Pseudohypoaldosteronism Type II
History, Arguments, Answers, and Still Some Questions
John K. Healy

Pseudohypoaldosteronism type I (PHAI) is sometimes dominantly inherited and is characterized by mutations causing a near-absence of mineralocorticoid receptors in the kidneys. This leads to salt-wasting and hyperkalemia, despite increased aldosterone levels. It starts in infancy but eases toward adulthood. There is also a recessive form of PHAII that is more severe, associated with loss of function mutations of epithelial sodium (Na+) channels (ENaC) in the late distal tubules (DTs), the connecting tubule and collecting ducts, and also in other tissues expressing the ENaC. It starts in the newborn, with life-threatening salt-wasting and hyperkalemia. Salt supplements of ≤45 g/d are required indefinitely, together with control of hyperkalemia. More than 100 cases of these forms of PHAI have by now been described.

PHAII is also inherited, but can be sporadic, in which hyperkalemia despite a normal glomerular filtration rate is the cardinal presenting feature. There is also acidosis and a low plasma renin level and a high incidence of hypertension. Plasma aldosterone levels are low to mildly but inadequately increased. This disease was named PHAII by Schambelan et al., but it has also been known as Familial Hyperaldosteronism and Hypertension, Gordon Syndrome, and Chloride Shunt Syndrome. The first case was described in 1964 by Paver and Pauline. In 1968, their patient, a white man aged 18 years, came under my care. He had a plasma potassium (K+) of 8.2 mmol/L, a normal glomerular filtration rate, acidosis, and a blood pressure of 180/120 mmHg. Although Paver and Pauline found that he had an extreme cold pressor response, we did not find it so in 1968, but meanwhile it may have been affected by treatment. Renal biopsy was normal. Plasma renin level was low, and plasma aldosterone was low normal. A 4-day balance study on a stable intake of 78 mmol/d of K+ showed a positive K+ balance of 113 mmol but only a 5-mmol positive balance of Na+.

The degree of response to PRAN has been assessed by comparison with control subjects, in the absence of abnormal Na+ or K+ intakes or mineralocorticoid administration or other K+ stimulatory substances. The data provided reveal that the average maximum K+ excretion reached during Na2SO4 infusion in PHAII subjects relative to the average maximum control values was 18.2% and 51.2%. For NaHCO3 infusion, it was 46.0% and 66.7% of average maximum controls. Another author reported no change in urinary or plasma acetzolamide intravenous caused a modest increase in U,V. The procedure was repeated twice after salt depletion and other stimuli to K+ secretion. Then U,V rose and approached, but did not equal the response of controls given this protocol (Figure S2). On the basis of the balance study and the Na2SO4 studies, we concluded that there was a primary defect in the patient’s distal nephron K+ secretion.

By now, ≈100 to 200 cases similar to ours have arisen, many dominantly inherited in large families. About the cause of hyperkalemia, 3 views have emerged: first, the possibility of directly reduced activity of the K+ secretory mechanism; second, there was a secondary deficiency in K+ secretion because of a lack of chloride (Cl-) reaching the ENaC; and third, there was a lack of Na+ reaching the ENaC for adequate exchange for K+ (Figure).

With regard to possible direct suppression of K+ secretion, the DT capacity in this regard can be tested by infusion of the poorly reabsorbed anions (PRAN) sulfate or the more effective bicarbonate (HCO3-), which stimulates K+ secretion. PRAN increase the lumen negativity at the ENaC, while supplying copious Na+ ions that can diffuse down a chemical gradient into the cells, which in turn stimulates the basolateral Na+/K+ exchange with more K+ entry into principal cells.

Enzymes associated with a practical test of DT K+ secretory capacity, primarily as a test of the ENaC. Emphasizing this, as will be seen below in genetics, upregulation of the ENaC in a mouse model of PHAII was associated with an exaggerated kaliuretic response to Na2SO4. A protocol for the use of PRAN has been provided by DeFronzo et al. with control data from 5 normal subjects, but it has not always been used, many authors assuming that any increase in K+ secretion is a normal response. Some quantitation is needed.

