

Review Article

Regulation of Epithelial Sodium Transport via Epithelial Na⁺ Channel

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Renal epithelial Na⁺ transport plays an important role in homeostasis of our body fluid content and blood pressure. Further, the Na⁺ transport in alveolar epithelial cells essentially controls the amount of alveolar fluid that should be kept at an appropriate level for normal gas exchange. The epithelial Na⁺ transport is generally mediated through two steps: (1) the entry step of Na⁺ via epithelial Na⁺ channel (ENaC) at the apical membrane and (2) the extrusion step of Na⁺ via the Na⁺, K⁺-ATPase at the basolateral membrane. In general, the Na⁺ entry via ENaC is the rate-limiting step. Therefore, the regulation of ENaC plays an essential role in control of blood pressure and normal gas exchange. In this paper, we discuss two major factors in ENaC regulation: (1) activity of individual ENaC and (2) number of ENaC located at the apical membrane.

1. Introduction

Total amount of our body fluid is kept constant by various regulatory systems. For example, the cortical collecting duct of the kidney plays an important role in maintenance of our body fluid amount by regulating Na⁺ transport. This Na⁺ transport in the cortical collecting duct is characterized to be blocked by amiloride and a more specific blocker, benzamil, an analog of amiloride, and is carried out in the following two-step process: (1) the first step is Na⁺ entry into the cytosolic space across the apical membrane via the amiloride-sensitive epithelial Na⁺ channel (ENaC) [1–3], and (2) the second step is Na⁺ extrusion from the cytosolic space across the basolateral membrane via the Na⁺, K⁺-pump

(ATPase) [4, 5]. It is, in general, recognized that the Na⁺ entry step is the rate-limiting step for the transepithelial Na⁺ transport [5]. Therefore, ENaC is the target of many factors regulating Na⁺ transport. Vasopressin (antidiuretic hormone), aldosterone, insulin, growth factors, and osmotic stress are known to regulate activity and localization of ENaC [4, 6–17]. For example, vasopressin binds to V₂ receptor connecting with adenylate cyclase, producing cyclic AMP. Increased cAMP stimulates translocation of ENaC to the apical membrane from the intracellular store site by activating protein kinase A (PKA) [7]. Intracellular trafficking (translocation) of ENaC is also stimulated by osmotic stress [10, 11, 13, 14]. Further, in the lung epithelial Na⁺ transport plays a crucial role in water clearance for normal

gas exchange [18–21]. This epithelial Na^+ transport is also regulated via some kinases activated by catecholamine and a cell volume change of alveolar epithelium [22, 23]. This review discusses how hormones, osmotic stress, and a cell volume change activate the epithelial Na^+ transport.

2. Characterization of Na^+ Transport in Epithelial Cells

As described above, the rate-limiting step of Na^+ transport in epithelial cells is the entry step of Na^+ into the cytosolic space from the apical side via ENaC, which consists of three subunits and is located in the apical membrane [1–3, 9]. ENaC is generally considered to play as a channel pore with 4 subunits; that is, 2α , 1β , and 1γ subunits [24]. Total amount of Na^+ transport via ENaC is determined by three components: (1) the activity of individual ENaC (open probability of ENaC as ion channel), (2) the total amount (number or density) of ENaC located at the apical membrane, and (3) the driving force for Na^+ entry via ENaC depending on the apical membrane potential and the equilibrium potential for Na^+ determined by the cytosolic and extracellular Na^+ concentrations. We discuss regulation of the activity and amount (number or density) of ENaC at the apical membrane by various stimulants such as vasopressin and osmotic stress, although the driving force for Na^+ is also regulated by changes in the membrane potential (potentials of both apical and basolateral membranes; see the detail [9]) and the equilibrium potential for Na^+ by modifying the cytosolic Na^+ concentration via changes in activities of Na^+ , K^+ -ATPase, $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter, Na^+/Cl^- cotransporter, Na^+/H^+ exchanger, $\text{Na}^+/\text{HCO}_3^-$ cotransporter, and so forth.

