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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 import 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 V_2 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, $Na^+/K^+/2Cl^-$ cotransporter, Na^+/Cl^- cotransporter, Na^+/H^+ exchanger, Na^+/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 responses 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) × 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 increases 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 translation 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

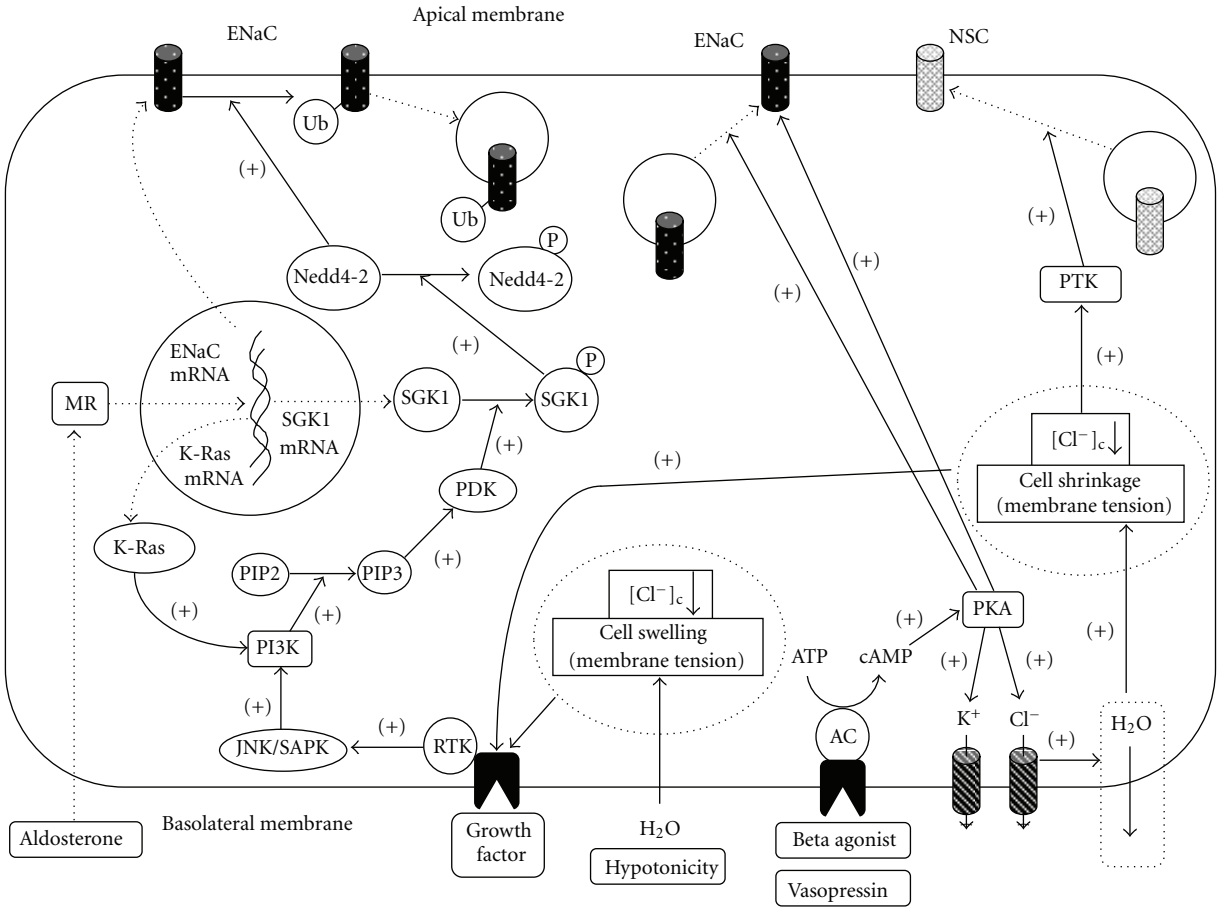

Figure 1: Regulatory pathways of ENaC and nonselective (NSC) channel in renal and fetal alveolar type II epithelial cells. Arrow lines without (+) mean the conversion to a form at the end point of arrow form a form at the starting point of arrow. Arrow lines with (+) mean that the compound at the starting 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). $[Cl^-]$ 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/SPAK 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 intraluminar flow in the lumen of cortical collecting ducts of rabbits increases the amiloride-sensitive Na^+ absorption across the cortical collecting ducts, suggesting the intraluminar 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 ($\alpha\beta$S518Kγ-mENaC) is insensitive to laminar shear stress while a mutated ENaC with a low open probability (αS580C$\beta\gamma$-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: nonselective 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 μM, 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 biding 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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References