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K⁺ during a NaHCO₃ infusion. As will be discussed below, we now know that there are 5 levels of severity of PHAII so that the response to PRAN may differ between individual cases. Given the hyperkalemia of these patients, one might have expected even a supranormal response to PRAN as seen below in the mouse model of PHAII.³² PRAN were used in 11 of the studies surveyed here and although some had a reduced kaliuretic response, in none was there a response greater than the normal controls.⁵,⁸,¹⁰,¹¹,¹³,¹⁷,¹⁹,²⁰ Therefore, given the hyperkalemia, these results indicate a mild degree of depression of ENaC function. This might have been expected to lead to a compensatory increase in activity of the major K⁺ secretory mechanism, the renal outer medullary K⁺ (ROMK) channels.¹⁴,¹⁵ This might imply that ROMK also was not functioning normally (Figure, Theory 1).

Another factor that could have suppressed the K⁺ secretion, particularly ROMK, was the acidosis, which is known to be because of hyperkalemia in PHAII.⁵,⁷,¹¹,¹² If PHAII is reversed by drug treatment (thiazide) and the drug is stopped, the hyperkalemia returns in 10 days before a return of the acidosis at 17 days,⁴ indicating the primacy of the hyperkalemia. If the ENaC is compromised to a degree, this period without acidosis would provide ROMK with a window of opportunity to control the rising plasma K⁺; this clearly does not happen.

DeFronzo et al.¹³ studied K⁺ secretion in sickle cell disease that damages the renal papillae and the medulla. They found a negligible response in K⁺ secretion to PRAN, yet hyperkalemia did not occur (average plasma K⁺ 3.78±0.01 mmol/L). This difference from PHAII might be explained by the fact that although ROMK shares the late DT, the connecting tubule and the collecting duct sites with ENaC, functioning isoforms ROMK 2 and 3 are present as well in the whole of the distal convoluted tubule (DCT).³⁴ Therefore, in sickle cell disease, these isoforms may have been intact in the DCT before the late DCT but perhaps not so in PHAII. PHAII and sickle cell disease cannot be compared pathologically, but these results reflect on the way the effects of PRAN are interpreted because they show that a negligible response in K⁺ secretion to PRAN is not obligatorily associated with hyperkalemia in humans.

Finally, Golbang et al.²⁶ (see below) have described a father and son with PHAII caused by a mutant gene shown by genetic testing to inhibit ROMK substantially.

The second view of the cause of hyperkalemia in PHAII is that a Cl⁻ shunt may play a role by increasing paracellular Cl⁻ absorption in the early DT (Figure, Theory 2). Schambelan et al.¹ in 1981 showed that with mineralocorticoid pretreatment, intravenous Na₂SO₄ and NaHCO₃ could both invoke an increase in K⁺ excretion in PHAII, but that intravenous sodium chloride (NaCl) was much less able to do so. They postulated that a Cl⁻ shunt proximal to the ENaC would result in less Cl⁻ delivery and thus less negativity at the ENaC, resulting in decreased K⁺ secretion. Support for this came from other authors,¹²,¹⁰,²⁰ and also from genetic studies (below) although mathematical modeling of the DCT and connecting tubule function has not demonstrated a need for a Cl⁻ shunt to explain PHAII.

The third concept (Figure, Theory 3) that excessive Na⁺ reabsorption occurs in a region before the ENaC was based on the effectiveness of thiazides in reversing the features of PHAII.⁵,¹⁰,¹¹,¹⁴,²⁷,³⁷,³⁸ This part of the DT was later found to be the site of the electroneutral thiazide-sensitive Na⁺–Cl⁻ cotransporter (NCC).³⁹ Excess salt retention at the NCC may cause hypertension in PHAII but is insufficient to lead to edema.

