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Renal Potassium Handling and Associated Inherited Tubulopathies Leading to Hypokalemia

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1. Introduction

Regulation of intracellular and extracellular potassium concentration is a fundamental process vital for cellular metabolism. Potassium intake, from the diet, is carefully balanced with excretion of potassium via the renal tract and gastrointestinal losses. Following a potassium load, extra-renal buffering of potassium occurs in peripheral tissues prior to its excretion. Thus potassium regulation is achieved by both short term and long term mechanisms. It has become clear that a series of potassium ion channels and transporter proteins have physiologically important roles throughout the length of the nephron. Our knowledge of normal physiological mechanisms has been increased by studying molecular defects responsible for variety of disorders associated with potassium transport. Studying renal tubular epithelial cell proteins and their regulation has improved the understanding of inherited tubular disorders which may cause hypokalemia.

Here, we review the normal renal tubular handling of potassium and discuss the molecular basis of clinical syndromes associated with hypokalemic alkalosis and hypokalemic forms of hypertension.

2. Renal tubular handling of potassium

2.1 Glomerular filtration and proximal tubule

Glomerular filtration produces >160 L of filtrate per day in a healthy adult, and 99% of this volume and majority of filtered solutes are reabsorbed along the nephron. The filtrate is identical to that of plasma with respect to water and solutes of low molecular weight, such as glucose, chloride, sodium, phosphate, urea, uric acid, creatinine and potassium.

The proximal convoluted tubule is responsible for reabsorption of glucose, amino acids, phosphate, sodium and low-molecular weight proteins. Around 65% of filtered sodium is reabsorbed in the proximal tubule. Potassium reabsorption is closely coupled to sodium transport (driven passively by the electrical gradient) and around 75% of filtered potassium is reabsorbed by the proximal convoluted tubule. The proximal straight tubule may secrete some potassium into the urine, and this secretion can be upregulated significantly in

patients with chronic kidney disease. Generalized defects in proximal tubule handling of solutes result in Fanconi syndrome. Specific proximal tubular handling defects leading to hypokalemia include proximal renal tubular acidosis, and have been recently reviewed elsewhere (Fry & Karet, 2007).

2.2 Potassium movement in the thin loop of Henle

Potassium may be secreted in the thin descending loops of Henle that penetrate the inner medulla, whilst the thin ascending loop is permeable to sodium and potassium and allows some uptake.

The thin ascending limbs of the loops of Henle (among other nephron segments) express the CLC-KA chloride channel, with its subunit Barttin. Polymorphisms in *CLCNKA* have recently been associated with a hyperreninemic hyperaldosteronism, implicating a key role for this channel in regulating renal salt handling and determining a set point for renin and angiotensin levels (Cappola, et al., 2011).

2.3 Potassium movement in thick ascending loop of Henle

In this part of nephron, ~25% of filtered sodium is reabsorbed together with ~15% of the filtered potassium. Transcellular sodium and potassium transport is achieved by the $\text{Na}^+\text{K}^+2\text{Cl}^-$ cotransporter (NKCC2) in the apical membrane, driven by the basolateral Na^+K^+ ATPase pump. Alternative names for NKCC2 include the bumetanide sensitive cotransporter, (BSC). NKCC2 is exclusively expressed in kidney tissue and is encoded by *SLC12A1* gene (Simon, et al., 1996a). The NKCC2 transporter may also transport ammonium ions, which compete with potassium ions.

Potassium entering the cell via NKCC2 is recycled back into tubule lumen via the apical membrane channel, ROMK1 (Simon, et al., 1996b), generating a lumen positive potential driving paracellular resorption of calcium and magnesium. Tight junction proteins, such as paracellin 1, mediate this divalent cation transport. ROMK1, also known as a KCNJ, is an ATPase sensitive potassium channel. Functional coupling of ROMK1 with NKCC2 is essential for NaCl reabsorption. Chloride exits the basolateral membrane of the TAL via the CLC chloride channel, CLC-KB, which is co-expressed with the subunit Barttin.