[1] C. M. Canessa, J. D. Horisberger, and B. C. Rossier, "Epithelial sodium channel related to proteins involved in neurodegeneration," *Nature*, vol. 361, no. 6411, pp. 467–470, 1993.

[2] C. M. Canessa, A. M. Merillat, and B. C. Rossier, "Membrane topology of the epithelial sodium channel in intact cells," *American Journal of Physiology*, vol. 267, no. 6, pp. C1682–C1690, 1994.

[3] C. M. Canessa, L. Schild, G. Buell et al., "Amiloride-sensitive epithelial Na^+ channel is made of three homologous subunits," *Nature*, vol. 367, no. 6462, pp. 463–467, 1994.

[4] Y. Marunaka, "Physiological requirement of aldosterone action on the Na^+/K^+ pump in ADH-stimulated Na^+ absorption in renal epithelium," *Japanese Journal of Physiology*, vol. 46, no. 4, pp. 357–361, 1996.

[5] N. Niisato and Y. Marunaka, "Activation of the Na^+-K^+ pump by hyposmolality through tyrosine kinase-dependent Cl^- conductance in Xenopus renal epithelial A6 cells," *Journal of Physiology*, vol. 518, no. 2, pp. 417–432, 1999.

[6] N. Niisato, A. Taruno, and Y. Marunaka, "Involvement of p38 MAPK in hypotonic stress-induced stimulation of β- and γ-ENaC expression in renal epithelium," *Biochemical and Biophysical Research Communications*, vol. 358, no. 3, pp. 819–824, 2007.

[7] Y. Marunaka and D. C. Eaton, "Effects of vasopressin and cAMP on single amiloride-blockable Na channels," *American Journal of Physiology*, vol. 260, no. 5, pp. C1071–C1084, 1991.

[8] Y. Marunaka, N. Hagiwara, and H. Tohda, "Insulin activates single amiloride-blockable Na channels in a distal nephron cell line (A6)," *American Journal of Physiology*, vol. 263, no. 3, pp. F392–F400, 1992.

[9] Y. Marunaka, "Hormonal and osmotic regulation of NaCl transport in renal distal nephron epithelium," *Japanese Journal of Physiology*, vol. 47, no. 6, pp. 499–511, 1997.

[10] A. Taruno, N. Niisato, and Y. Marunaka, "Hypotonicity stimulates renal epithelial sodium transport by activating JNK via receptor tyrosine kinases," *American Journal of Physiology*, vol. 293, no. 1, pp. F128–F138, 2007.

[11] A. Taruno, N. Niisato, and Y. Marunaka, "Intracellular calcium plays a role as the second messenger of hypotonic stress

in gene regulation of SGK1 and ENaC in renal epithelial A6 cells," *American Journal of Physiology*, vol. 294, no. 1, pp. F177–F186, 2008.

[12] N. Niisato and Y. Marunaka, "Src kinase-dependent osmoregulation of Na^+ reabsorption in renal A6 cells," *Journal of Physiological Sciences*, vol. 56, supplement 1, p. S115, 2006.

[13] A. Taruno and Y. Marunaka, "Analysis of blocker-labeled channels reveals the dependence of recycling rates of ENaC on the total amount of recycled channels," *Cellular Physiology and Biochemistry*, vol. 26, no. 6, pp. 925–934, 2010.

[14] N. Niisato, W. Van Driessche, M. Liu, and Y. Marunaka, "Involvement of protein tyrosine kinase in osmoregulation of Na^+ transport and membrane capacitance in renal A6 cells," *Journal of Membrane Biology*, vol. 175, no. 1, pp. 63–77, 2000.