In 1970, Gordon et al.²⁶ hypothesized that increased Na⁺ reabsorption before the distal npheron Na⁺/K⁺ exchange site would result in decreased Na⁺ delivery to that site and so suppression of K⁺ secretion. However, they did not test their theory in any of their cases by the use of PRAN. Others did so, as mentioned above, and in 3 controlled studies increased Na⁺ delivery with PRAN revealed a reduced kaliuretic response when compared with controls.⁵,²⁷,³² In 1990, Gordon et al did find correction of hyperkalemia with a saline infusion in 2 patients with mild hyperkalemia with PHAII but only after 33 days of a low K⁺ diet (50 mmol K⁺/d), which could have affected results,⁴¹,⁴² and 12 days of severe Na⁺ restriction (10 mmol/d). Their protocol involved 2 L of normal saline in 2 hours with no normal controls, making the results difficult to interpret. Salt depletion in others’ studies caused a reduction,¹¹,¹⁵ no change,⁴,⁹,¹⁰,¹²,²¹ or an increase,¹⁷,³⁷ in plasma K⁺.
Gordon et al. also reported normalization of plasma K+ with 5 months of moderate (50 mmol/d) Na+ restriction, but this study was unsatisfactory because pre- and poststudy plasma K+ levels were not given, only a plasma K+ level of 5.2 mmol/L after a further week of severe Na+ restriction (10 mmol/d) at the end of the 5-month study. This study followed a year of investigation and possible treatment, and the plasma K+ at its start may not have been the same as at original presentation. Dietary K+ intake, which was not stated, may have been reduced and can have a marked effect on $U_V$ in man and animals.26

As Perez et al.11 and Sanjad et al.11 point out, reduction of plasma K+ with salt restriction does not rule out a defect in K+ secretion.

There is nevertheless convincing evidence in genetic studies (below), as well as from the effects of thiazides, that the NCC is causing increased salt absorption in PHAII, and this may decrease the supply of Na+ to the ENaC, reducing K+ secretion. The obvious distinction clinically between low renin hypertension is often severe but may be absent in $\approx 20\%$ of cases,24,29 discussed later.

However, a diagnostic problem arises in distinguishing the hypertension in PHAII from low renin hypertension. Low renin hypertension is characterized by a suppressed plasma renin and normal plasma aldosterone level, together with salt-sensitive hypertension and possible relative volume expansion.24 Plasma K+ is usually normal, but levels of $\leq 5.3$ mmol/L have been reported.45 There is a good response to thiazides. If PHAII is suspected, plasma K+ and blood pressure of all relatives may help. The obvious distinction clinically between low renin hypertension and PHAII should be the hyperkalemia of the latter, together with the acidosis. Upper normal value of plasma K+ for adults is 4.6 mmol/L, but for children is 5.6 mmol/L, and for newborn infants is 5.7 mmol/L, although many laboratories allow $\leq 5.0$ mmol/L for adults. In 3 of the 27 studies of PHAII reported here, plasma K+ reached <6.0 mmol/L.24,28,29 As well, normotensive patients with PHAII present a difficulty. Ambulatory blood pressure monitoring may unveil masked hypertension in some cases.47 However, faced with only mild hyperkalemia, the only certain way to diagnose PHAII is to do genetic studies. Thus, Osawa et al.48 in 2003 found a mutant cullin3 ($CUL3$; see below) in a 1-year-old boy with hypertension and mild hyperkalemia, which sealed the diagnosis of PHAII.

There is marked variation in the clinical presentation of PHAII. On one hand, 1 example of PHAII was of a girl of 13 years who came to hospital seriously ill with a blood pressure of 240/140 mm Hg and a plasma K+ of 6.1 mmol/L. Urgent treatment with diazoxide failed, and then sodium nitroprusside intravenously and other antihypertensive drugs saved her.11 On the other hand,28 a 26-year-old man presented only on a low K+ diet and had a blood pressure of 150/95 and a plasma K+ of 8.2 mmol/L because of PHAII and no other clinical findings were found. No deaths from PHAII have been reported, possibly because of adaptation to the hyperkalemia, as also occurs in chronic renal failure. Our own patient,2 still on thiazide since age 18 years, died suddenly with chest pain at the age of 41 years, despite a recent plasma K+ of 4.4 mmol/L and blood pressure of 120/70 mm Hg.