3. Regulation of ENaC at the Apical Membrane

It is well known that vasopressin (antidiuretic hormone) is released from pituitary posterior lobe responding to elevation of interstitial fluid osmolarity and plays an essential role in controlling serum and interstitial fluid osmolarity [25]. Targets of vasopressin in the kidney are principal cells of the distal renal nephron expressing ENaC like aquaporin, which responds to vasopressin increasing water permeability of the apical membrane of the cells for facilitation of water reabsorption from tubular fluid [25]. In addition to an increase in water permeability (water reabsorption) via the principal cells of the distal renal nephron, it has been reported that vasopressin regulates activity of ENaC expressed in the principal cells. Activity (open probability) of ENaC is reported to be increased by vasopressin in a manner dependent on PKA [26]. Bugaj et al. [26] have indicated that in isolated, split-open murine collecting ducts NPo ($= N$ (number of ENaC) \times Po (open probability); see the detail [7, 27]) is increased from 0.30 ± 0.04 to 0.57 ± 0.04 ($n = 16$) within 2–3 min after application of vasopressin, and that the vasopressin-induced increase in NPo is abolished by pretreatment with a PKA inhibitor, Rp-cAMPS or H89. Based on this result, they [26] indicate that a PKA-dependent phosphorylation is required for an increase in Po . However,

it is still unclear which parts of ENaC are phosphorylated for activation, although some reports indicate the site of phosphorylation of ENaC [28–30]. On the other hand, vasopressin is reported to have no effects on Po of ENaC expressed in an amphibian renal epithelial A6 cells using a single channel recording technique [7], which is also applied for the work by Bugaj et al. [26]. Bugaj et al. have studied the relatively early (2~20 min) effect of vasopressin on Po of ENaC while Marunaka and Eaton have studied the relatively late (40~50 min) effect of vasopressin on Po of ENaC. The effect of vasopressin might be variable in a time-dependent manner; that is, vasopressin would acutely increase Po of ENaC, the stimulatory action of vasopressin on Po of ENaC would maintain for 2~20 min after application of vasopressin [26], and the stimulatory action might disappear around 40~50 min after application of vasopressin [7]. Another possibility for apparently different effects of vasopressin on Po of ENaC might be due to the different systems; that is, murine collecting ducts and an amphibian kidney A6 cell line. Further investigation should be required for clarification of vasopressin action on Po of ENaC. It has been reported that in *Xenopus* renal epithelial A6 cells vasopressin increases the density (number) of ENaC localized in the apical membrane by stimulating translocation of ENaC to the apical membrane in kinase-dependent manners [7] (Figure 1). Bugaj et al. [26] have also reported a similar observation in the principal cells of murine collecting ducts (Figure 1). In a case of vasopressin, PKA stimulates translocation of ENaC to the apical membrane from the intracellular store site via a mechanism similar to the process of AQP translocation to the apical membrane from the intracellular store site [7, 14, 30] via a PKA-dependent phosphorylation of AQP itself [31, 32], although the part of phosphorylated site of ENaC regarding translocation of ENaC is not yet clear.

In addition to the vasopressin-cAMP-PKA-mediated pathway, translocation of ENaC is stimulated by osmotic stress such as hypotonic shock [6, 10, 11, 13–15, 17, 33]. Via a ligand-free pathway, hypotonic shock stimulates Na^+ transport mainly by increasing the number of ENaC at the apical membrane through stimulation of ENaC translocation from the intracellular store site via a protein tyrosine kinase (PTK)-dependent manner [14]. Hypotonic shock mimics the stimulatory action of vasopressin on translocation of ENaC to the apical membrane without any ligand binding to receptors. The action of vasopressin is mediated via a PKA-dependent pathway [26] while hypotonic shock mimicking the action of vasopressin shows its action via a PTK-dependent pathway [14]. However, at the time when Niisato et al. [14] reported the point, it was not yet known what type of PTK is involved in the hypotonic action on translocation of ENaC. Growth factors such as IGF [34, 35] and EGF [36] have been reported to stimulate Na^+ transport. Further, growth factor receptors themselves act as PTKs [36–40]. Moreover, osmotic stress can activate receptor tyrosine kinases (RTKs) and/or other types of kinases without any ligand binding to the receptors [13, 41, 42]. Kajimoto et al. [42] have indicated that cell swelling induced by hypoxic shock activates protein kinase N1 (PKN1), a serine/threonine protein kinase and a homolog of Pkc1. A Rho family small

