Review

Clinical features and molecular basis of pseudohypoaldosteronism type 1

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Abstract. Pseudohypoaldosteronism (PHA) type 1 is a disease showing mineralocorticoid resistance in the kidney and/or other mineralocorticoid target tissues. Patients with PHA1 present very high plasma aldosterone and renin levels, but they develop excessive salt wasting. There are three types of PHA1. The systemic form of PHA1 is inherited in an autosomal recessive manner and causes severe life-long salt loss in multiple target tissues, such as sweat glands, salivary glands, the colonic epithelium, and the lung. In the systemic form of PHA1, life-long salt supplementation is necessary. The second type is the renal form, where aldosterone resistance is shown only in the kidney, and its inheritance is autosomal dominant. In the renal form of PHA1, salt supplementation generally becomes unnecessary by 1–3 yr of age. The third type is the secondary PHA1, which is strongly associated with urinary tract infections and/or urinary tract malformations. This review summarizes the clinical features and molecular basis of PHA1. Understanding of its pathogenesis can be helpful for the early diagnosis and clinical care of affected children with PHA1.

Key words: pseudohypoaldosteronism 1 (PHA1), kidney, *NR3C2*, urinary tract infection

Introduction

Pseudohypoaldosteronism type 1 (PHA1) was first described in 1958 by Cheek and Perry (1). PHA1 results in mineralocorticoid resistance of the kidney and/or other mineralocorticoid target tissues, despite very high levels of plasma aldosterone and renin (2, 3). There are three types of PHA1 (Table 1). The systemic form of PHA1 causes severe life-long salt wasting in multiple target tissues, such as sweat glands, salivary glands, the colonic epithelium, and lung. The second type is the renal form, where aldosterone resistance is restricted only in the kidney. The third type is secondary PHA1, which is strongly associated with urinary tract infections (UTI) and/or urinary tract malformations.

Here, we review the clinical features and molecular basis of PHA1. An understanding of its pathogenesis can be helpful for early diagnosis

Table 1. Three types of pseudohypoaldosteronism 1

Type	Symptoms	Cause Type of inheritance
Systemic form	Dehydration, vomiting Failure to thrive Respiratory symptoms Cardiac dysrhythmias Skin eruption Cholelithiasis Short stature	Mutations of *SCNN1A*, *SCNN1B* and *SCNN1G* Autosomal recessive
Renal form #	Dehydration, vomiting Failure to thrive	Mutations of *NR3C2* Autosomal dominant De novo *
Secondary #	Dehydration, vomiting Failure to thrive	Urinary tract malformations Urinary tract infection

* Many de novo mutations have been reported. # life-threatening episodes soon after birth have been reported in these types like the systemic form.

and clinical care of affected children.

Mineralocorticoid Receptor (MR) and Its Action in the Distal Nephron of the Kidney

Aldosterone and its receptor MR play a crucial role in the regulation of water balance and potassium homeostasis. Aldosterone is secreted in response to hypovolemia, hypotension, and hyperkalemia, and binds to MR. Human MR belongs to the steroid hormone receptor family, consists of 984 amino acids, and has three domains: an N-terminal domain, a DNA binding domain (DBD), and a C-terminal ligand binding domain (LBD) (4, 5) (Fig. 1). The N-terminal domain, which has an autonomous activation function (AF-1), is constitutively active and interacts with co-activators, co-repressors, and the LBD (2, 3, 5). The DBD has two zinc-finger structures that are required for DNA binding and receptor dimerization. In each zinc finger, there are four cysteines that can bind a zinc ion. The LBD has a ligand-dependent activation function AF-2 (2, 3). In addition to ligand binding, the LBD is required for nuclear localization and receptor dimerization (2, 3, 5).

MR is expressed in the distal tubules of the kidneys, the airway epithelium of the lung, and the salivary and sweat glands (2–5). Recent studies have shown MR expression also in the heart, large vessels, the hippocampus, the hypothalamus, leukocytes, the pancreas, and adipose tissue (6, 7).