There are some less controversial areas of PHAII. The cause of the acidosis is the hyperkalemia itself.5,7,11,12 Hypercalciuria occurs in some forms of PHAII.16,19,21,29,49 and will be discussed below.

The Discovery of With-No-Lysine K and Other Genes and Their Mutations

In 2000, Xu et al.50 cloned and characterized a mammalian gene, which coded for a serine-threonine kinase lacking lysine (=K) in a crucial site for catalytic action. This was named with-no-lysine K 1 (WNK1). Soon, WNKs 2, 3, and 4 were found, and together these kinases were regulators of electrolyte handling.51 PHAII-causing mutations have only been found in WNKs I and 4 so comments will be restricted to these kinases.

Wild-type WNK4 suppressed the NCC to limit Na+ reabsorption.52 WNK1 had no direct effect on NCC, but as an upstream regulator of WNK4 it can inhibit WNK4’s suppression of NCC.53 However, a shortened form of WNK1, kidney-specific (KS) WNK1 reversed the negative effect of WNK1 by reducing the abundance of NCC at the cell surface, so decreasing Na+ and Cl− reabsorption.54 The net effect on Na+ and Cl− was determined by a balance between these forms of WNKs.

The ENaC is suppressed by WNK4,55 but aldosterone reverses this.56 WNK1 stimulates ENaC.57 KS-WNK1 and aldosterone stimulate ENaC.58 WNK4 increases Cl− reabsorption by the paracellular pathway.59

WNK4 strongly inhibits ROMK in vitro,60 this too being reversed by aldosterone.56 WNK1 inhibits ROMK, but KS-WNK1 blocks this action.61 Dietary restriction of K+ reduces KS-WNK1, and dietary excess of K+ causes an increase in KS-WNK1 and so a rise in $U_V$.62 WNK4 inhibits the KCC (potassium chloride cotransporter),63 and it also increases the activity of TRPV5, a calcium reabsorptive channel.64

Mutant WNKs

Mutant WNK4 reverses the ability of WNK4 to inhibit the NCC,52 and so can lead to increased Na+ reabsorption, thereby helping to explain the suspected increase in extracellular fluid (ECF) volume in PHAII and the effectiveness of thiazides. Mutant WNK4 also can abolish the inhibitory effect of WNK4 on the ENaC, which may then contribute to increased Na+ reabsorption in PHAII.63 WNK1 mutations are because of deletions in intron 1 of $WNK1$ and increase $WNK1$ expression.53 Mutant WNK1 also increases KS-WNK1 but increases WNK1 more, so it may, therefore, prevent WNK4 inhibition of the NCC and accentuate ROMK inhibition.53

Mutant WNK4 strongly downregulates ROMK activity to an even greater degree than wild-type WNK4 so reducing K+ secretion.26,60 Mutant WNK4 also stimulates chloride reabsorption via the paracellular pathway.59 This is supportive evidence for the chloride shunt hypothesis of Schambelan et al.3
Patients with the WNK4 mutation causing their PHAII have thiazide-sensitive hypercalciuria. Hypercalciuria is associated with increased NCC activity, which increases intracellular Na\(^+\) and so suppresses basolateral Na\(^+\)/Ca\(^2+\) exchange. This decreases Ca\(^2+\) absorption from the DT. Interestingly, WNK1 mutant-induced PHAII does not lead to hypercalciuria.\(^{24}\)