[15] N. Niisato, D. C. Eaton, and Y. Marunaka, "Involvement of cytosolic Cl^- in osmoregulation of α-ENaC gene expression," *American Journal of Physiology*, vol. 287, no. 5, pp. F932–F939, 2004.

[16] N. Niisato and Y. Marunaka, "Cytosolic Cl^- acts as a signal molecule in hypotonic stress by regulating tyrosine phosphorylation state of src kinase," *Journal of Physiological Sciences*, vol. 57, supplement 1, p. S61, 2007.

[17] N. Niisato, A. Taruno, and Y. Marunaka, "Aldosterone-induced modification of osmoregulated ENaC trafficking," *Biochemical and Biophysical Research Communications*, vol. 361, no. 1, pp. 162–168, 2007.

[18] T. Nakahari and Y. Marunaka, "Regulation of cell volume by β_2-adrenergic stimulation in rat fetal distal lung epithelial cells," *Journal of Membrane Biology*, vol. 151, no. 1, pp. 91–100, 1996.

[19] H. Tohda, J. K. Foskett, H. O'Brodovich, and Y. Marunaka, "Cl^- regulation of a Ca^{2+}-activated nonselective cation channel in β- agonist-treated fetal distal lung epithelium," *American Journal of Physiology*, vol. 266, no. 1, pp. C104–C109, 1994.

[20] N. Hagiwara, H. Tohda, Y. Doi, H. O'Brodovich, and Y. Marunaka, "Effects of insulin and tyrosine kinase inhibitor on the short-circuit current in fetal alveolar epithelial cells of the lung," *Biochemical and Biophysical Research Communications*, vol. 187, no. 2, pp. 802–808, 1992.

[21] T. Nakahari and Y. Marunaka, "Regulation of whole cell currents by cytosolic cAMP, Ca^{2+}, and Cl^- in rat fetal distal lung epithelium," *American Journal of Physiology*, vol. 269, no. 1, part 2, pp. C156–C162, 1995.

[22] Y. Marunaka and N. Niisato, "Catecholamine regulation of amiloride-sensitive Na^+ transport in the fetal rat alveolar epithelium," in *Current Topics in Membranes*, D. J. Benos, Ed., pp. 255–278, Academic Press, New York, NY, USA, 1999.

[23] N. Niisato, Y. Ito, and Y. Marunaka, "cAMP stimulates Na^+ transport in rat fetal pneumocyte: involvement of a PTK- but not a PKA-dependent pathway," *American Journal of Physiology*, vol. 277, no. 4, part 1, pp. L727–L736, 1999.

[24] D. Firsov, I. Gautschi, A. M. Merillat, B. C. Rossier, and L. Schild, "The heterotetrameric architecture of the epithelial sodium channel (ENaC)," *EMBO Journal*, vol. 17, no. 5, pp. 344–352, 1998.

[25] R. A. Fenton and M. A. Knepper, "Mouse models and the urinary concentrating mechanism in the new millennium," *Physiological Reviews*, vol. 87, no. 4, pp. 1083–1112, 2007.

[26] V. Bugaj, O. Pochynyuk, and J. D. Stockand, "Activation of the epithelial Na^+ channel in the collecting duct by vasopressin contributes to water reabsorption," *American Journal of Physiology*, vol. 297, no. 5, pp. F1411–F1418, 2009.

[27] D. C. Eaton and Y. Marunaka, "Ion channel fluctuations: "noise" and single-channel measurements," in *Current Topics Membranes and Transport*, S. I. Helman and W. Van Driessche, Eds., pp. 61–114, Academic Press, New York, NY, USA, 1990.

[28] L. M. Yang, R. Rinke, and C. Korbmacher, "Stimulation of the epithelial sodium channel (ENaC) by cAMP involves putative ERK phosphorylation sites in the C termini of the channel's β- and γ-subunit," *Journal of Biological Chemistry*, vol. 281, no. 15, pp. 9859–9868, 2006.