In MR target tissues, aldosterone binds MR, and the resulting complex translocates to the nucleus, where it binds to the regulatory regions of several MR responsive genes, resulting in increased expression of the epithelial sodium channel (ENaC) and the Na^+-K^+-ATPase (2, 3, 5). ENaC is a heteromultimetric protein consisting of three subunits: α, ß, and ɣ (8, 9). Each subunit has two transmembrane regions, an extracellular loop, and intracellular N- and C- terminal parts (8, 9). In the principal cells of the distal nephron, Na^+ is reabsorbed by ENaC and subsequently released through the basolateral cell membrane by the Na^+-K^+-ATPase, thus maintaining body Na^+ and water homeostasis (Fig. 2A) (2, 3, 8). The apical K^+ channel, renal outer medullary potassium channel (ROMK), excretes K^+ into the urine and maintains the electrolyte balance (Fig. 2A) (2, 3). In intercalated cells, aldosterone
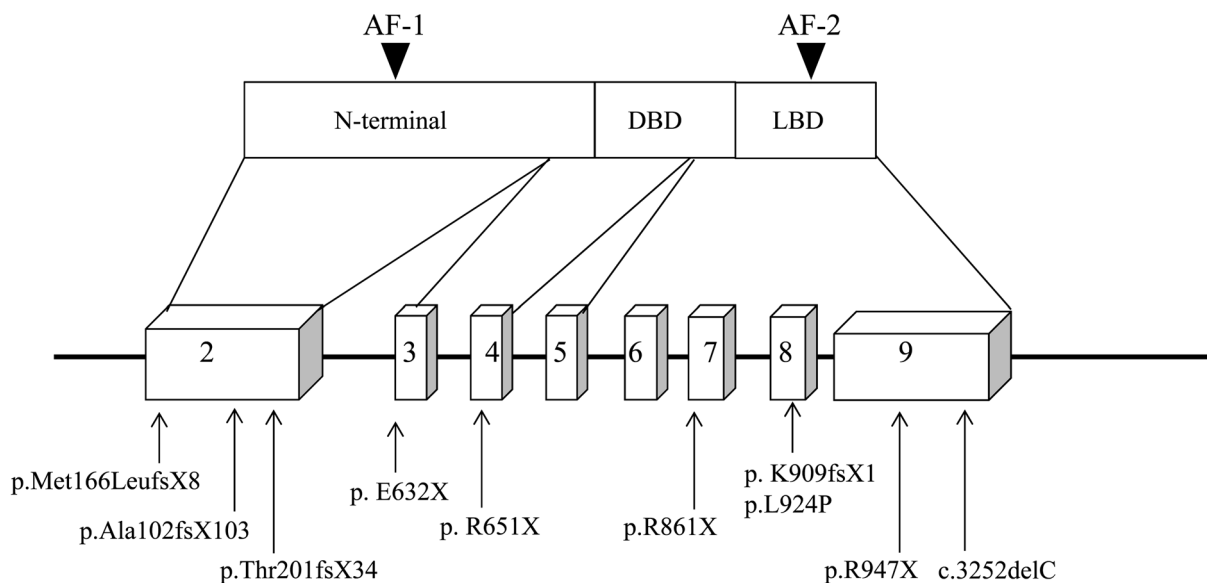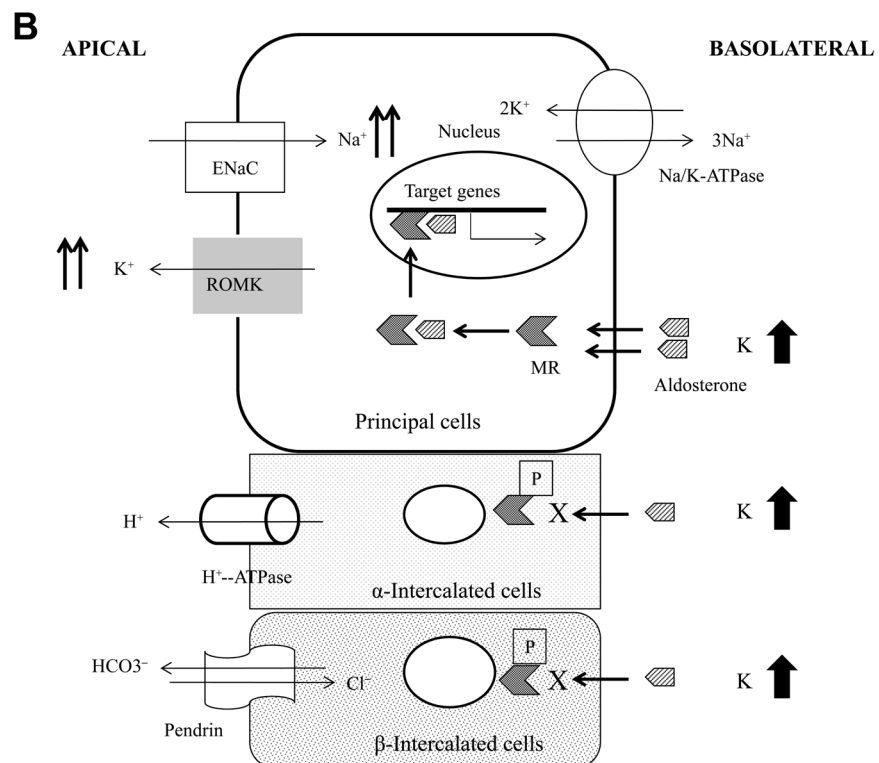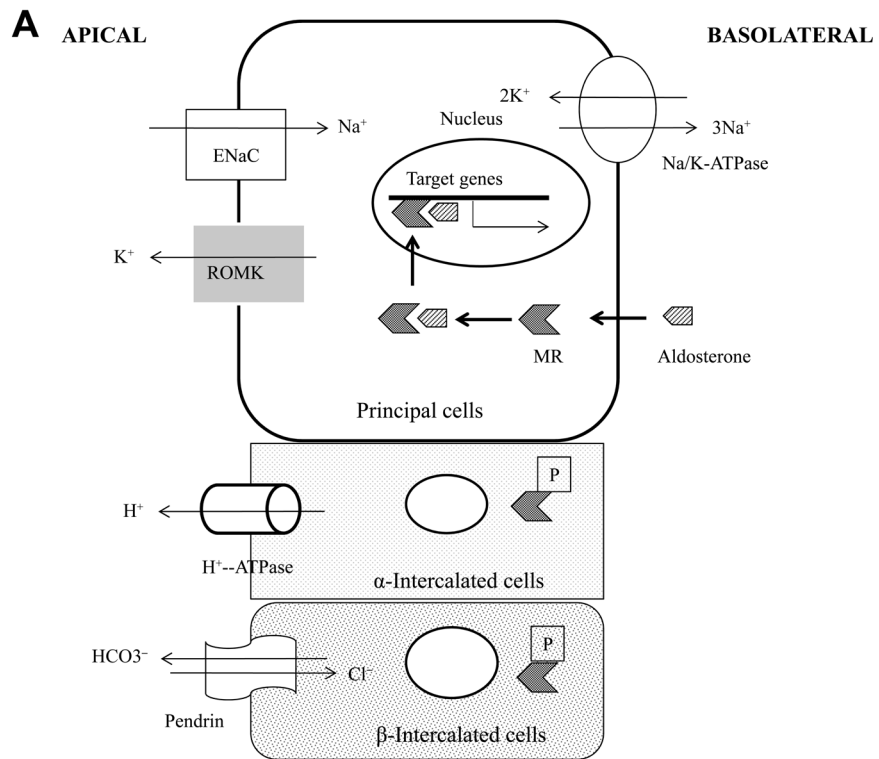
Fig. 1. Schematic representation of MR and mutations of *NR3C2* identified in Japan. The N-terminal domain of MR has an autonomous activation function (AF-1), and is thought to be constitutively active and play a key role in the interaction with transcriptional regulators. In the LBD, an AF-2 domain, with a ligand-dependent activation function, is present.
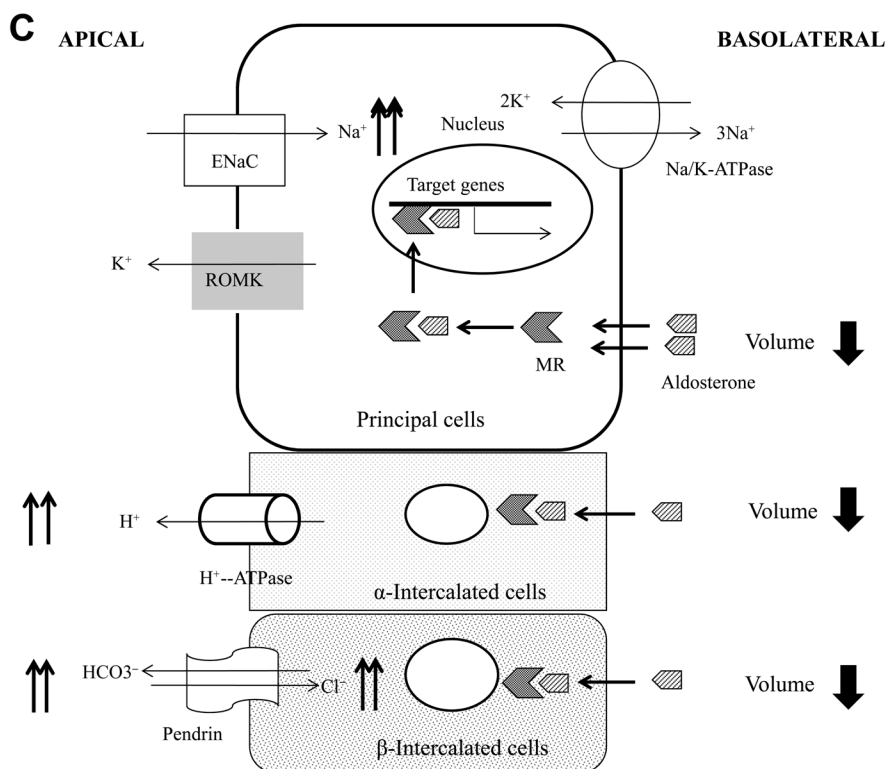
induces H^+ secretion into the urine by the H^+-K^+-ATPase (Fig. 2A) (2, 3). Recently, Shibata *et al.* (10) have elegantly clarified a new mechanism of MR signaling. According to their study, the LBD of MR in intercalated cells, but not in principal cells, is phosphorylated, leading to inhibition of aldosterone binding to MR, allowing the cells to selectively control MR signaling (Fig. 2A–C) (10, 11). In hyperkalemia, MR phosphorylation is maintained in intercalated cells and thus, aldosterone can bind MR only in principal cells, resulting in the activation of ENaC and ROMK. Therefore, only active K^+ excretion can occur. (Fig. 1B) (10, 11). Upon volume depletion, aldosterone binds to MR in principal cells. In addition, MR in intercalated cells is dephosphorylated and thus, becomes able to bind to aldosterone, resulting in increased activities of apical H^+-ATPase and Cl^--HCO_3^- exchanger (pendrin) (Fig. 1C) (10, 11). Subsequently, Cl^- reabsorption increases, leading to the neutralization of the negative potential of the lumen. Therefore, excessive K^+ excretion by ROMK does not occur (Fig. 1C) (10, 11). By this

