating the involvement of ENaC with the progression of PE. One of the causes of PE is an inadequate cytotrophoblast migration and since β-ENaC mediates cytotrophoblast migration, an altered expression of ENaC contributes to placenta ischemia and hypertension (Warrington et al., 2014). A genetic variant of the β-subunit of ENaC was shown to be associated with the pathogenesis of PE and hypertension (Dhanjal, Owen, Anthony, Davidson, & Rayner, 2006; Jones, Owen, & Rayner, 2012).

Therefore, ET-1 is considered to be a key pathological factor in PE (Jain, 2012) and uncovering ET-1-mediated signaling pathways which contribute to hypertension in PE is of particular importance. The ET-1-mediated inhibition of ENaC could be one of the underappreciated mechanisms by which ET-1 is implicated in pathobiology of PE. ETRA antagonists showed some promise for the treatment of pregnancy-induced hypertension, but the potential problem of teratogenicity cannot be ignored (Speed & Pollock, 2013). Similar to colon cancer, the connection between overexpression of ET-1 and ENaC activity in PE has not been sufficiently investigated so far. It seems that the initial studies testing effects of ET-1 antagonists upon ENaC activity in cell cultures derived from placenta and animal models of preeclampsia are due.

6. Molecular mechanisms of inhibition of ENaC by ET-1

There are several proposed molecular mechanisms of ET-1 effects on ENaC in CDs. Both Src kinases and MAPK1/2 signaling were shown to mediate ET-1-dependent decreases in ENaC P_o in NIH 3T3 cells stably expressing genes for all three (α, β, and γ) ENaC subunits (Gilmore et al., 2001) and the split-open collecting duct (Bugaj et al., 2008). The inhibitory effect of ET-1 on ENaC could be completely blocked when cells were pretreated with the selective Src family kinase inhibitor, PP2. Further studies revealed that basal Src family kinase activity strongly regulates ENaC inhibition. Inhibition of MAPK also abolishes ET-1 effects on ENaC (Bugaj et al., 2008). No roles for phospholipase C (PLC) or protein kinase C (PKC) in the rapid response of ENaC to ET-1 were identified.

Potential role for NO in the control of ENaC by ET-1 was proposed (Kohan, 2013) since it was reported that ET-1 increases NOS expression and NO production in the CDs (Stricklett, Hughes, & Kohan, 2006; Schneider, Ge, Pollock, Pollock, & Kohan, 2008; Sullivan, Goodchild, Cai, Pollock, & Pollock, 2007; Hyndman & Pollock, 2013). Inhibition of ENaC by NO in cultured cells was previously reported (Yu, Bao, Self, Eaton, & Helms, 2007; Helms et al., 2005). Furthermore, it was shown that NO reduces Cl^- absorption in the mouse CCDs through an ENaC-dependent mechanism (Pech et al., 2013). However, role of NO in ET-1 mediated effects on ENaC was not directly studied yet and remains to be investigated.