[29] W. Yan, L. Suaud, T. R. Kleyman, and R. C. Rubenstein, "Differential modulation of a polymorphism in the COOH terminus of the α-subunit of the human epithelial sodium channel by protein kinase Cδ," *American Journal of Physiology*, vol. 290, no. 2, pp. F279–F288, 2006.

[30] P. M. Snyder, "Minireview: regulation of epithelial Na^+ channel trafficking," *Endocrinology*, vol. 146, no. 12, pp. 5079–5085, 2005.

[31] E. Klussmann, K. Maric, B. Wiesner, M. Beyermann, and W. Rosenthal, "Protein kinase A anchoring proteins are required for vasopressin- mediated translocation of aquaporin-2 into cell membranes of renal principal cells," *Journal of Biological Chemistry*, vol. 274, no. 8, pp. 4934–4938, 1999.

[32] R. A. Fenton and H. B. Moeller, "Recent discoveries in vasopressin-regulated aquaporin-2 trafficking," *Progress in Brain Research*, vol. 170, pp. 571–579, 2008.

[33] N. K. Wills, L. P. Millinoff, and W. E. Crowe, "Na^+ channel activity in cultured renal (A6) epithelium: regulation by solution osmolarity," *Journal of Membrane Biology*, vol. 121, no. 1, pp. 79–90, 1991.

[34] B. L. Blazer-Yost and M. Cox, "Insulin-like growth factor 1 stimulates renal epithelial Na^+ transport," *American Journal of Physiology*, vol. 255, no. 3, part 1, pp. C413–C417, 1988.

[35] B. L. Blazer-Yost, M. Cox, and R. Furlanetto, "Insulin and IGF I receptor-mediated Na^+ transport in toad urinary bladders," *American Journal of Physiology*, vol. 257, no. 4, part 1, pp. C612–C620, 1989.

[36] N. Markadieu, R. Crutzen, D. Blero, C. Erneux, and R. Beauwens, "Hydrogen peroxide and epidermal growth factor activate phosphatidylinositol 3-kinase and increase sodium transport in A6 cell monolayers," *American Journal of Physiology*, vol. 288, no. 6, pp. F1201–F1212, 2005.

[37] B. L. Blazer-Yost, N. Shah, L. Jarett, M. Cox, and R. M. Smith, "Insulin and IGF1 receptors in a model renal epithelium: receptor localization and characterization," *Biochemistry International*, vol. 28, no. 1, pp. 143–153, 1992.

[38] T. Hunter, R. A. Lindberg, D. S. Middlemas, S. Tracy, and P. van der Geer, "Receptor protein tyrosine kinases and phosphatases," *Cold Spring Harbor Symposia on Quantitative Biology*, vol. 57, pp. 25–41, 1992.

[39] M. A. Lemmon and J. Schlessinger, "Cell signaling by receptor tyrosine kinases," *Cell*, vol. 141, no. 7, pp. 1117–1134, 2010.

[40] I. Vivanco, D. Rohle, M. Versele et al., "The phosphatase and tensin homolog regulates epidermal growth factor receptor (EGFR) inhibitor response by targeting EGFR for degradation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 14, pp. 6459–6464, 2010.

[41] C. Rosette and M. Karin, "Ultraviolet light and osmotic stress: activation of the JNK cascade through multiple growth factor and cytokine receptors," *Science*, vol. 274, no. 5290, pp. 1194–1197, 1996.

[42] K. Kajimoto, D. Shao, H. Takagi et al., "Hypotonic swelling-induced activation of PKN1 mediates cell survival in cardiac myocytes," *American Journal of Physiology*, vol. 300, no. 1, pp. H191–H200, 2011.

[43] H. Shibata, H. Mukai, Y. Inagaki et al., "Characterization of the interaction between RhoA and the amino-terminal region of PKN," *FEBS Letters*, vol. 385, no. 3, pp. 221–224, 1996.

[44] M. Bickle, P. A. Delley, A. Schmidt, and M. N. Hall, "Cell wall integrity modulates RHO1 activity via the exchange factor ROM2," *EMBO Journal*, vol. 17, no. 8, pp. 2235–2245, 1998.