mechanism, aldosterone strongly activates K^+ excretion in hyperkalemia, whereas it activates Na^+ reabsorption without excessive K^+ excretion in volume depletion.

Systemic Form of PHA1

Inactivating mutations in sodium channel, non-voltage-gated 1 α gene (*SCNN1A),* sodium channel, non-voltage-gated 1 β gene *(SCNN1B)* and sodium channel, non-voltage-gated 1 γ (*SCNN1G),* which encode the three α, β and γ subunits of ENaC subunits, respectively, are the cause of systemic PHA1 (12). ENaC is expressed in the distal convoluted tubule, the connecting tubule, and the collecting duct in the kidney and the distal colon, salivary and sweat glands, and the lung (9, 12). Therefore, ENaC impairment shows systemic symptoms, such as severe dehydration, failure to thrive, cholelithiasis, skin infections, dermatitis, and respiratory symptoms from the neonatal period (9, 12). Respiratory symptoms are caused by impaired absorption of liquids from

A APICAL

BASOLATERAL

ENaC → Na⁺

Nucleus

2K⁺ ←
→ 3Na⁺
Na/K-ATPase

Target genes

K⁺ ← ROMK

MR ← Aldosterone

Principal cells

H⁺ ← H⁺--ATPase

P

α-Intercalated cells

HCO3⁻ ← Pendrin → Cl⁻

P

β-Intercalated cells

B APICAL

BASOLATERAL

ENaC → Na⁺ ⇑⇑

Nucleus

2K⁺ ←
→ 3Na⁺
Na/K-ATPase

Target genes

⇑⇑ K⁺ ← ROMK

MR ← Aldosterone K ⬆

Principal cells

H⁺ ← H⁺--ATPase

P
X ← K ⬆

α-Intercalated cells

HCO3⁻ ← Pendrin → Cl⁻

P
X ← K ⬆

β-Intercalated cells

Fig. 2. Mechanism of aldosterone-dependent volume and electrolyte balance in the distal nephron of the kidney. In MR target tissues, aldosterone binds MR and the resulting complex translocates into the nucleus, where it binds to the regulatory regions of MR responsive genes, resulting in increased expression of the epithelial sodium channel (ENaC) and the Na^+-K^+-ATPase. In principal cells of the distal nephron, Na^+ is reabsorbed by ENaC and excreted through the basolateral cell membrane by the Na^+-K^+-ATPase. ROMK excretes K^+ into the apical side. Upon volume depletion, in addition to its action in principal cells, aldosterone stimulates Cl^- reabsorption through the combined activities of the apical H^+-ATPase and the apical Cl^--HCO_3^- exchanger in intercalated cells.

the airway surfaces (13). Patients show coughing, wheezing, and recurrent infections of the upper and lower respiratory system. In addition, recurrent episodes of salt loss occur and frequent hospitalization is required. However, several patients with missense mutations in *SCNN1A* have been reported to show less severe symptoms (14–16). Edelheight *et al*. (14) reported a patient with the p.G327C and c.1404delC compound heterozygous mutations in *SCNN1A*, who showed severe salt loss at 3 d of age and required high salt supplementation (11 g/d) and cation exchange (1 g/kg/d). However, beyond infancy, he has been

healthy with only high salt supplementation (8 g/d) and has not developed any salt-losing crisis and respiratory symptoms. Ahluwalia *et al*. (15) have reported a patient with the p.R139K and c.1360+1G>T compound heterozygous mutations also in *SCNN1A*. The patient developed severe salt loss and hyperkalemia at 7 d of age and intensive treatment was required, but his NaCl supplementation (5 g/d) has not been increased for almost 2 yr. Moreover, he has just had mild upper respiratory infections.

From Japan, Adachi *et al*. (17) reported a patient with the systemic form of PHA1, caused

by a *SCNN1G* mutation. During childhood, this patient showed recurrent salt-losing episodes requiring hospitalization, despite high salt supplementation (6–7 g/d). However, with advancing age, his salt-losing episodes decreased, and at 11 yr of age salt supplementation was stopped (18). To elucidate the mechanism underlying these observations, the researchers analyzed the expression of the urine Na⁻-Cl⁻ cotransporter (NCC), which is normally expressed in the distal convoluted tubule, and its expression is induced by aldosterone (19). They found that NCC expression increased in that patient compared with healthy individuals. Based on these findings, they speculated that increased NCC expression can compensate for the loss-of-function of ENaC. Thus, in addition to genotypic contributions, this mechanism might be responsible for the improvement observed with advancing age in patients with systemic PHA1.

Renal Form of PHA1

Geller *et al.* (20) were the first to identify heterozygous mutations in *NR3C2*, the gene encoding MR, in familial and sporadic cases of renal PHA1. Thereafter, more than 100 heterozygous mutations have been reported. In Japanese patients, several mutations have been identified and described in the literature (Fig. 1B) (21–25). Mutations are found in all exons and there is no mutation hot spot. Nonsense and frameshift mutations leading to premature stop codon are the most frequent. Therefore, the disease mechanism is thought to be haploinsufficiency. However, a few of missense mutations have been reported in the DBD and LBD. We reported the first missense mutation (L924P) of MR (21). An *in vitro* study demonstrated that this mutant lost its transactivation capacity. This might be due to the lack of aldosterone binding, since this mutation is located in the LBD. In addition, this mutant did not exert a dominant negative effect onto the wild-type receptor. Sartorato *et al.* (26)

also reported the functional consequences of the G633R, Q776R, and L979P MR mutations. According to their study, G633R in the DBD had reduced transactivation capacity than wild-type MR, and Q776R and L979P showed reduced or no aldosterone binding. Similar to our study, G633R and Q776R did not show a dominant negative effect to the wild-type MR, whereas L979P did have such an effect. Thus, rare dominant negative mutations, as well as haploinsufficiency, may contribute to the development of MR-related diseases. Recently, Kawashima *et al.* (25) reported the c.3252delC mutation of *NR3C2*. This deletion, located in exon 9, changes the open reading frame following the mutation, resulting in a protein 10 amino acids longer than wild-type MR. An *in vitro* study demonstrated that this mutant has lost its transactivation capacity. Furthermore, it is associated with reduced MR expression levels, although the levels of *NR3C2* mRNA are not reduced. These findings indicate that this mutant may be rapidly eliminated due to increased protein degradation.

