Pseudohypoaldosteronism Type 1

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Pseudohypoaldosteronism (PHA), a rare syndrome of systemic or renal mineralocorticoid resistance, is clinically characterized by hyperkalemia, metabolic acidosis, and elevated plasma aldosterone levels with either renal salt wasting or hypertension. PHA is a heterogeneous disorder both clinically and genetically and can be divided into three subgroups; PHA type 1 (PHA1), type 2 (PHA2) and type 3 (PHA3). PHA1 and PHA2 are genetic disorders, and PHA3 is a secondary disease of transient mineralocorticoid resistance mostly associated with urinary tract infections and obstructive uropathies. PHA1 includes two different forms with different severity of the disease and phenotype: a systemic type of disease with autosomal recessive inheritance (caused by mutations of the amiloride-sensitive epithelial sodium channel, ENaC) and a renal form with autosomal dominant inheritance (caused by mutations of the mineralocorticoid receptor, MR). In the kidneys, the distal nephron takes charge of the fine regulation of water absorption and ion handling under the control of aldosterone. Two major intracellular actors necessary for the action of aldosterone are the MR and the ENaC. Impairment of the intracellular aldosterone signal transduction pathway results in resistance to the action of mineralocorticoids, which leads to PHA. Herein, ion handling the distal nephron and the clinico-genetic findings of PHA are reviewed with special emphasis on PHA type 1.

Key words: Aldosterone, Distal nephron, Epithelial sodium channel, Mineralocorticoid receptor, Pseudohypoaldosteronism

Introduction

In physiologic condition, almost 95% of filtered Na^+ load is reabsorbed by proximal nephron segments, from proximal convoluted tubules to early distal convoluted tubules, and the remaining Na^+ load is reabsorbed in more distal nephron segments variably to maintain fine balance of body fluid and electrolytes. Aldosterone is the key regulator of the final urinary Na^+ and K^+ concentration in the distal nephron.^{1,2)}

There are several kinds of disorders involving dysfunction of aldosterone. Hyperaldosteronism is a condition with an increased plasma aldosterone level either of primary or secondary causes and typically presents with volume overload and hypokalemia.

Hypoaldosteronism is an opposite condition with a decreased plasma aldosterone level accompanies hyperkalemia with/without volume depletion. Pseudohypoaldosteronism (PHA) is another category of disorders characterized by mineralocorticoid resistance due to dysfunction of the intracellular aldosterone signaling pathway. Patients with PHA display elevated plasma aldosterone levels, hyperkalemia and metabolic acidosis. Some patients may have renal salt wasting also. PHA includes a heterogeneous, both phenotypically and genetically, group of disorders.

This paper includes brief reviews of ion transport mechanisms in the distal nephron and the clinico-genetic characteristics of PHA, with special emphasis on PHA type 1, for better understanding of

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this rather complicated disease by general clinicians and clinical nephrologists.

Ion transport in the distal nephron

The aldosterone-sensitive distal nephron includes the late distal convoluted tubules (DCT2), the connecting tubules (CNT), and the cortical and medullary collecting ducts (CCD and MCD). There are three different types of cells in the CNT and CCD; the principal cells and the α - and β -intercalated cells. In the principal cell, Na^+ is reabsorbed via the electrogenic amiloride-sensitive epithelial Na^+ channel (ENaC) and K^+ is secreted via the apical K^+ channels, renal outer medullary potassium channel (ROMK) and Maxi-K. The active transport at the basolateral membrane is mediated by the Na^+/K^+ -ATPase. Cl^- is absorbed paracellularly in principal cells and may be reabsorbed transcellularly in intercalated cells as well. The intercalated cells execute K^+ reabsorption and H^+ and HCO_3^- secretion (Fig. 1).

Two major stimuli for aldosterone release are volume depletion and hyperkalemia.^{1,3,4)} Aldosterone plays its role by binding to its cytosolic receptor, mineralocorticoid receptor (MR). The MR, a member of the classic steroid-thyroid-retinoid nuclear receptor family, acts as ligand-dependent transcription factors that regulate a variety of physiological processes.⁵⁾ Cortisol is a natural glucocorticoid and has equal affinity for the MR. The circulating level of cortisol is several-fold higher than that of aldosterone. In the distal nephron, 11β -hydroxysteroid dehydrogenase

type 2 metabolizes cortisol to the inactive cortisone allowing aldosterone unrestricted access to MR.^{6,7)} After binding to MR, aldosterone-MR complex translocates into the nucleus and binds to specific DNA sequences and then activates or represses the transcription of a variety of aldosterone-sensitive target genes (Fig. 2).⁸⁾ Some of the target genes induce accumulation of ENaC at the plasma membrane and enhance the transcription and translation of ENaC subunits, basolateral Na^+/K^+ -ATPase, and other factors of the sodium transport machinery.