[45] Y. Kamada, H. Qadota, C. P. Python, Y. Anraku, Y. Ohya, and D. E. Levin, "Activation of yeast protein kinase C by Rhol GTPase," *Journal of Biological Chemistry*, vol. 271, no. 16, pp. 9193–9196, 1996.

[46] N. Niisato, M. Post, W. Van Driessche, and Y. Marunaka, "Cell swelling activates stress-activated protein kinases, p38 MAP kinase and JNK, in renal epithelial A6 cells," *Biochemical and Biophysical Research Communications*, vol. 266, no. 2, pp. 547–550, 1999.

[47] H. Miyazaki, A. Shiozaki, N. Niisato, and Y. Marunaka, "Physiological significance of hypotonicity-induced regulatory volume decrease: reduction in intracellular Cl^- concentration acting as an intracellular signaling," *American Journal of Physiology*, vol. 292, no. 5, pp. F1411–F1417, 2007.

[48] N. Niisato and Y. Marunaka, "Osmortransduction through volume-sensitive Cl^- channels," in *Mechanosensitive Ion Channels*, A. Kamkin and I. Kiseleva, Eds., pp. 179–202, Springer, 2008.

[49] R. Soundararajan, D. Melters, I. C. Shih, J. Wang, and D. Pearce, "Epithelial sodium channel regulated by differential composition of a signaling complex," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 19, pp. 7804–7809, 2009.

[50] O. Pochynyuk, V. Bugaj, and J. D. Stockand, "Physiologic regulation of the epithelial sodium channel by phosphatidylinositides," *Current Opinion in Nephrology and Hypertension*, vol. 17, no. 5, pp. 533–540, 2008.

[51] P. C. Henry, V. Kanelis, M. C. O'Brien et al., "Affinity and specificity of interactions between Nedd4 isoforms and the epithelial Na^+ channel," *Journal of Biological Chemistry*, vol. 278, no. 22, pp. 20019–20028, 2003.

[52] H. L. Ji, C. M. Fuller, and D. J. Benos, "Osmotic pressure regulates $\alpha\beta\gamma$-rENaC expressed in Xenopus oocytes," *American Journal of Physiology*, vol. 275, no. 5, pp. C1182–C1190, 1998.

[53] M. S. Awayda and M. Subramanyam, "Regulation of the epithelial Na^+ channel by membrane tension," *Journal of General Physiology*, vol. 112, no. 2, pp. 97–111, 1998.

[54] M. D. Carattino, S. Sheng, and T. R. Kleyman, "Epithelial Na^+ channels are activated by laminar shear stress," *Journal of Biological Chemistry*, vol. 279, no. 6, pp. 4120–4126, 2004.

[55] L. M. Satlin, S. Sheng, C. B. Woda, and T. R. Kleyman, "Epithelial Na^+ channels are regulated by flow," *American Journal of Physiology*, vol. 280, no. 6, pp. F1010–F1018, 2001.

[56] S. Y. Chen, A. Bhargava, L. Mastroberardino et al., "Epithelial sodium channel regulated by aldosterone-induced protein sgk," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 5, pp. 2514–2519, 1999.

[57] O. Staub, I. Gautschi, T. Ishikawa et al., "Regulation of stability and function of the epithelial Na^+ channel (ENaC) by ubiquitination," *EMBO Journal*, vol. 16, no. 21, pp. 6325–6336, 1997.

[58] D. Rotin, "Regulation of the epithelial sodium channel (ENaC) by accessory proteins," *Current Opinion in Nephrology and Hypertension*, vol. 9, no. 5, pp. 529–534, 2000.

[59] O. Staub, H. Abriel, P. Plant et al., "Regulation of the epithelial Na^+ channel by Nedd4 and ubiquitination," *Kidney International*, vol. 57, no. 3, pp. 809–815, 2000.

[60] D. C. Eaton, B. Malik, H. F. Bao, L. Yu, and L. Jain, "Regulation of epithelial sodium channel trafficking by ubiquitination," *Proceedings of the American Thoracic Society*, vol. 7, no. 1, pp. 54–64, 2010.