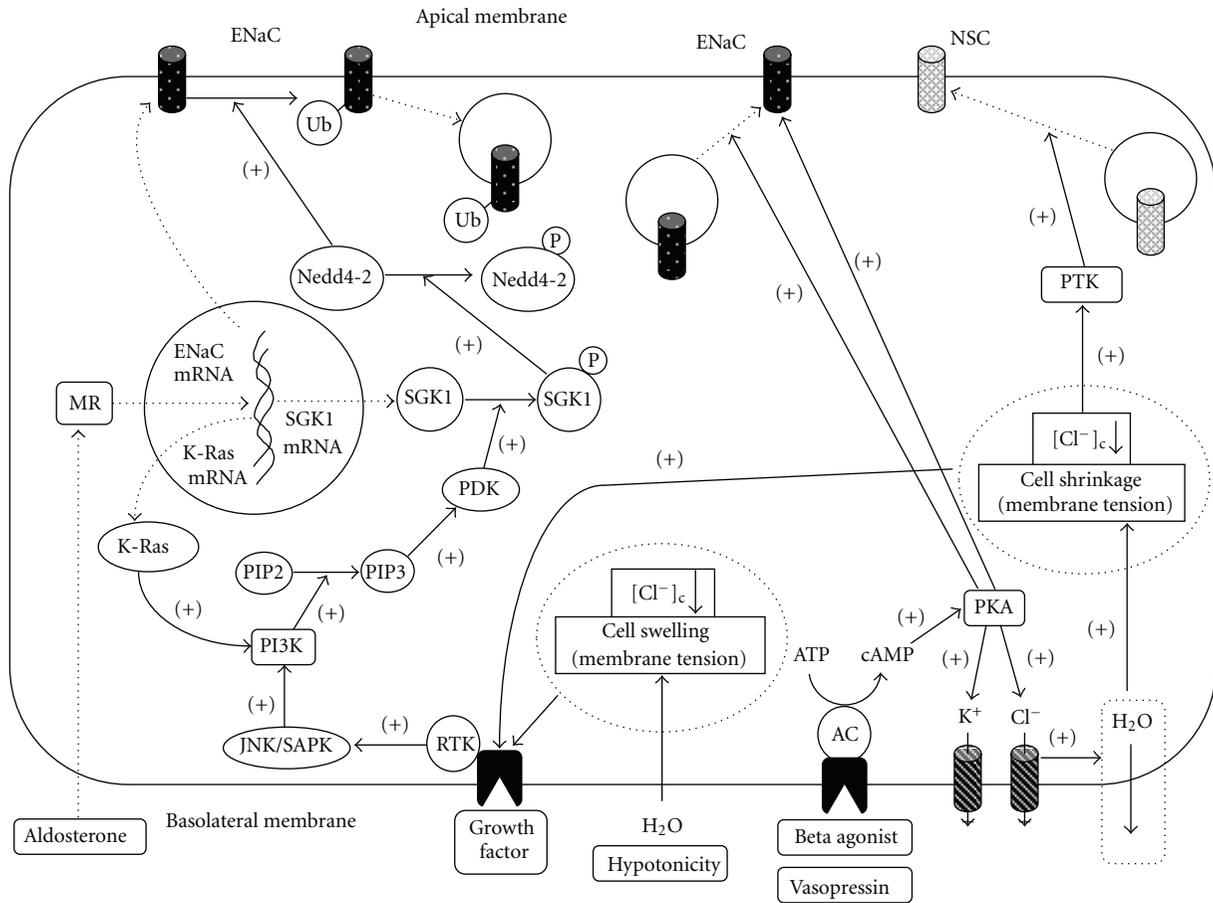


FIGURE 1: Regulatory pathways of ENaC and nonselective (NSC) channel in renal and fetal alveolar type II epithelial cells. Arrow lines without (+) mean the conversion to a form at the end point of arrow from a form at the starting point of arrow. Arrow lines with (+) mean that the compound at the starting point of arrow; (1) stimulates the conversion indicated by an arrow without (+), (2) activates an enzyme, or (3) induces the indicated condition. Arrowheads with dashed lines mean that the compound at the start point of the arrowhead with dashed line moves to the end point of the arrowhead with dashed line (translocation). $[Cl^-]_c$ is the concentration of cytosolic Cl^- . Circled P means a phosphorylated form.