2.4 The distal convoluted tubule

The distal convoluted tubule is responsible for ~8% of filtered sodium reabsorption. This is achieved via an apical Na^+Cl^- cotransporter (NCCT, alias the thiazide sensitive sodium chloride transporter). This transporter is regulated by a group of serine-threonine protein kinases, including WNK4. In healthy individuals, WNK4 inhibits NCCT function by reducing its expression on the membrane.

Recent data has suggested that potassium channels control DCT function. An apically expressed potassium channel Kv1.1 is postulated to stabilise the luminal membrane potential in this nephron segment (Glaudemans, et al., 2009). and facilitates effective magnesium transport via the apical TRPM6 magnesium channel. At the basolateral membrane of the DCT a potassium channel Kir4.1 is thought to allow potassium recycling, allowing maintenance of the basolateral Na^+K^+ ATPase activity, the driving force for NaCl reabsorption via NCCT in this nephron segment (Bockenhauer, et al., 2009, Scholl, et al., 2009).

2.5 The collecting ducts

The connecting tubules, initial collecting tubule and the cortical collecting duct, are major sites of regulated potassium secretion. Indeed, potassium secretion in these nephron segments may be upregulated to exceed the filtered load of potassium. In addition, if potassium reabsorption is required, this part of the nephron and regions of the medullary collecting duct may reabsorb potassium. In the cortical collecting duct two important cell types mediate potassium transport: principal cells and intercalated cells.

In principal cells, sodium entry occurs via selective sodium channels (ENaCs), located on apical membrane. Potassium secretion in these cells occurs by a transcellular movement of potassium, mediated by a basolateral Na⁺K⁺ATPase pump and apical ROMK potassium channels. Potassium secretion is directly linked to sodium entry via ENaC.

The distribution of ENaC channels within the apical membrane is regulated by effects of aldosterone on the mineralocorticoid receptor. The ENaC channel has three subunits: alpha, beta and gamma encoded by genes *SCNN1A*, *SCNN1B* and *SCNN1C*. Alpha-intercalated cells in the cortical collecting duct mediate potassium reabsorption. An apical H⁺K⁺ATPase pump allows potassium reabsorption coupled to proton excretion, whilst an apical proton pump transports hydrogen ions into the lumen. In states of potassium depletion, there is upregulation of the apical H⁺K⁺ATPase pump in alpha intercalated cells.

3. When hypokalemia may be the presentation of an inherited tubulopathy?

Physiological serum potassium levels are usually tightly maintained between 3.5-5.0 mmol/L. Hypokalemia represents a deviation from this regulation and may be defined as mild, moderate or severe. Mild hypokalemia (Serum K⁺ 3.0-3.5 mmol/L) is usually asymptomatic whilst moderate hypokalemia (Serum K⁺ 2.5-3.0 mmol/L) may present with muscle weakness, myalgia, arrhythmias, cramps and constipation. With severe hypokalemia, (K⁺ <2mmol/L), hyporeflexia, flaccid paralysis and occasionally rhabdomyolysis occur. There are many causes of hypokalemia to be considered before a renal tubulopathy is suspected. These can be divided into an assessment of potassium intake, potassium distribution within tissues and potassium excretion (see Table 1). In order to assess this, a careful history including history of drugs and over the counter medications, and the presence of Gastrointestinal (GI) disturbance (vomiting or diarrhoea) should be sought. Clinical examination (including blood pressure (BP) and orthostatic changes in BP) is also necessary. This, combined with serum and urine biochemistry (including osmolality) will help to assess the causes of hypokalemia. Occasionally, a high WBC count may be associated with a spurious low serum potassium level. Pseudohypokalemia has recently been reported in 2 patients with hereditary spherocytosis secondary to AE1 mutations (Norgett, et al., 2011).