[61] J. D. Stockand, B. J. Spier, R. T. Worrell, G. Yue, N. Al-Baldawi, and D. C. Eaton, "Regulation of Na^+ reabsorption by the aldosterone-induced small G protein K-Ras2A," *Journal of Biological Chemistry*, vol. 274, no. 50, pp. 35449–35454, 1999.

[62] A. Staruschenko, P. Patel, Q. Tong, J. L. Medina, and J. D. Stockand, "Ras activates the epithelial Na^+ channel through phosphoinositide 3-OH kinase signaling," *Journal of Biological Chemistry*, vol. 279, no. 36, pp. 37771–37778, 2004.

[63] D. C. Eaton, M. N. Helms, M. Koval, H. F. Bao, and L. Jain, "The contribution of epithelial sodium channels to alveolar function in health and disease," *Annual Review of Physiology*, vol. 71, pp. 403–423, 2009.

[64] P. J. Kemp and R. E. Olver, "G protein regulation of alveolar ion channels: implications for lung fluid transport," *Experimental Physiology*, vol. 81, no. 3, pp. 493–504, 1996.

[65] B. Han, X. H. Bai, M. Lodyga et al., "Conversion of mechanical force into biochemical signaling," *Journal of Biological Chemistry*, vol. 279, no. 52, pp. 54793–54801, 2004.

[66] M. Liu, Y. Qin, J. Liu, A. K. Tanswell, and M. Post, "Mechanical strain induces pp60src activation and translocation to cytoskeleton in fetal rat lung cells," *Journal of Biological Chemistry*, vol. 271, no. 12, pp. 7066–7071, 1996.

[67] Y. Marunaka, N. Niisato, and Y. Ito, "Beta agonist regulation of sodium transport in fetal lung epithelium: roles of cell volume, cytosolic chloride and protein tyrosine kinase," *Journal of Korean Medical Science*, vol. 15, pp. S42–S43, 2000.

[68] D. Alcorn, T. M. Adamson, T. F. Lambert, J. E. Maloney, B. C. Ritchie, and P. M. Robinson, "Morphological effects of chronic tracheal ligation and drainage in the fetal lamb lung," *Journal of Anatomy*, vol. 123, no. 3, pp. 649–660, 1977.

[69] M. J. Brown, R. E. Olver, and C. A. Ramsden, "Effects of adrenaline and of spontaneous labour on the secretion and absorption of lung liquid in the fetal lamb," *Journal of Physiology*, vol. 344, pp. 137–152, 1983.

[70] S. Matalon and H. O'Brodovich, "Sodium channels in alveolar epithelial cells: molecular characterization, biophysical properties, and physiological significance," *Annual Review of Physiology*, vol. 61, pp. 627–661, 1999.

[71] R. E. Olver, E. E. Schneeberger, and D. V. Walters, "Epithelial solute permeability, ion transport and tight junction morphology in the developing lung of the fetal lamb," *Journal of Physiology*, vol. 315, pp. 395–412, 1981.

[72] H. O'Brodovich, V. Hannam, M. Seear, and J. B. M. Mullen, "Amiloride impairs lung water clearance in newborn guinea pigs," *Journal of Applied Physiology*, vol. 68, no. 4, pp. 1758–1762, 1990.

[73] Y. Marunaka, N. Niisato, H. O'Brodovich, and D. C. Eaton, "Regulation of an amiloride-sensitive Na^+-permeable channel by a β_2-adrenergic agonist, cytosolic Ca^{2+} and Cl^- in fetal rat alveolar epithelium," *Journal of Physiology*, vol. 515, no. 3, pp. 669–683, 1999.

[74] Y. Marunaka, "Amiloride-blockable Ca^{2+}-activated Na^+-permeant channels in the fetal distal lung epithelium," *Pflügers Archiv*, vol. 431, no. 5, pp. 748–756, 1996.

[75] Y. Marunaka and N. Niisato, "The essential role of cytosolic Cl^- in Ca^{2+} regulation of an amiloride-sensitive channel in fetal rat pneumocyte," *Journal of Membrane Biology*, vol. 180, no. 1, pp. 91–99, 2001.