It is thought that renal PHA1 is usually milder than systemic PHA1 and salt supplementation is sufficient to resolve the symptoms. However, Gellet *et al.* (27) reported that several patients showed failure to thrive soon after birth and one patient developed shock at 1 mo of age. The phenotypic differences in the renal form of PHA1 are as broad as those of the systemic form of PHA1 (22, 26, 27).

In the renal form of PHA1 salt supplementation generally becomes unnecessary by 1–3 yr of age despite elevated aldosterone levels. Martinerie *et al.* (28) showed that during human embryogenesis, MR protein expression was not found in late gestation nor at birth. Moreover, although MR protein expression in the human kidney was not observed at 10 mo of age, it was observed at 11 mo. These findings indicate that the increased MR expression with advancing age may compensate for the haploinsufficiency of MR caused by *NR3C2* mutations.

As already mentioned, patients with the renal

form of PHA1 respond to salt supplementation, but plasma aldosterone levels remain high in adulthood (26, 29), and the effect of constantly elevated plasma aldosterone on human morbidity is not well understood. Walker *et al.* (29) analyzed whether the constantly elevated aldosterone levels caused by *NR3C2* mutations affect the hypothalamic-pituitary adrenal (HPA) axis. According to their study, adult patients with *NR3C2* mutations had higher morning cortisol and increased 24-h urinary excretion of cortisol metabolites than healthy individuals, as well as low HDL-cholesterol and central adiposity. This study suggests that MR haploinsufficiency may cause activation of the HPA axis, resulting in excessive production of cortisol (29, 30). Therefore, regular follow-up of patients after medication discontinuation is required.

Secondary Form of PHA1

Secondary PHA1 in infancy is a transient condition that occurs in infants between 6 and 12 mo of age, manifesting acute urinary tract infections (UTI), urinary tract malformations, or both (2, 3, 31, 32). The symptoms are resolved after therapy with antibiotics for bacteriuria or repair of the underlying urinary tract structural abnormalities. The exact mechanism of secondary PHA1 has not been determined. It is speculated that several cytokines, such as transforming factors, tumor necrosis factors, and interleukin-1, 6 are increased in UTI, resulting in the down regulation of the aldosterone receptor (31, 32). Indeed, one study showed that in two patients, MR expression in lymphocytes was reduced with urinary tract malformation (33).

Secondary PHA1 has generally an insidious course, and in several cases, it led to life-threatening events. Kibe *et al.* (34) reported a 4-mo old boy with cardiopulmonary arrest due to secondary PHA1 caused by bilateral hydronephrosis. Gines *et al.* (35) also reported a 19-d-old boy with critical course (serum Na = 112 mEq/l and serum K = 11.3 mEq/L). This patient also had bilateral hydronephrosis. Bowden *et al.* (36) reported 14-d-old boy manifesting severe dehydration and hyperkalemia. Since he had UTI and posterior urethral valves, he was considered to be secondary PHA1. However, after UTI recovery and repair of the posterior urethral valves, failure to thrive persisted and the elevated levels of plasma aldosterone and PRA were not normalized. Further investigation identified a deletion of exons 3–5 of *NR3C2*, along with the surrounding intronic region. Although this case is rare, some genetic factors including *NR3C2* and aldosterone-MR signaling system may contribute to the development of secondary PHA1.

Conclusion

We summarized the clinical features and molecular basis of PHA1, especially those of renal PHA1. Because the symptoms of PHA1 in infants, such as failure to thrive, poor weight gain, and vomiting, are non-specific, the diagnosis of PHA1 may be delayed. In addition, several cases with PHA1 develop life threatening hyponatremia and hyperkalemia soon after birth. Pediatricians should keep in mind PHA1 during differential diagnosis of common infant complaints that can lead to life-threatening salt loss.

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