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Among the signaling molecules which contribute significantly to ET-1-mediated inhibition of ENaC are protein kinase A (PKA) and guanine nucleotide exchange factor (GEF) βPix. This mechanism of inhibition of ENaC by ET-1 is likely to be coupled to retention of ability of NEDD4-2 to modulate ENaC despite serum and glucocorticoid regulated kinases- (SGK) mediated phosphorylation. SGK and PKA are important signaling molecules that has been shown to up-regulate ENaC activity (Baines, 2013). Other kinases shown to up-regulate ENaC include CK2, GRK2, IKKβ and PKD1, whilst PKC, ERK1/2 and AMPK are inhibitory (Baines, 2013). Aldosterone-induced SGK1 is widely considered as one of principal regulators of ENaC (Pao, 2012; Soundararajan, Lu, & Pearce, 2012). SGK1 not only associates with the apical membrane to regulate open probability of ENaC, but also is recruited by scaffold proteins to multiunit signaling complexes to modulate ENaC expression (Pao, 2012). For SGK1 to be functionally active it must be phosphorylated within its carboxy-terminal domain by serine-threonine kinase mammalian target of rapamycin (mTOR) (Lu et al., 2010). ENaC is known to be regulated by ubiquitylation following the binding of ubiquitin ligase Nedd4-2 protein-protein interaction domain WW to a PY motif in the ENaC subunits (Snyder, 2009; Rotin & Staub, 2012; Ronzaud & Staub, 2014). It appears that the phosphorylation of Nedd4-2 and two of ENaC subunits (β and γ) are main convergence targets for the action of kinases regulating ENaC. Phosphorylation of Nedd4-2 by SGK1 reduces Nedd4-2 ability to bind to ENaC, due to the interaction of phosphorylated Nedd4-2 with 14-3-3 proteins, and hence increases ENaC activity (Wiemuth et al., 2010). 14-3-3 proteins associate with SGK1-phosphorylated Nedd4-2 to maintain its phosphorylated/inactive state and thereby obstruct its physical association with ENaC (Bhalla et al., 2005; Ichimura et al., 2005; Liang, Peters, Butterworth, & Frizzell, 2006; Liang, Butterworth, Peters, Walker, & Frizzell, 2008; Nagaki et al., 2006). PKA also phosphorylates Nedd4-2 and, accordingly, regulates ENaC by decreasing Nedd4-2 binding to ENaC and congruently interfering with Nedd4-2 E3 ubiquitin-protein ligase activity that targets ENaC for degradation (Snyder, Olson, Kabra, Zhou, & Steines, 2004). The proposed mechanism of negative regulation of ENaC by ET-1 suggests that ET-1-mediated formation of the complex comprising of βPix, which acts as a scaffold in this case, and adaptor protein 14-3-3, is sufficient to prevent ubiquitin ligase Nedd4-2 from association with 14-3-3. Accordingly, phosphorylated Nedd4-2 retains ability to modify ENaC which results in the decrease of ENaC function. It has been shown that SGK1 and Nedd4-2 physically associate with each other and with ENaC (Soundararajan et al., 2012). We have shown that ET-1 mediated recruitment of 14-3-3β by β_1Pix impairs the interaction of 14-3-3β with the ubiquitin ligase Nedd4-2, thereby promoting ubiquitination and degradation of ENaC (Pavlov et al., 2010). It is of note that βPix-mediated ET-1-triggered inhibition of ENaC activity is dispensable of βPix action as GEF (Pavlov et al., 2010), but depends on its ability to act as a scaffold protein (Staruschenko & Sorokin, 2012). The cellular model shown in Figure 3 reveals a proposed signal transduction pathway coupling the ET receptors to ENaC.

In addition to described above mechanisms, it was reported that ET-1 gene is negatively regulated by the circadian clock protein Period 1 (Per1) (Richards et al., 2014). Interestingly, transcription of α-ENaC subunit is also regulated by Per1 (Gumz et al., 2009; Gumz et al., 2010). Besides, Per1 knockout mice have a hypotensive phenotype with a significant increase in cortical and medullary ET-1 production (Stow et al., 2012). These data suggest

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that the lower blood pressure in Per1 knockout mice may be linked to increased ET-1-dependent natriuresis/diuresis and ENaC is involved in this molecular mechanism. Epigenetic factors altering endothelin signaling (Welch, Jacobs, Wingo, & Cain, 2013; Stow, Jacobs, Wingo, & Cain, 2011) might be also involved in the control of ENaC activity since this channel is under control of several epigenetic mechanisms (Kone, 2013). However, these pathways and their connection remain to be studied in more details to make any definite conclusions.

7. Conclusions and Future Directions

The precise regulation of ENaC is important for normal Na^+ and fluid homeostasis in kidneys, lung and colon. These organs are also well established bridgeheads for ET-1 actions and signaling. Even though inhibition of ENaC by ET-1 has been studied and reliably demonstrated in the context of renal cells, there is a high probability that modulation of ENaC by ET-1 also takes place in pulmonary channelopathies, preeclampsia and distal colon. Whereas antagonists of ETRA represent probable candidates for being able to serve as modulators of ENaC function, no systematic analysis of their efficiency to contribute to resolution of renal, lung and colon channelopaties caused by ENaC dysfunction has been carried out so far.

Molecular mechanisms of inhibition of ENaC by ET-1 are likely to be coupled to its effects through Src kinases and MAPK1/2 and retention of ability of NEDD4-2 to modulate ENaC despite SGK1-mediated phosphorylation. The current understanding of ET-1 effect upon ENaC function is based mostly upon cultured cell based techniques. The major challenge is to confirm the validity of these mechanisms in the context of whole organism. Future breakthroughs in the field are likely to come from analysis of renal function in models of channelopaties with animals in which precise modification of genes encoding proteins, involved in ET-1-mediated ENaC inhibition has been achieved. The recent advances in targeted genome editing techniques suggest that this task could be achieved within next few years (Cheng & Alper, 2014).