[76] B. Loeh, E. Baloglu, A. Ke, P. Börtsch, and H. Mairböurl, "β_2-adrenergic stimulation blunts inhibition of epithelial ion transport by hypoxia of rat alveolar epithelial cells," *Cellular Physiology and Biochemistry*, vol. 25, no. 1, pp. 123–134, 2010.

[77] L. M. O'Mullane, D. I. Cook, and A. Dinudom, "Purinergic regulation of the epithelial Na^+ channel," *Clinical and Experimental Pharmacology and Physiology*, vol. 36, no. 10, pp. 1016–1022, 2009.

[78] Y. Gu, "Effects of $[Ca^{2+}]_i$ and pH on epithelial Na^+ channel activity of cultured mouse cortical collecting ducts," *Journal of Experimental Biology*, vol. 211, no. 19, pp. 3167–3173, 2008.

[79] B. K. Berdiev, R. Latorre, D. J. Benos, and I. I. Ismailov, "Actin modifies Ca^{2+} block of epithelial Na^+ channels in planar lipid bilayers," *Biophysical Journal*, vol. 80, no. 5, pp. 2176–2186, 2001.

[80] N. Niisato, T. Nakahari, A. K. Tanswell, and Y. Marunaka, "β_2-agonist regulation of cell volume in fetal distal lung epithelium by cAMP-independent Ca^{2+} release from intracellular stores," *Canadian Journal of Physiology and Pharmacology*, vol. 75, no. 8, pp. 1030–1033, 1997.

[81] K. I. Nakajima, H. Miyazaki, N. Niisato, and Y. Marunaka, "Essential role of NKCC1 in NGF-induced neurite outgrowth," *Biochemical and Biophysical Research Communications*, vol. 359, no. 3, pp. 604–610, 2007.

[82] K. Nakajima, H. Miyazaki, N. Niisato, and Y. Marunaka, "Implication of chloride transporter, NKCC1, in neurite outgrowth," *Journal of Physiological Sciences*, vol. 57, supplement 1, p. S121, 2007.

[83] K. Nakajima, N. Niisato, and Y. Marunaka, "Molecular mechanism of degradation and turnover of NKCC1," *Journal of Physiological Sciences*, vol. 58, supplement 1, p. S205, 2008.

[84] K. Nakajima, N. Niisato, and Y. Marunaka, "The role of chloride ion in dynamics of microtubule," *Journal of Physiological Sciences*, vol. 59, supplement 1, p. S350, 2009.

[85] K. Nakajima, N. Niisato, and Y. Marunaka, "Flavonoids stimulate NGF-induced neurite outgrowth in PC12 cells via activation of $Na^+/K^+/2Cl^-$ cotransporter," *Journal of Physiological Sciences*, vol. 60, supplement 1, p. S106, 2010.

[86] A. Shiozaki, H. Miyazaki, N. Niisato, H. Itoi, H. Yamagishi, and Y. Marunaka, "The role of intracellular Cl^- concentration in cell proliferation," *FASEB Journal*, vol. 20, no. 5, p. A1460, 2006.

[87] A. Shiozaki, H. Miyazaki, N. Niisato et al., "Furosemide, a blocker of $Na^+/K^+/2Cl^-$ cotransporter, diminishes proliferation of poorly differentiated human gastric cancer cells by affecting G_0/G_1 state," *Journal of Physiological Sciences*, vol. 56, no. 6, pp. 401–406, 2006.

[88] H. Miyazaki, R. Ohsawa, N. Niisato, and Y. Marunaka, "Intracellular chloride regulates the G_1/S cell cycle check point in human gastric cancer MKN28 cells," *Journal of Physiological Sciences*, vol. 59, supplement 1, p. 304, 2009.

[89] H. Miyazaki, R. Ohsawa, A. Shiozaki, N. Niisato, and Y. Marunaka, "Intracellular chloride regulates the G_1/S cell cycle checkpoint in MKN28 human gastric cancer cells," *Journal of Physiological Sciences*, vol. 58, supplement 1, p. S207, 2008.

[90] H. Miyazaki, A. Shiozaki, N. Niisato, and Y. Marunaka, "Cl^--dependent regulatory mechanisms of proliferation of human gastric cancer cells via G_0/G_1 arrest," *Journal of Physiological Sciences*, vol. 57, supplement 1, p. S20, 2007.