Potassium is present in a wide variety of foods (citrus fruits, vegetables, meat). Therefore, examples of inadequate intake are limited to anorexia, bulimia, alcoholism and starvation. Certain factors may affect the distribution of potassium from extracellular to intracellular compartments, leading to hypokalemia. Endogenous or administered insulin, catecholamines, beta-agonists and metabolic alkalosis will all promote cellular uptake of potassium. Excretion of potassium may be grouped into extra renal loss and renal loss. Extra renal loss of potassium is mainly via the gastrointestinal tract (GI) and may occur with diarrhoea, GI fistulas, and laxative abuse. Renal loss of potassium may be associated with a variety of acquired and inherited tubular disorders and drugs. Amphotericin B, aminoglycosides and cisplatin all increase renal potassium losses. Many diuretics, apart

from potassium-sparing ones, cause increased urinary losses of potassium. Magnesium depletion may also lead to renal potassium wasting. A 24 h urine collection can be used to assess renal potassium excretion in a hypokalemia patient. This should be < 15 mmol/24 h if there is extra renal potassium wasting. In a similar way, a spot urine for a potassium/creatinine ratio should be less than 1 in the presence of extra renal potassium wasting. Calculations of transtubular potassium gradient will give similar information. Urinary chloride will also be low in cases of significant GI volume losses (vomiting, diarrhoea, laxative abuse). If renal K wasting is suspected and confirmed then further thought regarding the blood pressure and acid base status of the patient aids the diagnosis of hypokalemia.

Extra-renal Hypokalemia		
Spurious	Extra-renal Loss	Redistribution
High WBC count	Diarrhoea	Acid-base disturbance
Hereditary spherocytosis	GI fistulas	Insulin excess
	Laxative abuse	Beta-adrenergic agonists
	Dietary insufficiency	Drugs / toxins e.g. Barium, catecholamines
	Cutaneous losses	Hypokalemic periodic paralysis (familial and thyrotoxic)

Table 1. Causes of extra-renal hypokalemia

Reasons to suspect an inherited tubulopathy may include evidence for a persistent electrolyte disturbance, the presence of renal impairment, nephrocalcinosis and renal stone formation (Sayer & Pearce, 2001). A detailed and extensive family history is necessary. In paediatric cases, faltering growth, abnormal growth patterns, developmental delay and deafness may all be clues to an inherited tubulopathy. Neonates may present with a salt-wasting crisis and are particularly sensitive to severe hypovolemia and electrolyte disturbance due to immature tubular physiology and low-salt intakes in standard feeds. With nephron maturation, the propensity to present with salt-wasting crises decreases. Individual tubular diseases can be differentiated by their serum and urine biochemical profiles (discussed below). Hypokalemia may be the only presenting feature of a tubulopathy and it is important to follow the diagnostic 'lead' to differentiate the many causes. Nephrocalcinosis should be thoroughly investigated and differential diagnosis such as hyperparathyroidism, vitamin D intoxication and sarcoidosis first excluded. Renal tubular disorders associated with nephrocalcinosis include Bartter's syndrome, Dent's disease, hypomagnesemic hypercalciuric nephrolithiasis, idiopathic hypercalciuria and distal renal tubular acidosis.

Renal tubulopathies are best investigated by urine pH and 24-hour urine collection for potassium, calcium, magnesium, citrate and phosphate along with serum biochemistry. Nevertheless, renal tubulopathies are rare and they should be considered only after

careful drug and dietary histories are taken, together with urine electrolytes and serum biochemistry.

4. Inherited tubulopathies leading to hypokalemic alkalosis

4.1 Bartter's syndrome

Bartter's syndrome is an autosomal recessive renal disorder described by Bartter et al. in 1962 (Bartter, et al., 1962). It has estimated incidence of 1.2 per million (Rudin, 1988). Impaired salt (sodium chloride) reabsorption in the thick ascending loop of Henle (TAL) leads to renal salt wasting and a hypokalemic metabolic alkalosis. The majority of cases present in the early neonatal period with salt-losing crises. An antenatal diagnosis can also be suspected if a pregnancy is complicated by polyhydramnios or premature birth (Sieck & Ohlsson, 1984). Bartter's syndrome is also associated with short stature, growth retardation in infancy, muscle weakness, polyuria and polydipsia. Some children have characteristic facies that are triangular-shaped with a prominent forehead, large eyes, protruding ears and a drooping mouth. Blood pressure is normal. Bartter's syndrome should be suspected in patient presenting with the above symptoms and signs and the following laboratory findings: hypokalemic alkalosis, high urinary chloride and urinary potassium levels and normal or raised urinary calcium level. Serum magnesium levels are typically normal or mildly low.