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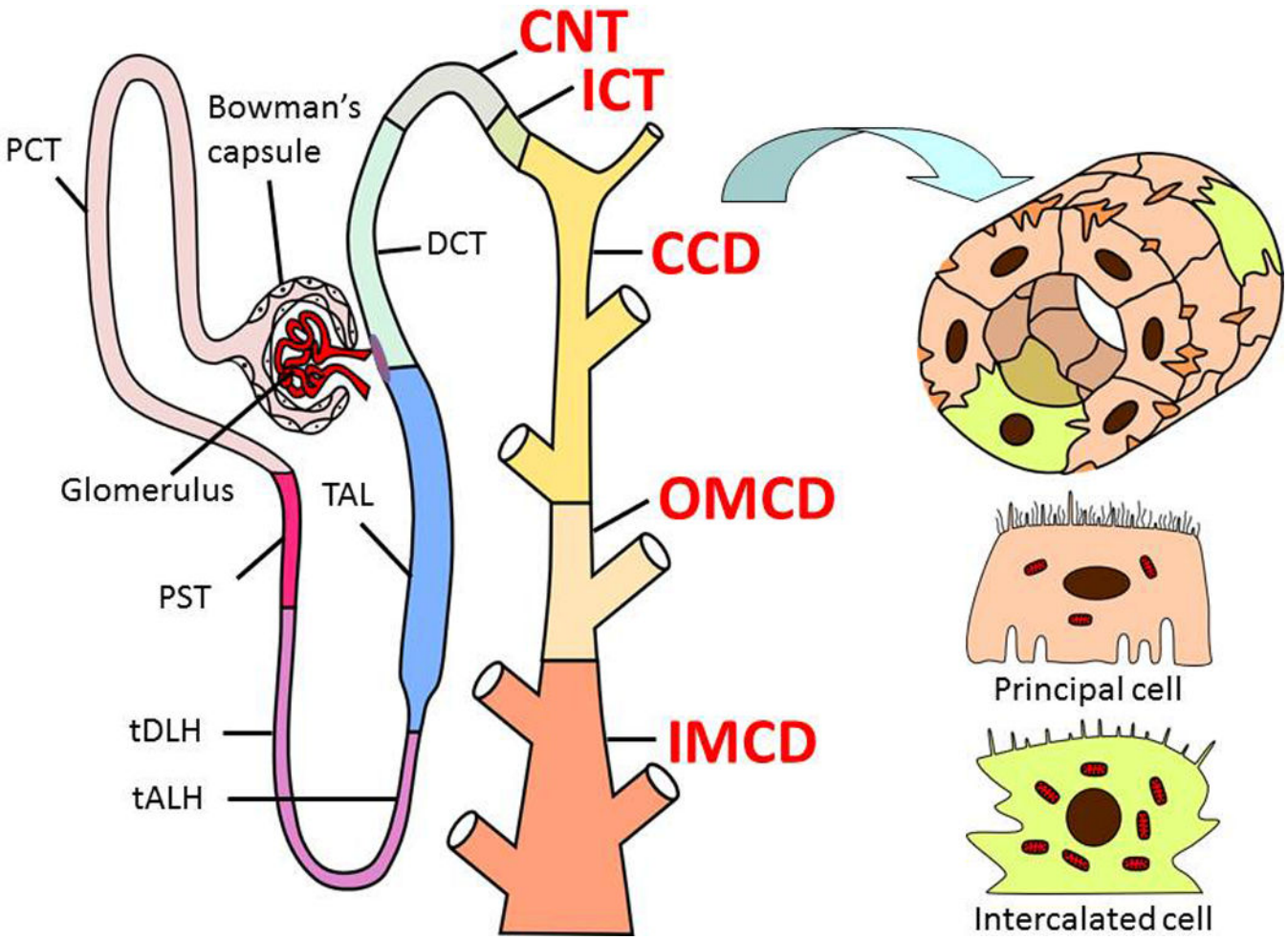

Figure 1.