In vivo studies have provided interesting data. Yang et al\(^{13}\) created mice knocked-in with a mutant Wnk4 (D561A). The D561A/+ mice developed hypertension, and average plasma K\(^+\) rose from 4.0 to 4.9 mmol/L (P<0.01), together with acidosis, all of which responded to thiazides. They found increased NCC expression and increased activity of ENaC. The increase in ENaC was probably the reason that a supranormal kaliuretic response occurred with intraperitoneal Na\(_2\)SO\(_4\). ROMK was not affected. This provided a good model of PHAII, in which increased NCC activity seemed to be the primary explanation. However, in man, the degree of hyperkalemia is much greater (Table S1) usually 6.0 to 8.5 mmol/L, and the effect of PRAN is not exaggerated, but is generally depressed. These findings do not support overactivity of the ENaC in human PHAII in spite of marked hyperkalemia. The lack of inhibition of ROMK in the mice created by Yang et al\(^{13}\) also differs from the findings of Shibata et al\(^{65}\) (below).

Further work was done by Chiga et al\(^{66}\) with mice triple knocked-in for the same Wnk D561A mutation and for mutated SPAK and OSR1. The last 2 are important in the activation of NCC. A PHAII phenotype failed to develop. This located the major genetic defect to the NCC.

However, WNK4 mutant D564A in humans, which corresponds to D561A in mice, caused marked inhibition of ROMK in Xenopus oocytes.\(^{26}\)

In another example, Ohta et al\(^{67}\) developed mice hypomorphic for Wnk4. These Wnk4 hypomorphs exhibited salt-sensitive hypotension. It was concluded that the physiological role of WNK4 is to activate NCC not to inhibit it, contradicting the general view. However, Gamba\(^{63}\) also postulated that although WNK4 inhibits NCC in a normovolemic state when the renin–angiotensin system is suppressed, in hypovolemic states angiotensin turns WNK4 into an activator of NCC to restore Na\(^+\) and volume.

Lalioti et al\(^{42}\) developed mice transgenic for a wild-type Wnk and for a PHAII mutant Wnk Q562E. The latter mice developed PHAII, with a rise in blood pressure and plasma K\(^+\), and showed an increase in NCC expression. These animals needed a limited K diet to survive, which emphasizes the importance of dietary K\(^+\) content in assessing and treating patients with PHAII.

Chowdhury et al\(^{68}\) recently created a reversible transgenic form of PHAII in mice. The Q562E Wnk mutation was used, and doxycycline was used to activate the process and withdrawal of doxycycline led to switching it off. Expression of NCC protein was increased. A rise in mean blood pressure of \(\approx 20\) mmHg and a rise in plasma K\(^+\) of \(\approx 1\) mmol/L occurred. Thiazide could reverse the findings. This reversible form of PHAII should serve well to study many aspects of PHAII (eg, the effect of induction and reversal on body weight and Na\(^+\) status in mice).

McCormick et al\(^{69}\) developed transgenic mice for NCC, which showed a 70% overexpression of NCC but failed to develop PHAII. The defect in PHAII because of a WNK1 mutation, therefore, may involve ion transport pathways other than the NCC or direct activation of NCC.

Hadchouel et al\(^{70}\) inactivated KS-WNK1 in mice. This resulted in a 2-fold increase in NCC in the DCT, but it did not produce PHAII. The degree of activation of NCC was not as strong as the effect of a WNK4 mutation. They considered that the increased NCC activity indirectly caused a compensatory downregulation of ENaC, so that despite increased NCC activity hypertension was prevented. Could the depression of ENaC in humans have a similar basis?

Thus, there is consistent evidence of increased Na\(^+\) reabsorption by the NCC, but definitive answers about the role of ROMK and ENaC are still to be found. Some of the differing conclusions between in vitro and in vivo work may arise from limitations in both methodologies.\(^{32}\)

### Other Gene Mutations Associated With PHAII

For \(>10\) years, mutations in WNK4 and WNK1 were the only recognized causes of PHAII. In 2012, Boyden et al\(^{71}\) reported new PHAII-causing mutations in kelch-like 3 (KLHL3) or cullin 3 (CUL3) in 52 kindreds that accounted for 79% of all the cases. WNK1 or WNK4 mutations were found in only 13%. Disease features in all were reversed by thiazides, which inhibit the NCC in the DT, suggesting that they are linked to Na\(^+\) and Cl\(^-\) reabsorption. Inheritance with KLHL3 mutations was in either the usual dominant form or for the first time in PHAII a recessive form.