The ENaC is a heteromultimer composed of α -, β -, and γ -subunits.⁹⁾ This channel is expressed in the apical membrane of DCT2 cells and the principal cells. The ENaC, the rate-limiting step in Na^+ reabsorption in the distal nephron,¹⁰⁾ is rapidly induced in response to decreased distal Na^+ delivery (Na^+ depletion) or

Fig. 2. The transepithelial sodium and potassium transport in the distal nephron.

Fig. 1. Transporters and ion channel expressed in each segment of the distal nephron; late distal convoluted tubules (A), connecting tubules (B), principal cells in cortical collecting ducts (C), and α -intercalated cells in cortical collecting ducts (D).

increased aldosterone level. Another Na-transporter in DCT2, the thiazide-sensitive electroneutral Na⁺-Cl⁻ cotransporter (NCCT), also respond to aldosterone as well.

In the kidney, K⁺ is mainly secreted in the principal cells of the CNT and the CCD via two apical K⁺ channels; a low-conductance ROMK and a large-conductance Maxi-K (BK).^{1,11} The driving force for K⁺ secretion is the lumen-negative potential difference generated by the reabsorption of Na⁺ via ENaC. A high dietary K⁺ intake stimulates aldosterone secretion and increases ROMK abundance at the apical membrane. The activity of the Maxi-K, a Ca²⁺-activated tetraethylammonium-sensitive channel, is increased by increased distal tubular flow rate.^{12,13} The α-intercalated cells in the CCD and MCD reabsorb K⁺ via the apical H⁺-K⁺-ATPase.¹⁴ A high K⁺ diet reduces the activity of the H⁺-K⁺-ATPase and reduces K⁺ reabsorption.

Cl⁻ enters the cell via apical NCCT and exits via a basolateral Cl channel (ClC-Kb)¹⁵ and a KCl cotransporter (KCC4)¹⁶ in DCT. The ClC-Kb channel requires a β-subunit, barttin, which may enhance ClC-Kb delivery to the basolateral membrane.¹⁷ While the ClC-Kb is expressed in the basolateral membrane of the CNT, the routes or channels involving apical transcellular transport of Cl⁻ in this segment have not been identified. In the α-intercalated cells, Cl⁻ enters across the basolateral membrane via a Cl⁻-HCO₃⁻ anion exchanger (AE1), which plays an important role in maintaining acid-base balance.¹⁸ In addition, a Na⁺-independent Cl⁻-HCO₃⁻ exchanger, pendrin, is expressed in the apical membrane of the β-intercalated cells in the CNT and CCD and it may participate in Cl⁻ reabsorption.¹⁹

Table 1. Classification of Pseudohypoaldosteronism (PHA)

Type	Genes	Summary of clinical features
AD-PHA1	<i>NR3C2</i>	Renal salt wasting, less severe form Hyponatremia, hyperkalemia, metabolic acidosis Elevated renin and aldosterone
AR-PHA1	<i>SCNN1A</i> , <i>SCNN1B</i> or <i>SCNN1G</i>	Systemic salt wasting, severe form Hyponatremia, hyperkalemia, metabolic acidosis Elevated renin and aldosterone Respiratory and dermatologic symptoms
PHA2	<i>WNK1</i> , <i>WNK4</i> , <i>CUL3</i> or <i>KLHL3</i>	Gordon syndrome, Familial hyperkalemic hypertension Autosomal dominant inheritance Hypertension, hyperkalemia, hyperchloremic metabolic acidosis Low renin and variable aldosterone levels
PHA3	none	Secondary to nephropathies or uropathies Hyponatremia, hyperkalemia, metabolic acidosis, Elevated renin and aldosterone, Low glomerular filtration rate

AD, autosomal dominant; AR, autosomal recessive

Pseudohypoaldosteronism

Pseudohypoaldosteronism (PHA) is a rare syndrome of mineralocorticoid resistance. PHA is a heterogeneous group of diseases and can be divided into two subgroups; PHA type 1 (PHA1) and type 2 (PHA2). PHA1 includes two different forms with different severity of the disease and phenotype: a systemic type of disease with autosomal recessive inheritance (sPHA1 or AR-PHA1) and a renal form with autosomal dominant inheritance (rPHA1 or AD-PHA1).²⁰⁻²³ In addition, there is a secondary form of PHA, may be called as PHA type 3 (PHA3), which is characterized by transient mineralocorticoid resistance associated with various kidney diseases, mostly urinary tract infections and obstructive uropathies (Table 1).