The biochemical abnormalities are a consequence of renal salt wasting in the TAL. This stimulates the renin-angiotensin II-aldosterone system (RAAS) and causes hyperplasia of juxtaglomerular apparatus, a feature originally noted by Bartter (Bartter, et al., 1962). Raised RAAS increases sodium reabsorption in the distal nephron (via ENaC) in exchange for K^+ and H^+ , which leads to hypokalemic alkalosis. Increases in prostaglandin E₂ synthesis aggravate the salt wasting by its effect on ROMK1 and NKCC2. Despite raised RAAS, leading to hyperreninemia and hyperaldosteronism, patients with Bartter's syndrome remain normotensive. The various phenotypes of Bartter's syndrome are now more simply classified by their underlying genetic mutation.

Antenatal Bartter's syndrome (Type 1) is caused by homozygous or compound heterozygous mutation in the *SLC12A1* gene, encoding NKCC2 (Simon, et al., 1996a). NKCC2 is kidney specific, electroneutral transporter protein, located at the apical membrane of the TAL (Simon, et al., 1996a).

Type 1 is a severe form of Bartter's syndrome which may present in utero with marked polyhydramnios and premature birth. Amniocentesis shows high chloride (and aldosterone) levels. Analysis of a pregnant mother's urine may also suggest the diagnosis, demonstrating low Na^+ , Cl^- and Ca^{2+} (Matsushita, et al., 1999). A definitive diagnosis may be made using mutational analysis of DNA from amniocytes (Konrad, et al., 1999).

Prenatal diagnosis is important as indomethacin may be a useful treatment for polyhydramnios (Smith et al., 1990). and early neonatal treatment may be life saving. Neonates typically present with severe salt-wasting crises, hypokalemic alkalosis, vomiting and diarrhoea. The latter two symptoms are due to renal activation of prostaglandin synthesis, as a consequence of hypokalemia. A feature that distinguishes this type from others is marked hypercalciuria, which causes nephrocalcinosis and osteopenia in infancy. Treatment is with potassium supplements, often combined with potassium-sparing diuretics (such as spironolactone and amiloride) and inhibitors of

prostaglandin-stimulated renin release (such as indomethacin and specific cyclooxygenase (COX-2) inhibitors).

Antenatal Bartter's syndrome (Type 2) is clinically indistinguishable from Type 1. It is caused by loss-of-function mutations in the *KCNJ1* gene (alias *ROMK1*) encoding the ATP-sensitive potassium channel ROMK1, also located apically in the TAL (Simon, et al., 1996b). ROMK1 allows potassium recycling from the TAL cells back to the luminal filtrate, and is electrogenic driving paracellular reabsorption of sodium, calcium and magnesium. ROMK1 is a regulator of the NKCC2 co-transporter and functional coupling of ROMK1 with NKCC2 is essential for effective NaCl reabsorption. Therefore, functional defects in the ROMK1 protein severely disrupt electrogenic chloride reabsorption in TAL, resulting in a similar antenatal phenotype, although the hypokalemia may be less severe (Kurtz, 1998). The treatment of Bartter's syndrome Type 2 is the same as for Bartter's syndrome Type 1.

Classic Bartter's syndrome (Type 3) is caused by mutations in *CLCNKB* encoding the CLC chloride channel member CLC-KB. This channel protein is located on the basolateral membrane of TAL cells, where it co-localizes with Barttin. The presentation of Type 3 / Classic Bartter's syndrome tends to be with weakness and hypovolemia during early childhood, with a milder defect of urinary concentrating ability and normal urinary calcium levels. Hence, nephrocalcinosis or nephrolithiasis is rarely a feature. Severe and chronic hypokalemia may lead to medullary cyst formation (Ariceta & Rodriguez-Soriano, 2006). Hyperuricemia may occur due to volume contraction. Renal function is usually preserved initially but may decrease as a result of chronic hypokalemia and tubulointerstitial damage. The primary defect alters chloride reabsorption, with defective basolateral exit of chloride via CLC-KB in the TAL. Clinical features in Type 3 Bartter's syndrome include short stature and salt wasting. However, *CLCNKB* mutations may present with variable phenotype, ranging from neonatal salt losing crises to asymptomatic patients detected in adulthood by routine electrolyte testing (Konrad, et al., 2000). A milder phenotype may be confused with Gitelman's syndrome. Indeed, some patients with *CLCKNB* mutations have profound hypomagnesaemia and hypocalciuria, closely mimicking Gitelman's syndrome (Jeck, et al., 2000, Konrad, et al., 2000).