There are significant differences in the phenotypic severity of PHAII. CUL3 mutants present at a younger age, have more severe hyperkalemia and acidosis, and 90% had hypertension before 18 years of age. In descending order of overall severity of PHAII were CUL3, recessive KLHL3, dominant KLHL3, WNK4 and WNK1. Our case\(^3\) would likely fit with a CUL3 mutation, in view of its severity. Supporting this work, Louis-Dit-Picard et al\(^{72}\) also identified KLHL3 as a gene coexpressed with the NCC responsible for PHAII.

Early in 2013, further remarkable data emerged. One should recall that WNK4 normally inhibits ROMK. Shibata et al\(^{65}\) noted that CUL3 and KLHL3 are components of an E3 ubiquitination ligase complex. They showed that mutants KLHL3 and CUL3 and mutations of WNK4 itself impair ubiquitination and the subsequent degradation of WNK4, which then accumulates. This leads to a fall in K\(^+\) secretion by inhibition of ROMK. Thus, these findings provide a genetic basis for the impaired K\(^+\) secretion in PHAII. It also keeps with previous evidence that WNK4 strongly inhibits ROMK.\(^{26,60}\) As yet, the functional consequences of KLHL3 binding to WNK1 are not known.

### Feedback, Volume, and Hypertension

Clearly, in PHAII, the plasma K\(^+\) stops rising at \(\approx 8.5\) mmol/L, and the ECF must stop expanding at some point. Some auto-suppression of the mechanisms leading to retention of Na\(^+\) and K\(^+\) must occur, or some other unexpected process occurs.

Hypertension in PHAII has been ascribed to ECF volume expansion. However, hypertension fails to develop for \(\approx 20\) or more years despite marked hyperkalemia in many patients with WNK1 and WNK4 mutant-induced PHAII.\(^{24,27}\) Lee et al\(^{10}\)
found total exchangeable body Na⁺ to be 37.8 mmol/kg body weight and plasma volume 31.8 mL/kg body weight (Table S1), both normal values in a patient with PHAII with a blood pressure of 170/110 mm Hg. Isenring et al11 found blood and plasma volumes subnormal in PHAII, and ECF volume close to upper normal or only slightly elevated. Other reports found that plasma volume was elevated a little.15,16 However, the central role of increased NaCl reabsorption in PHAII is established. As well, the marked sensitivity to the cold pressor test in some cases4,6,18 suggests an expanded ECF volume. It has been proposed that in some pathological states a brief period of salt retention can lead to increased vascular resistance, then a natriuresis with a fall in intravascular volume, but persistence of increased vascular resistance and hypertension.73 Another possible explanation for the discrepancy in rate of onset of hypertension might relate to a difference in the reaction of animals to chronic salt ingestion (in this case salt retention) on the luminal surface stimulating maxi-K⁺ channels.78,79

How Do Thiazides Work in PHAII?

Thiazide use in hypertension and presumably in PHAII causes an initial diuresis with hypovolemia, but after several weeks the diuresis ceases, and a milder state of hypovolemia persists.75 To explain a continuing benefit to the blood pressure, peripheral resistance may remain low:75 Possible thiazide effects on vascular tone are not clinically established.75

Thiazides could increase Na⁺ delivery to the ENaC to stimulate K⁺ secretion. However, another possible explanation for the control of plasma K⁺ by thiazides in PHAII may be that arginine vasopressin (AVP), released acutely by hypovolemia, then possibly chronically by continuing mild underhydration, might contribute to augmentation of K⁺ secretion (Figure S3). In isolated cortical renal tubules from dehydrated rabbits,76 we found that the intracellular K⁺ level fell by 15.8 mmol/L and medium K⁺ rose from 3.9 to 6.0 mmol/L. Field et al76 showed in micropuncture studies that AVP stimulates K⁺ secretion. AVP stimulates K⁺ secretion not only by the basolateral V2 receptors in the DT acting on ROMK but also through V1 receptors on the luminal surface stimulating maxi-K⁺ channels.78,79