The three mandatory clinical features of PHA are hyperkalemia, metabolic acidosis and elevated plasma aldosterone levels. Salt wasting is an additional feature in PHA1 and PHA3. While PHA1 and PHA3 are primarily salt losing syndromes, PHA2 is primarily a potassium retaining syndrome.²²

Autosomal dominant pseudohypoaldosteronism type 1

AD-PHA1 (OMIM #177735) is characterized by an isolated renal resistance to aldosterone, leading to renal salt wasting, dehydration and failure to thrive during infancy.^{1,20-25} The main clinical symptom is insufficient weight gain due to chronic dehydration, and the cardinal laboratory abnormalities are hyponatremia, hyperkalemia, and metabolic acidosis despite elevated plasma renin activity and aldosterone levels.²⁰⁻²⁵ AD-PHA1 is caused by inactivating mutations in the *NR3C2* gene encoding MR,²⁶ and heterozygous mutations have been detected in approximately 75% of patients with this disease. To date, more than 50 *NR3C2* mutations have been described in association with AR-PHA1.²² Most of the patients have positive family history, but some sporadic cases also have been described.²⁷⁻³⁰ There has been no report of linkage analysis study in pedigrees without pathogenic mutations in the *NR3C2* gene, therefore the possibility of other candidate gene(s) remains to be unknown. Functional studies of a few of the *NR3C2* mutations revealed that the mutations result in impaired ligand binding, DNA binding, or diminished trans-activation function.^{24, 25, 28, 31, 32} Therefore, some mutations result in haploinsufficiency from hypomorphic or null allele, while others may functions in a dominant negative function. In Korea, only one mutational

report of a *de novo* heterozygous c.2146_2147insG mutation in NR3C2 has been described.³⁰⁾

Reduced MR function results in Na⁺ wasting and impairment in K⁺ and H⁺ secretion in the distal nephron, which leads to hyponatremia, hyperkalemia and metabolic acidosis. These electrolyte and acid-base imbalance usually manifests in neonates or early childhood. Exogenous mineralocorticoid treatment has no effect in patients with AD-PHA1, and patients usually respond well to sufficient enteral or parenteral salt supplementation.^{1, 22, 23)} Hyperkalemia is generally mild, and chronic ion exchange resin therapy to control hyperkalemia is rarely required. Interestingly, these abnormalities improve with increasing age in most cases, and the salt treatment becomes generally unnecessary by 2 to 3 years of age.^{1, 22, 23, 26, 27)} The reason for such spontaneous resolution of symptoms after infancy is not well understood, but it can be explained by (1) the change in diet from low-sodium human breast milk to higher salt diet, (2) maturation of Na⁺ reabsorption function of the renal tubules with increasing age, (3) chronically upregulated renin-angiotensin-aldosterone system, and (4) replacement of distal sodium reabsorption by proximal parts of the tubules.^{20, 26, 27)} However, high plasma aldosterone levels may persist even after normalization of other laboratory findings in most cases.²⁷⁾ Therefore, the elevated serum aldosterone level was the only biochemical marker of AR-PHA1. However, reports from several families suggest that adult carriers of NR3C2 mutations might also have normal levels of aldosterone.³³⁾

When compared to AR-PHA1, the salt loss in AD-PHA1 is less severe, restricted to the kidneys, and improves spontaneously with age. Although mild in its course, it has been reported that AD-PHA1 can be associated with a high infant mortality rate. Geller et al²⁷⁾ reported a number of unexplained deaths in infants at risk for AD-PHA1, which suggests that AD-PHA1 is potentially fatal to neonates. Therefore, early diagnosis and prophylactic salt supplementation for neonates at risk for AD-PHA1 is essential.