Bartter's syndrome Type 4A is a form of infantile Bartter's syndrome caused by a mutation in the gene *BSND* encoding Barttin (Estevez, et al., 2001). Barttin is two-transmembrane protein and an essential subunit of the CLC chloride channels CLC-KB and CLC-KA. Barttin modulates both membrane insertion and function of both CLC-KA and CLC-KB (Scholl, et al., 2006, Waldegger, et al., 2002). In the kidney Barttin is expressed in the thin limb and the TAL of Henle. This type of Bartter's syndrome is associated with congenital sensorineural deafness (termed BSND) which may explained by the localisation of Barttin protein as a subunit for CLC-KA in inner ear cells. Again, the phenotype can be severe neonatal salt wasting or a more mild adult presentation (Miyamura, et al., 2003).

Type 4B Bartter's syndrome is associated with simultaneous mutations in both chloride channel genes, *CLCNKA* and *CLCNKB* resulting in sensorineural deafness and renal salt wasting. This form of Bartter's syndrome is rare but should be considered when BSND mutations are not detected. Children from consanguineous parents with homozygous mutations in both genes (Schlingmann, et al., 2004) and non consanguineous parents with digenic compound heterozygous mutations have been described (Nozu, et al., 2008).

Bartter's syndrome Type 5 is better known as autosomal dominant hypocalcaemia with Bartter's syndrome. Mutations in the *CASR* gene encoding the Calcium-sensing receptor can occasionally be associated with a Bartter's like phenotype (Vargas-Poussou, et al.,

2002, Watanabe, et al., 2002). The mechanism leading to this phenotype is thought to be constitutive activation of the mutant CASR, located on the basolateral membrane of the TAL, by normal serum calcium levels, leading to a secondary inhibition of sodium chloride transport in the TAL, thus mimicking Bartter's syndrome. Of note, the degree of metabolic alkalosis in these patients was mild (Sayer & Pearce, 2003).

4.2 Pseudo Bartter's syndrome

Pseudo antenatal Bartter's syndrome has been reported in a preterm child with cyanotic heart disease treated with high dose prostaglandins (Langhendries, et al., 1989). The biochemical phenotype of Bartter's may also be mimicked by loop diuretic abuse. Hypokalemic metabolic alkalosis may also be seen in patients with cystic fibrosis, bulimia and laxative abuse. In such cases, urinary chloride levels are low, given the salt wasting is not secondary to a tubular defect.

4.3 Gitelman's syndrome

Gitelman's syndrome refers to an autosomal recessive congenital condition, which is characterized by a hypokalemic alkalosis with hypocalciuria and often hypomagnesaemia (Gitelman, et al., 1966). Gitelman's syndrome has incidence of 1:40,000, which makes it one of the commonest inherited tubulopathies. The electrolyte disturbance mimics that of chronic thiazide diuretic use. Patients with this syndrome have genetic defect in the *SLC12A3* gene encoding the thiazide-sensitive sodium-chloride cotransporter (NCCT) (Simon, et al., 1996a). This cotransporter is located in the apical membrane of distal convoluted tubular (DCT) cells. Defects in NCCT result in reduced sodium reabsorption in the DCT, leading to increased delivery of sodium to the CCD. This leads to increased absorption of sodium via ENaC, coupled with K excretion, leading to hypokalemia. Subsequent stimulation of K reabsorption via H⁺K⁺ATPase in intercalated cells results in a metabolic alkalosis. Within the DCT, transcellular absorption of magnesium (via the apical magnesium channel TRPM6 and a putative basolateral Na⁺/Mg²⁺ exchanger) is also reduced. The exact mechanism of hypocalciuria has been the subject of speculation for some time. Evidence from studying thiazide treatment in murine models now suggests that as result of volume contraction enhanced proximal tubular sodium reabsorption occurs, and with it, an increase in proximal tubular paracellular absorption of calcium (Nijenhuis, et al., 2005).