[91] H. Miyazaki, A. Shiozaki, N. Niisato et al., "Chloride ions control the G_1/S cell-cycle checkpoint by regulating the expression of p21 through a p53-independent pathway in human gastric cancer cells," *Biochemical and Biophysical Research Communications*, vol. 366, no. 2, pp. 506–512, 2008.

[92] K. Hiraoka, H. Miyazaki, N. Niisato, and Y. Marunaka, "Intracellular chloride regulates cell proliferation of androgen-independent prostate cancer PC3 cell," *Journal of Physiological Sciences*, vol. 59, supplement 1, p. 303, 2009.

[93] M. Maki, H. Miyazaki, K. I. Nakajima et al., "Chloride-dependent acceleration of cell cycle via modulation of Rb and cdc2 in osteoblastic cells," *Biochemical and Biophysical Research Communications*, vol. 361, no. 4, pp. 1038–1043, 2007.

[94] M. Maki, H. Miyazaki, N. Niisato, T. Morihara, Y. Marunaka, and T. Kubo, "Blockers of K^+/Cl^- transporter/channels diminish proliferation of osteoblastic cells," *Biomedical Research*, vol. 30, no. 2, pp. 137–140, 2009.

[95] K. Nakajima, N. Niisato, and Y. Marunaka, "Genistein enhances the NGF-induced neurite outgrowth," *Biomedical Research*. In Press.

[96] R. Ohsawa, H. Miyazaki, E. Otsuji, N. Niisato, and Y. Marunaka, "Intracellular chloride-dependent mechanism of stress-activated protein kinases in human gastric cancer MKN28 cells," *Journal of Physiological Sciences*, vol. 59, supplement 1, p. 303, 2009.

[97] R. Ohsawa, H. Miyazaki, A. Shiozaki, E. Otsuji, N. Niisato, and Y. Marunaka, "Reduction of intracellular Cl^- concentration induces the G_1/S cell cycle arrest through the activation of stress-activated protein kinases in MKN28 human gastric cancer cells," *Journal of Physiological Sciences*, vol. 58, supplement 1, p. S207, 2008.

[98] R. Ohsawa, H. Miyazaki, N. Niisato et al., "Intracellular chloride regulates cell proliferation through the activation of stress-activated protein kinases in MKN28 human gastric cancer cells," *Journal of Cellular Physiology*, vol. 223, no. 3, pp. 764–770, 2010.

[99] K. Nakajima, N. Niisato, and Y. Marunaka, "Quercetin stimulates NGF-induced neurite outgrowth in PC12 cells via activation of $Na^+/K^+/2Cl^-$ cotransporter," *Cellular Physiology and Biochemistry*, vol. 28, no. 1, pp. 147–156, 2011.

[100] T. Yamada, N. Niisato, and Y. Marunaka, "Effects of extracellular chloride ion on epithelial sodium channel (ENaC) in arginine vasotocin (AVT)-stimulated renal epithelial cells," *Biomedical Research*, vol. 30, no. 3, pp. 193–198, 2009.

[101] Y. Marunaka, T. Nakahari, and H. Tohda, "Cytosolic $[Cl^-]$ regulates Na^+ absorption in fetal alveolar epithelium?: roles of cAMP and Cl^- channels," *Japanese Journal of Physiology*, vol. 44, supplement 2, pp. S281–S288, 1994.

[102] Y. Marunaka, H. Tohda, N. Hagiwara, and H. O'Brodovich, "Cytosolic Ca^{2+}-induced modulation of ion selectivity and amiloride sensitivity of a cation channel and beta agonist action in fetal lung epithelium," *Biochemical and Biophysical Research Communications*, vol. 187, no. 2, pp. 648–656, 1992.

[103] L. G. Dobbs, M. D. Johnson, J. Vanderbilt, L. Allen, and R. Gonzalez, "The great big alveolar TI cell: evolving concepts and paradigms," *Cellular Physiology and Biochemistry*, vol. 25, no. 1, pp. 55–62, 2010.