In patients with PHAII, 2 striking results have been reported. Nahum et al10 found that water deprivation and 1-desamino-8-D-AVP both promptly increased U_k, V and reduced the elevated plasma K⁺ level to normal. Also, Rodríguez-Soriano et al15 found that the transtubular K⁺ gradient was markedly depressed in PHAII but rose to normal with 1-desamino-8-D-AVP administration and plasma K⁺ fell. In addition, hypercalciuria was reduced. Thiazides are known to correct the hypercalciuria of mutant WNK4 PHAII.34

It seems not to be known whether plasma AVP is increased in patients with PHAII (or others) treated with thiazides. AVP, released by mild underhydration, may be involved in maintenance of K⁺ secretion in PHAII under the influence of thiazides (Figure S3).

Perspectives

There is no clinical test of the function of ROMK, the main K⁺ secretory mechanism in the distal nephron. ROMK function must be considered indirectly. If patients show a decrease or even no increase in ENaC activity in the face of serious hyperkalemia, ROMK function must also come under suspicion. Genetic studies have recently reported depression of ROMK in PHAII. Increased NCC activity causing excess salt absorption accompanied by hypertension implies that the excess salt must be adequately dealt with on the basolateral side by a healthy Na⁺-K⁺ ATPase. Another recent consideration has been the possibility that activation of NCC may cause a compensatory downregulation of the ENaC to limit the hypertensive response.70 Others80 have also suggested possible cross-talk between these 2 main Na⁺ reabsorption channels. If downregulation of ENaC occurred on this basis in PHAII, it might decrease Na⁺ uptake and ease hypertension, but it would probably aggravate hyperkalaemia. Future research is needed on feedback control, the sometimes slow onset of hypertension and the effect of dietary K⁺ restriction in PHAII. Genetic testing of hyperkalemic cases of low renin hypertension may reveal some cases of PHAII. Measurement of AVP levels in patients with PHAII on thiazide therapy could be helpful.

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Disclosures

None.

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In the *Hypertension* article by Healy (Healy JK. Pseudohypoaldosteronism Type II: History, Arguments, Answers, and Still Some Questions. *Hypertension*. 2014;63:648–654), several corrections were needed.

1. On page 651, first column, in the third paragraph, the first sentence read, “Further work was done by Chiga et al\(^6\) with mice triple knocked-in for the same Wnk D564A mutation....” It has been changed to read, “Further work was done by Chiga et al\(^6\) with mice triple knocked-in for the same Wnk D561A mutation....”

   The publisher apologizes for the error.

2. On page 651, first column, in the fifth paragraph, the first 2 sentences read, “In another example, Ohta et al\(^\text{67}\) developed mice hypomorphic for Wnk. These Wnk hypomorphs exhibited salt-sensitive hypotension.” They have been changed to read, “In another example, Ohta et al\(^\text{67}\) developed mice hypomorphic for Wnk4. These Wnk4 hypomorphs exhibited salt-sensitive hypotension.”

   The author apologizes for the error.

These corrections have been made to the current online version of the article, which is available at http://hyper.ahajournals.org/content/63/4/648.full.
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1. Abstract.