Gitelman's syndrome is often asymptomatic into adult life, presenting with weakness, paraesthesia, fatigue and tetany. Salt craving may be a feature. Typically the patients are normotensive and may have polyarthritides and chondrocalcinosis secondary to severe and longstanding hypomagnesaemia (Cobeta-Garcia, et al., 1998). Clinical diagnostic features for Gitelman's syndrome include a low urinary calcium:creatinine ratio (typically <0.2), low serum magnesium (<0.65 mmol/L) and a hypokalemic metabolic alkalosis, once thiazide use is ruled out. Surreptitious ingestion of thiazide may be ruled out by screening the urine. Cisplatin nephrotoxicity may resemble Gitelman's syndrome as may some of the magnesium wasting tubulopathies (Knoers et al., 2003) discussed below. Treatment is with lifelong potassium and magnesium supplements and diet rich in sodium and potassium. Amiloride and spironolactone may also be useful treatments to ensure maintained serum potassium levels. Occasionally, a severe childhood onset phenotype

may occur, mimicking Bartter's syndrome in terms of severity. Early replacement of electrolytes is important and in common with Bartter's syndrome, NSAIDs have been used to good effect to promote growth in these children (Liaw, et al., 1999). Patients with Gitelman's syndrome have very good long term prognosis, however sudden cardiac deaths associated with prolonged QT intervals and cardiac arrhythmias have been reported (Cortesi, et al., 2010). In keeping with this less than benign phenotype, Gitelman's patients may have severe symptoms which are debilitating. For example, weakness, tetany and cramps are often so severe that emergency admissions to hospitals are required for intravenous potassium and magnesium replacement. Indeed, following quality of life questionnaires, Gitelman's patients' scores were comparable to patients with congestive heart failure (Cruz, et al., 2001). As discussed previously, mutations in *CLCNKB* encoding the basolateral chloride channel can also cause a Gitelman's phenotype. CLC-KB is expressed in the DCT as well as the TAL, accounting for this phenotypic overlap. Indeed, patients within the same family with identical *CLCNKB* mutation may present with a spectrum of phenotypes including both Bartter's and Gitelman's syndrome (Zelikovic, et al., 2003). In a recent large cohort of 448 Gitelman's patients, *CLCNKB* mutations accounted for just 3% of cases (Vargas-Poussou, et al., 2011).

4.4 "Pseudo" Gitelman's syndrome and reverse phenotypes

The molecular basis for the syndrome of autosomal dominant hypomagnesemia has recently been made (Glaudemans, et al., 2009). This syndrome presents in childhood with recurrent muscle cramps, tetanic episodes, tremor, and muscle weakness. Patients have low serum Mg^{2+} levels, while serum K^+ and Ca^{2+} levels and urinary Ca^{2+} excretion are not affected. This condition is therefore biochemically different from both Gitelman's syndrome and other forms of inherited hypomagnesemia. Mutations were identified in the *KCNA1* gene, encoding the Kv1.1 potassium channel, expressed in the apical membrane of the DCT and connecting tubule (Glaudemans, et al., 2009). This potassium channel is thought to work to stabilize the apical membrane, in the context of TRPM6 mediated magnesium reabsorption in these nephron segments. Loss of function mutations leads to a depolarisation of the membrane and defective magnesium reabsorption, resulting in hypermagnesuria and hypomagnesemia.

In contrast to Gitelman's, the biochemical phenotype of patients with familial hypomagnesemia with hypercalciuria and nephrocalcinosis secondary to mutations in the genes encoding claudin 16 and claudin 19 includes hypercalciuria rather than hypocalciuria. Isolated dominant hypomagnesemia caused by mutations in *FXD2* leads to hypocalciuria, and can resemble Gitelman's syndrome. Patient may be relatively symptom free as magnesium levels are mildly low, and may also have chondrocalcinosis (Geven, et al., 1987, Meij, et al., 2000). Recently a complex syndrome including epilepsy, ataxia, sensorineural deafness and a tubulopathy resulting in Gitelman's like biochemical derangement has been described (Bockenhauer, et al., 2009, Scholl, et al., 2009). The syndrome has been named both EAST syndrome (Bockenhauer, et al., 2009) and SeSAME syndrome (Scholl, et al., 2009). The biochemical defects are hypokalemia, metabolic alkalosis, hypomagnesemia and hypocalciuria. Mutations have been identified in the *KCNJ10* gene encoding the renal Kir4.1 potassium channel, located on the basolateral membrane of the DCT. Loss of function mutations therefore disrupt DCT tubular handling

of salts in a similar manner to NCCT defects, leading to secondary activation of the renin-angiotensin-aldosterone axis.