Structure of the nephron and specific segments involved in effects of ET-1 on ENaC. Every nephron contains a renal corpuscle (glomerulus and Bowman's capsule), a proximal tubule (proximal convoluted and straight tubules; PCT and PST, respectively), a loop of Henle (thin descending limb of Henle's loop (tDLH), thin ascending limb of Henle's loop (tALH), and thick ascending limb of Henle's loop (TAL)), a distal convoluted tubule (DCT), connecting tubule (CNT), and the collecting duct system, which includes the initial collecting tubule (ICT), the cortical collecting duct (CCD), the outer medullary collecting duct (OMCD), and the inner medullary collecting duct (IMCD). Structure of the CCD as a cross-section and schematic presentation of principal and intercalated cells that comprise these segments are also shown. Modified from (Staruschenko, 2012).

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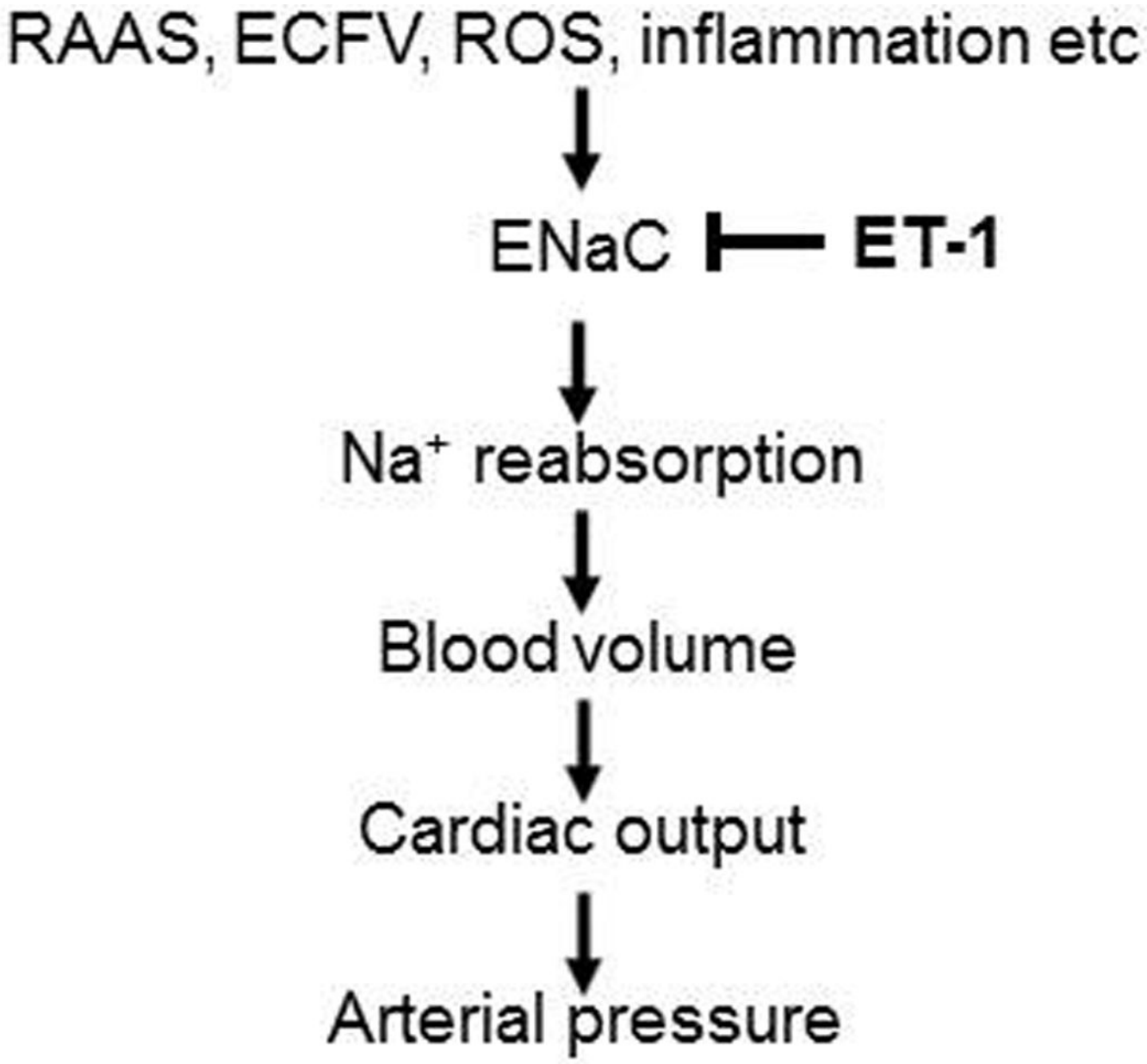

Figure 2.