GTP-binding protein, RhoA, binds to the NH₂-terminal regulatory region of PKN1, activating PKN1 when it is bound by GTP [43]. Increased wall stress including hypotonic stress-induced cell swelling activates Rho1 (yeast Rho1 is homologous to human RhoA) controlling signal transmission through Pkc1 (PKN1) [44, 45], and activating a MAPK family, ERK1/2. Hypotonic shock also activates some other members of MAPK family. Niisato et al. [46] have indicated that hypotonicity-induced cell swelling activates p38 MAPK and JNK. In particular, it is clearly indicated that the activation of p38 MAPK and JNK is prolonged when cell swelling is maintained by Cl^- channel blocker, NPPB [46]. As described in these reports [42–46], hypotonic shock activates some kinases without any ligand binding to receptors via a change of membrane tension caused by hypotonicity-induced cell swelling [46, 47].

As described above, hypotonic shock activates translocation of ENaC via a PTK-dependent pathway. However, it is not yet clear what type of PTK or RTK is involved in hypotonicity-induced stimulation of ENaC translocation. It is indicated that hypotonic shock elevates cell membrane

tension due to cell swelling via water influx driven by an osmotic pressure change [46, 48]. Based on this information, Taruno et al. [10] have recently reported activation of epidermal growth factor receptor (EGFR) by hypotonic stress via a ligand-independent manner (Figure 1). Taruno et al. [10] have further reported that hypotonicity-induced activation of JNK/p38 is mediated through activation of RTK involved in EGFR, and that the activation of JNK/p38 following activation of the RTK of EGFR is involved in the hypotonicity-induced translocation of ENaC (Figure 1). This report [10] also indicates that hypotonic shock activates a PI3-kinase pathway based on the observation that protein kinase B (PKB), the phosphorylation (activation) of which is mediated by PI3-kinase, is phosphorylated at both Ser 473 and Thr 308 by hypotonic shock through the RTK-JNK/SAPK cascade (Figure 1). These observations [10] indicate that activation of JNK/SPAK caused by hypotonic stress-induced RTK involved in EGFR without any ligand binding to EGFR stimulates translocation of ENaC (Figure 1). PI3-kinase has been reported to stimulate translocation of ENaC to the apical membrane [49]. Hypotonic stimulation on

ENaC translocation is dependent on PI3-kinase activated by the RTK-JNK/SPAK cascade, leading to production of PIP3 that activates PDK [10]. PIP3 would directly act on ENaC [50] in addition to its indirect action on ENaC via a PDK-dependent SGK1-mediated Nedd4-2 pathway stimulating endocytosis of ENaC [51] (Figure 1). Further, osmotic stress including hypotonic stress has been reported to directly stimulate ENaC. Benos and his colleagues [52] have reported that in *Xenopus* oocytes expressing $\alpha\beta\gamma$ -rENaC, cell swelling caused by hypotonic stress decreases ENaC currents while cell shrinkage caused by hypertonic stress increases ENaC currents. On the other hand, an apparently opposite effect of cell shrinkage caused by hypertonic stress on Po of ENaC is reported in *Xenopus* oocytes expressing $\alpha\beta\gamma$ -rENaC. Namely, Awayda and Subramanyan [53] have reported that cell shrinkage caused by hypertonic stress decreases ENaC currents, and that this inhibitory effect of cell shrinkage is completely blocked by cytochalasin B, indicating that the cell shrinkage-induced inhibitory effect on ENaC currents is mediated via actin filament depolymerization. Awayda and Subramanyam [53] have treated *Xenopus* oocytes with a hypertonic solution containing 50 mM sucrose (about 25% increase in osmolarity) for 45 min while Benos and his colleagues [52] have measured ENaC currents about 5 min after application of a hypertonic solution with about 1.8~2.5-fold increase in osmolarity. These apparently opposite effects of cell shrinkage on ENaC currents would be due to time durations with hypertonic solutions and/or magnitudes of osmolarity of hypertonic solutions. Further, Kleyman and his colleagues have reported that laminar shear stress [54] and flow [55] affect ENaC activity. An increase of intraluminal flow in the lumen of cortical collecting ducts of rabbits increases the amiloride-sensitive Na^+ absorption across the cortical collecting ducts, suggesting the intraluminal flow activates ENaC [55]. Laminar shear stress provided across *Xenopus* oocytes expressing $\alpha\beta\gamma$ -mENaC [54] activates ENaC with a very short half time of ~ 5 s for activation. Further, a pore region mutant of ENaC with a high open probability ($\alpha\beta\text{S518K}\gamma$ -mENaC) is insensitive to laminar shear stress while a mutated ENaC with a low open probability ($\alpha\text{S580C}\beta\gamma$ -mENaC) is activated by laminar shear stress similar to wild-type mENaC [54]. This report [54] indicates that laminar shear stress directly acts on the pore region of ENaC activating ENaC. Taken together, changes in tension of plasma membrane affect Po and number of ENaCs localized at the apical membrane directly and indirectly.