Autosomal recessive pseudohypoaldosteronism type 1

AR-PHA1 (OMIM #264350) is caused by mutations of any of the three genes (*SCNN1A*, *SCNN1B*, and *SCNN1G*) encoding three subunits (α-, β-, and γ-subunits, respectively) of the ENaC channel.^{34, 35)} Patients typically manifest severe volume depletion associated with hypotension, failure to thrive, feeding difficulty within the first week of life. The laboratory tests reveal

hyponatremia, hyperkalemia, metabolic acidosis, and marked elevation of plasma renin and aldosterone levels.^{21, 36)} These renal symptoms are similar to those of AD-PHA1 but more severe in degree and earlier onset. Some patients present during pregnancy with polyhydramnios.^{37, 38)} AR-PHA1 is not a renal tubule-restricted disease as AD-PHA1 but a systemic disease. Excessive salt wasting occurs via saliva and sweat as well as via urine.²⁰⁾ High salt concentration in sweat may cause miliaria-like rash on the face and trunk.^{39, 40)} In addition, pulmonary manifestations associated with increased airway secretion, such as chronic cough and recurrent respiratory infections, frequently develop in older children.^{36, 41)} Newborn patients may develop respiratory distress also, although the incidence is rare.^{42, 43)}

AR-PHA1 is a disease with a high mortality, especially early in life.^{36, 44)} Therefore, sick infants should be treated urgently; saline infusion to correct volume depletion and hyponatremia, and ion exchange resin or emergency dialysis to control hyperkalemia. After recovery from acute crises, patients can be managed with high dose of oral salt supplements and chronic ion exchange resin therapy, and most patients require life-long salt supplementation.²¹⁾

Other types of pseudohypoaldosteronism

PHA2 (OMIM #145260), also called as Gordon syndrome or familial hyperkalemic hypertension, was first reported in 1964⁴⁵⁾ and described as a syndrome by Gordon's group, in 1970.⁴⁶⁾ PHA2 is clinically characterized by hyperkalemia, hypertension, variable degree of hyperchloremic metabolic acidosis, and suppressed plasma renin activity with highly variable plasma aldosterone concentrations. These features are compatible with mirror image of those of Gitelman syndrome caused by loss-of-function mutations in the *SLC12A3* gene encoding the thiazide sensitive NCCT. PHA2 is genetically heterogeneous and is associated with, at least, four disease-causing genes; *WNK1* (type 2C, OMIM #614492), *WNK4* (type 2B, OMIM #614491), *CUL3* (type 2E, OMIM #614496), and *KLHL3* (type 2D, OMIM #614495) genes^{47, 48)} as well as a unknown gene (type 2A, OMIM #145260) located at chromosome 1q31-q42. All subtypes of PHA2 can be easily managed with low doses of thiazide diuretics.²²⁾

PHA3 comprises transient and secondary forms of salt-losing states caused by various pathologies. Urinary tract infections and obstructive uropathies in neonates and young infants are the most frequent causes.^{22, 49)} In addition, a number of drugs may cause resistance to aldosterone, leading to secondary

PHA; drugs blocking ENaC activity (amiloride, triamterane, trimethoprim and pentamidine), drugs blocking MR function (spironolactone), drugs interfering with the renin-angiotensin-aldosterone system (angiotensin converting enzyme inhibitors and the angiotensin II receptor antagonists), the cyclooxygenase inhibitors (inhibit renin release), heparin (inhibits aldosterone synthase), the beta-adrenergic antagonists (decrease Na^+/K^+ -ATPase activity and inhibit renin release), and the calcineurin inhibitors (cyclosporine A and tacrolimus).^{50,51)} Very rarely, major intestine resection or sweat gland dysfunction can also cause PHA3.^{22, 49)}

The clinical feature of PHA3 is almost same as that of AD-PHA1. However, contrary to PHA1 and PHA2, the glomerular filtration rate is decreased in PHA3. This clinical and laboratory findings usually improve rapidly with medical or surgical treatment of the underlying cause and volume resuscitation. However, salt supplementation and control of hyperkalemia with ion exchange resin may be required in some patients.²³⁾

Conclusion

PHA1, especially AR-PHA1, is a potentially life-threatening disorder in neonates and infants. Therefore, early diagnosis and treatment is essential for saving lives of the critically ill patients. The recent discovery of the underlying molecular pathophysiology in PHA has enabled better understanding of the physiological role of the distal nephron and the pathophysiology PHA. In addition, we, near future, can discover novel therapeutic target molecules and develop new drugs based on this understanding.

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