Simplified hypothesis to explain mechanisms of ENaC regulation by ET-1 in the setting of development of hypertension. Changes in extracellular fluid volume (ECFV), inflammation, oxidative stress, the Renin-Angiotensin-Aldosterone System (RAAS) and other systems and mechanisms positively modulate ENaC activity. Endothelin system represent feedback mechanism, which plays protective role in the maintenance of ENaC-mediated sodium absorption in the kidney and blood pressure, respectively.

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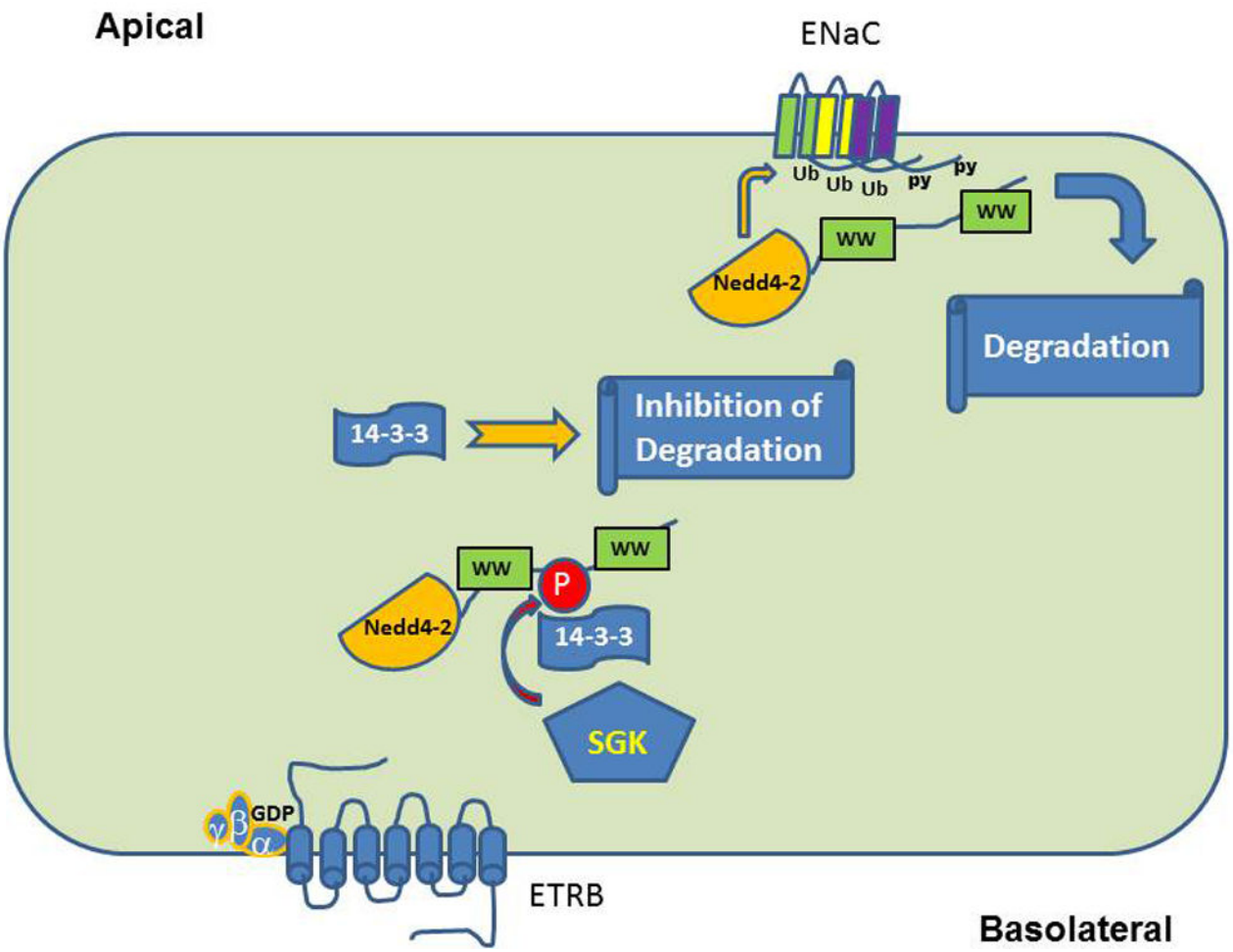