Aldosterone acts on mineralocorticoid receptor, then produces two major proteins related to the subject of this review article, ENaC and SGK1 [56] (Figure 1). SGK1 phosphorylates Nedd4-2 [57–60] (Figure 1). Dephosphorylated Nedd4-2, an active form ubiquitinating ENaC, stimulates endocytosis of ENaC while phosphorylated Nedd4-2, an inactive form for ENaC ubiquitination, has no ability stimulating ENaC endocytosis. SGK1 phosphorylates Nedd4-2 diminishing endocytosis of ENaC [57–60] (Figure 1). Thus, aldosterone increases the number of ENaCs localized in the apical membrane via two pathways: (1) direct stimulation of ENaC synthesis and (2) inhibition of ENaC endocytosis via inactivation of Nedd4-2-mediated ubiquitination of ENaC

[57–60] (Figure 1). Further, aldosterone has stimulatory action on ENaC via a K-Ras-dependent PI3K pathway [61, 62] (Figure 1).

We next discuss regulation of Na^+ transport in distal (alveolar) lung epithelial cells. Throughout gestation the fetal lung epithelium produces Cl^- secretion via a transcellular pathway into the lung's lumen [22, 63, 64] followed by paracellular Na^+ secretion, generating an osmotic driving force for fluid (water) secretion into the lung's lumen. This fluid produces a positive pressure to the lung epithelial cells from the lung's lumen, activating PTK [65–67]. This fluid plays an important role in the lung development by activating PTK [68]; however, it must be cleared from alveolar spaces immediately after birth to allow normal gas exchange [22, 69, 70]. Beta-adrenergic stimulation in the alveolar epithelium induces clearance of the alveolar fluid at birth [22, 69] by activating amiloride-sensitive Na^+ absorption [19, 22, 23, 71–75]. In the alveolar space of the lung (lung distal area), Na^+ transport plays a crucial role in gas exchange, since the amiloride-sensitive Na^+ transport (absorption) provides a driving force for water absorption from the alveolar space to the interstitial space by decreasing osmotic pressure of the fluid in the alveolar space, reducing the alveolar fluid amount [22, 63, 76]. Two types of amiloride-sensitive Na^+ -permeable channels have been reported in rat fetal alveolar type II epithelial cells [19, 22, 73, 74]. Both types of amiloride-sensitive channels are activated by cytosolic Ca^{2+} [19, 22, 73, 74] unlike other types of amiloride-sensitive channels (ENaCs), which are inhibited by cytosolic Ca^{2+} via a PKC-dependent pathway [77–79]. It has been reported that beta-agonist stimulates the fluid clearance from alveolar space [69]. One of the amiloride-sensitive channels has about 28 pS of single channel conductance and Na^+ permeability identical to K^+ permeability (K^+ permeability/ Na^+ permeability = 0.9; non-selective cation (NSC) channel) but not Cl^- permeability (Cl^- permeability/ Na^+ permeability < 0.02) [22, 73, 74]. The other type of amiloride-sensitive channel has 12 pS of single channel conductance and is highly selective for Na^+ over K^+ or Cl^- (K^+ permeability/ Na^+ permeability < 0.1; Cl^- permeability/ Na^+ permeability < 0.02; Na^+ channel) [22, 74]. However, beta-agonist activates 28 pS NSC channel but not 12 pS Na^+ channel [22, 73]; namely, the open probability of the 28 pS NSC but not 12 pS Na^+ channel is elevated by beta-agonist. Further, beta-agonist increases the number of functional 28 pS NSC channels (Figure 1) but not 12 pS Na^+ channel at the apical membrane [22]. The stimulatory action of beta-agonist is mediated via beta-adrenergic receptor, and the activation of the receptor increases cytosolic cAMP concentration by activating adenylate cyclase [22] (Figure 1). This increase in cytosolic cAMP concentration induces activation of PKA, which activates K^+ and Cl^- channels [22] (Figure 1). This activation of K^+ and Cl^- channels induces water efflux by reducing intracellular osmolarity via KCl efflux through the activated K^+ and Cl^- channels (Figure 1), resulting in reduction of cell volume (cell shrinkage) [18] associated with reduction of intracellular Cl^- concentration [19]. Cell shrinkage [18] associated with reduction of intracellular Cl^- concentration [19] activates PTK [23] (Figure 1).