Recent molecular genetic studies have identified the basis of Gordon syndrome, also known as pseudohypoaldosteronism type II or chloride shunt syndrome, an autosomal dominant form of hypertension. It is noteworthy and mentioned here given that the diagnostic features resemble a mirror image of Gitelman's syndrome. This includes hyperkalemia, hypertension and hyperchloraemic metabolic acidosis. It can present in early neonatal period with hyperkalemic acidosis or later in life with hypertension. Additional clinical features include short stature, muscle weakness, intellectual impairment and dental abnormalities. Laboratory findings include low fractional excretion of sodium, low renin and aldosterone levels and normal renal function. This syndrome is caused by mutations in the gene encoding WNK4 (Laloti, et al., 2006), which is a member of serine-threonine protein kinases. In humans, WNK4 is present exclusively in kidney. WNK4 acts as an inhibitor of thiazide-sensitive sodium-chloride co-transporter (NCCT). Mutations in WNK4 relieve this inhibition causing excess sodium retention and subsequent hypertension. Hyperkalemia is explained by inhibition of potassium ROMK channels. Treatment of Gordon syndrome is with low potassium diet and use of thiazide diuretics. Sodium loading should be avoided as it may worsen hypertension.

4.5 Liddle's syndrome

Liddle's syndrome, also called pseudoaldosteronism, is an autosomal dominant disorder which is characterized by early onset severe hypertension, suppressed renin and aldosterone levels and hypokalaemic metabolic alkalosis (Liddle, et al., 1963). This syndrome is a familial renal disorder simulating primary aldosteronism but with negligible aldosterone secretion and is caused by up regulation of epithelial Na channel (ENaC) located in the collecting duct. Up regulation leaves the ENaC in 'open' state which enhances sodium reabsorption and causes hypertension. ENaC is a heterotrimeric protein, its three subunits named alpha, beta and gamma. Mutations in the beta and gamma subunits can cause constitutive channel opening (Hansson, et al., 1995a, Hansson, et al., 1995b). The beta and gamma subunits of ENaC are encoded by *SCNN1B* and *SCNN1G* genes, respectively. A key regulator of ENaC is NEDD4L, which is able to ubiquitinate ENaC leading to its removal from the luminal cell membrane in the renal collecting ducts. It has been postulated that loss of function defects in NEDD4L or alternative splicing of NEDD4L may also lead to hypertension (Dunn, et al., 2002). Patients with Liddle's syndrome are often asymptomatic and they are usually investigated after incidental finding of hypertension. Affected children may have symptomatic polyuria and polydipsia and faltering growth. A strong family history of premature stroke may prompt investigations. Liddle's syndrome should be suspected in a young person with high blood pressure, a family history of hypertension and low serum potassium together with a metabolic alkalosis. However, Liddle's syndrome may mimic essential hypertension as hypokalemia may not always be present (Rossi, et al., 2011). Indeed, genetic variants in ENaC genes may be found in patients with presumed essential hypertension (Hannila-Handelberg, et al., 2005). In Liddle's syndrome, there is a high variability of penetration which appears to be dependent on environmental factors such as dietary salt intake. Because serum and urine aldosterone levels are low, differential diagnosis should include certain forms of congenital adrenal hyperplasia, syndrome of apparent mineralocorticoid

excess, chronic licorice ingestion and carbenoxolone therapy. Treatment of Liddle's syndrome consists of sodium restriction and potassium-sparing diuretics, like amiloride and triamterene, which directly inhibit the ENaC. There is no benefit of using mineralocorticoid antagonists, such as spironolactone, as in this syndrome the up regulation of ENaC is not mediated by aldosterone.