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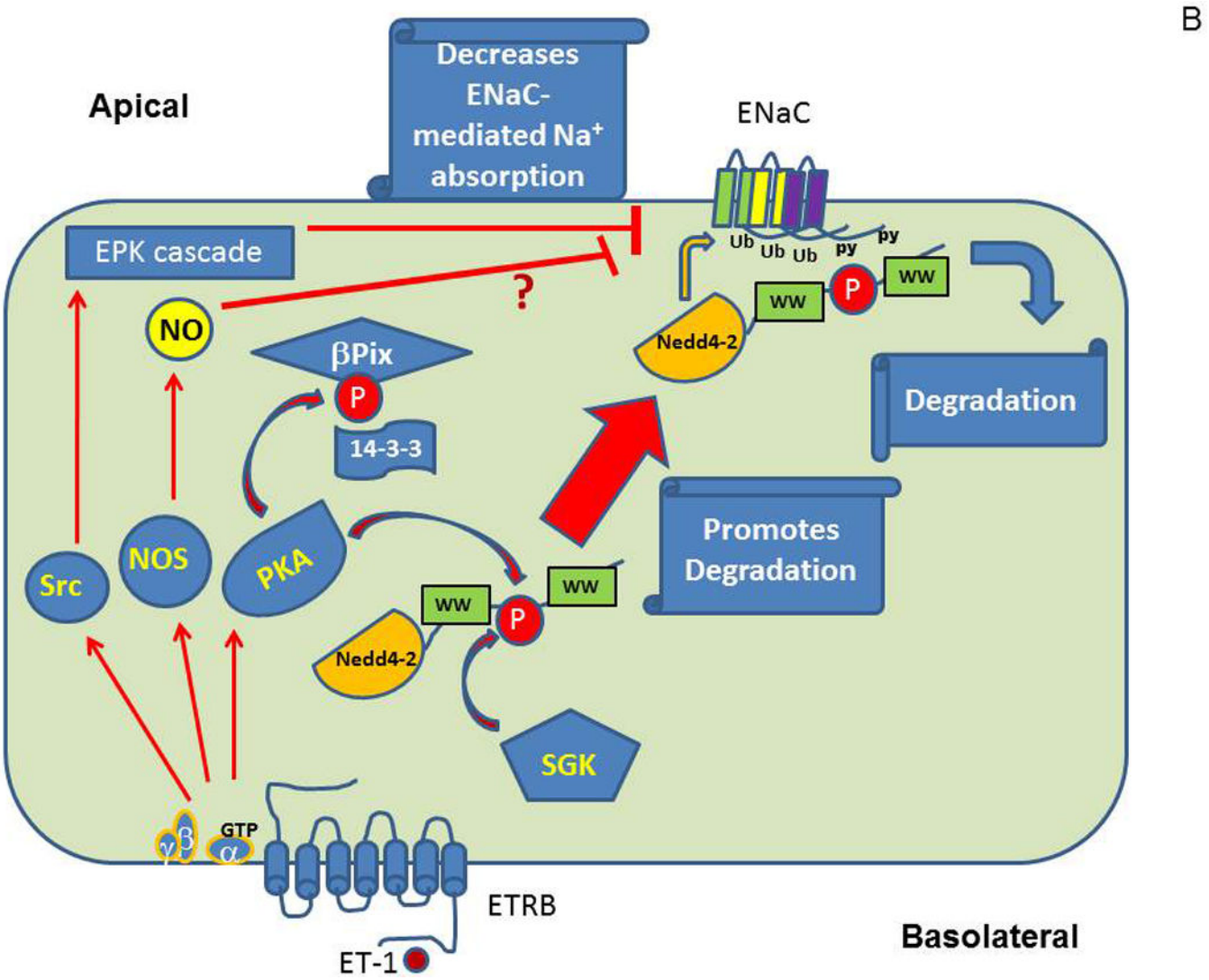

Figure 3.

Proposed molecular mechanisms of ET-1-mediated inhibition of ENaC in CDs. (A) Quiescent cells with unoccupied ETRB. (B) Cells after activation of ET-1 signaling cascade.