In the search for the basis of essential hypertension, rare genetic disorders have been studied. Pseudohypoaldosteronism is an example. There are two types: Type I is outlined, and Type II fully reviewed. Type II is characterized by marked hyperkalemia in spite of a normal glomerular filtration rate, low renin levels and usually hypertension. Differentiation from low renin hypertension is discussed. The hyperkalemia in pseudohypoaldosteronism Type II may be due to direct inhibition of distal tubular potassium secretory mechanisms, or to indirect inhibition of epithelial sodium channels from lack of chloride or sodium reaching them. There is clinical and genetic evidence for all three theories, but their relative contributions are not established. Genetic evidence confirms over-activity of the thiazide-sensitive sodium chloride co-transporter, explaining the therapeutic efficacy of this drug. Inheritance of this condition is usually dominant, occasionally recessive. Five levels of severity have been found. In some patients vasopressin has resolved the hyperkalemia. Thiazide causes mild chronic hypovolemia, which might raise the vasopressin level. This could be a factor in the response of the hyperkalemia to thiazides, as vasopressin is known to directly stimulate potassium secretion.

2. How acetazolamide stimulates K⁺ secretion.

Acutely, acetazolamide decreases proximal tubular bicarbonate absorption, thus increasing bicarbonate delivery to the distal tubule causing increased K⁺ secretion.

3. The K⁺-Cl⁻ co-transporter.

Poorly reabsorbed anions, sulphate and bicarbonate (PRAN), can be used to stimulate K⁺ secretion. An unexpected factor has arisen in the response to PRAN from micro-puncture studies by Amorim et al.¹, in which some K⁺ secretion remained after the lumen negativity was collapsed by amiloride. An electro-neutral K⁺-Cl⁻ co-transporter was proposed as an explanation. However, from a physiological viewpoint, this transporter would only be operative in patients on a low salt diet or with a metabolic alkalosis, so PRAN can be used as a test of K⁺ secretion in PHAII in patients on a normal diet with acidosis.

4. PPARγ

In relation to hypertension, some comments were made regarding this relatively new topic. A recent report showing that dominant negative (DN) mutation in the nuclear hormone receptor peroxisome proliferator-activated receptor gamma (PPARγ) cause hypertension. DN PPARγ increases Rho-A and Rho-kinase activity which increase vascular tone. Their inhibitors decrease tone. These authors also found that cullin-3 correlated with increased Rho-A levels, but their suggestion that cullin-3 regulates arterial pressure needs further
confirmation, notably with direct evidence from manipulation of cullin-3. If so, it could lead to an interesting association with CUL-3 mutations.

References.


TABLE S1. Characteristics of Patients in 25 Reports of Pseudohypoaldosteronism Type II.

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<th>P.Cl− mmol/l</th>
<th>P.HCO3− mmol/l</th>
<th>BP mmHg</th>
<th>Cold Pressor Response</th>
<th>GFR ml/min</th>
<th>Plasma Renin</th>
<th>Plasma Aldosterone Response to thiazides</th>
<th>Plasma volume</th>
<th>Blood volume ml/m² S.A.</th>
<th>ECF volume ml/m² S.A.</th>
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F=familial, S=sporadic; cold pressor response ++=increased; plasma renin and aldosterone not numerical due to varying methodologies, L=low, N=normal, H=high; plasma volume *=ml/kg BW, otherwise ml/m² SA on normal salt intake; ENa=total body exchangeable Na, mmol/kg BW, except reference 21 where mmol/m² SA. In reference 24 average results given. ST = renal stone former. ++ = hypercalciuria. References 28 & 29 (omitted) involve varying average figures.
Figure S1. The effect of IV sodium sulphate for 90 minutes, then an injection of acetazolamide (Diamox) IV, on urinary $K^+$ excretion. Performed on two occasions in patient and in two separate control subjects. Time periods 30-40 minutes.
Figure S2. The effect of IV sodium sulphate for 90 minutes, then an injection of acetazolamide performed twice on the patient after 3 days of NaCl restriction (30 mmol/day), ethacrynic acid, and 9α fluorohydrocortisone. Two control subjects were given the same protocol. Time periods 30-40 minutes.
Figure S3. The effect of thiazide on Na\(^+\) and K\(^+\) homeostasis in PHA II. Acutely there is significant fluid loss and plasma vasopressin very likely increases but even in long-term use, mild hypovolemia persists and plasma vasopressin might be elevated.