4.6 Syndrome of Apparent Mineralocorticoid Excess (AME)

This autosomal recessive syndrome is characterised by hypertension, hypokalemia, metabolic alkalosis, with suppressed renin and aldosterone levels. Hypercalciuria and nephrocalcinosis may occur. Typically, an affected child will have polyuria and polydipsia, low birth weight and faltering growth. The molecular basis for this syndrome is secondary to mutations in the *HSD11B2* gene encoding the enzyme 11-beta-hydroxysteroid dehydrogenase 2 (Wilson, et al., 1995). This enzyme normally inactivates cortisol to cortisone, preventing overstimulation of the mineralocorticoid receptor (MR). Mutations lead to an excess of cortisol which is able to have a mineralocorticoid-like affect and stimulate sodium retention, volume expansion and renin and aldosterone suppression.

This syndrome may be mimicked by licorice ingestion (Walker & Edwards, 1994). Licorice contains glycyrrhizic acid, which inhibits 11-beta-HSD2. Carbenoxolone also inhibits this enzyme. The treatment of choice for AME is a mineralocorticoid receptor blocker such as spironolactone or eplerenone.

4.7 Activating mutations of the mineralocorticoid receptor

In a family with familial hypertension, hypokalemia and suppressed aldosterone levels, heterozygous mutations were identified in the *NR3C2* gene encoding the mineralocorticoid receptor (MR), resulting in a gain of function (Geller, et al., 2000). Additionally, the specificity of the MR was altered such that progesterone was able to bind to it and activate it. Thus pregnant females in this family presented with severe hypertension.

4.8 Glucocorticoid remediable hypertension

Glucocorticoid remediable hypertension (also known as familial hyperaldosteronism type I) is characterised by autosomal dominant hypertension, low plasma renin levels, normal plasma aldosterone levels and hypokalemia (McMahon & Dluhy, 2004). The age of onset of hypertension is usually in teenage years, but may be in adulthood. Hypertension is typically refractory to treatment. The molecular basis for disease is secondary to a chimeric gene, involving *CYP11B1*, encoding 11-beta-hydroxylase and *CYP11B2*, encoding aldosterone synthase. The chimeric gene results in aldosterone synthesis under the regulatory control of ACTH, resulting in hyperaldosteronism (Lifton, et al., 1992). Thus, the causative mutation affects the cortical collecting duct indirectly, and therefore this is not a "tubulopathy". Traditionally, diagnosis has been made by a dexamethasone suppression test, which results in reduced plasma aldosterone levels. A specific urinary profile of 18 oxotetrahydrocortisol and 18 hydrocortisol may be sought, but molecular genetic testing also allows a definitive diagnosis. Treatment with glucocorticoids (using shorter acting agents prednisone or hydrocortisone) is often effective, but additional antihypertensives may be needed as adjuncts.

5. Conclusions

The ability to provide a definitive molecular genetic diagnosis to a patient with an inherited tubulopathy allows a confidence in the diagnosis, despite phenotypic variabilities (which may be intrafamilial). A molecular genetic diagnosis also allows the targeted pharmacology to be employed to achieve normalization / improvement in symptoms, serum biochemistry and blood pressure. The discovery of renal tubular transporters and channels has allowed significant gains in our understanding of this group of renal diseases, with families with inherited tubulopathies providing the ultimate “animal model”. Although perhaps uncommon, the discovery of the molecular players of salt and water handling within the nephron has allowed applications to be made to sufferers of “essential hypertension”.

It is certainly true that a patient with hypokalemia / metabolic alkalosis, no matter how mild, warrants further evaluation to determine the underlying cause.

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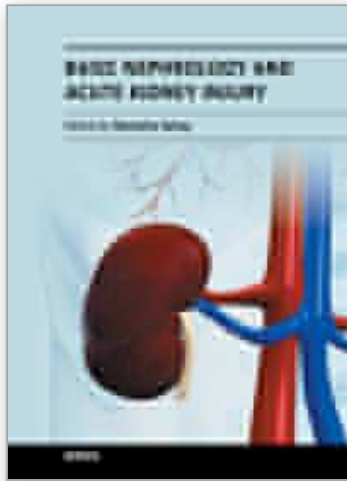
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