This activation of protein tyrosine kinase would be a receptor type of PTK (Figure 1), and might stimulate translocation of the 28 pS NSC channel to the apical membrane via a JNK/SPAK-PI3K-mediated pathway (Figure 1) in a way similar to that is activated by hypotonic stress observed in *Xenopus* renal A6 cell lines as described above. Furthermore, it has been reported that beta-agonist increases the cytosolic Ca^{2+} concentration in cAMP-dependent and -independent manners [80]. The cAMP-dependent pathway for elevation in cytosolic Ca^{2+} concentration is due to an increase in Ca^{2+} influx while the beta-agonist stimulates Ca^{2+} release from the intracellular Ca^{2+} store site via a cAMP-independent pathway in addition to elevation of Ca^{2+} influx via a cAMP-dependent pathway [80]. The beta-agonist-induced increase in cytosolic Ca^{2+} concentration reaches transiently over $1 \mu\text{M}$, declining to the baseline [75, 80]. The role of this transient increase in cytosolic Ca^{2+} concentration is to decrease the cytosolic concentration of Cl^- [75], which plays various essential roles in cell function including regulation of various types of key enzymes controlling cell growth and GTPase and so forth [81–100]. This Ca^{2+} -mediated decrease in the cytosolic concentration of Cl^- [75] is mediated through activation of K^+ and Cl^- channels (Figure 1). Further, the cytosolic Cl^- has an inhibitory action on the 28 pS channel [73], and the level of cytosolic Ca^{2+} concentration after beta-agonist-induced transient increase is a little bit larger than that under the basal condition [75, 101, 102]. The cytosolic Ca^{2+} at the concentration after beta-agonist-induced transient increase alone is not large enough to activate either the 28 pS NSC or 12 pS channel [74]. However, beta-agonist has a stimulatory action on the 28 pS NSC channel, but not the 12 pS channel [73]. The beta-agonist-induced transient increase in cytosolic Ca^{2+} concentration causes the cell shrinkage, which decreases the cytosolic Cl^- concentration [22, 47] as shown in Figure 1. This decrease in cytosolic Cl^- concentration plays an essential role in the beta-agonist-stimulation on the 28 pS NSC channel; that is, beta-agonist diminishes the sensitivity of the 28 pS NSC channel to cytosolic Cl^- , and the beta-agonist-modified 28 pS NSC channel is able to be activated at the decreased level of the cytosolic Cl^- concentration [75] via an unknown mechanism, which might be mediated through a PKA-dependent phosphorylation. The gating mechanism sensitive to Ca^{2+} and Cl^- modified by beta-agonist is described in a report by Marunaka and his colleagues [73]. Recently, alveolar type I epithelial cells have been reported to participate in fluid absorption from the alveolar space to the interstitial space in adult lungs [103]. Alveolar type I epithelial cells have also two types of amiloride-sensitive Na^+ -permeable channels [63], which would play a crucial role in keeping alveolar water constant under a physiological and pathophysiological conditions.

4. Conclusion

Epithelial Na^+ transport is mediated via two steps: (1) the entry step of Na^+ via ENaC located at the apical membrane and (2) the extrusion step of Na^+ via the Na^+ , K^+ -ATPase located at the basolateral membrane. The rate-limiting step

of epithelial Na^+ transport is the entry step of Na^+ via ENaC. ENaC activity (open probability) is regulated by PKA, PTK (RTK), and PKN. Further, hypotonic stress activates the epithelial Na^+ transport by stimulating translocation of ENaC to the apical membrane from the intracellular store site via activation of RTK mediated by a change in membrane tension and/or a change in cytosolic Cl^- concentration without any ligand binding to RTK-involved receptors. The changes in the activity and localization of ENaC control the blood pressure and the alveolar fluid amount of our body and keeping homeostasis of our body environments.

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