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Review

Potassium-related inherited tubulopathies

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Abstract. Hyper- and hypokalemia may carry severe clinical consequences. Different regulatory mechanisms, including the kidney, exert a tight regulation of plasma potassium levels. The renal pathway of potassium handling begins in the proximal tubule followed by the fine-tuning of its secretion or absorption at the distal tubule, including the thick ascending limb of Henle's loop, the distal convoluted tubule and the cortical collecting duct. Genetic studies in recent years have clarified the role of specific tubular channels and transporters in the pathogenesis of unique hyper- and hypokalemic tubulopathies, some of them non-hypertensive (pseudohypoaldosteronism, Bartter and Gitelman syndromes) and others hypertensive by definition (including Liddle and Gordon syndromes). This article reviews the genetic and clinical spectrum of hypokalemic and hyperkalemic tubulopathies.

Keywords. Bartter syndrome, Gitelman syndrome, loop of Henle, Liddle syndrome, Gordon syndrome, aldosterone.

Physiology of renal potassium handling [1]

Potassium (K) is mostly absorbed along the proximal tubule, generally through paracellular pathways. K transport is not specifically regulated in this portion of the nephron, and net K absorption is closely coupled to sodium and water absorption. Although hypokalemia is seen in proximal tubular dysfunction (as exists in Fanconi syndrome), its underlying etiology is usually secondary to distal tubular mechanisms. At the medullary thick ascending limb of Henle's loop (TAL) hypotonic urine is generated due to a net absorption of sodium chloride (NaCl) (Fig. 1). Transepithelial chloride (Cl^-) transport in the TAL is a complex process that involves coordinated interplay between the luminal, bumetanide-sensitive Na^+–K^+–$2Cl^-$ co-transporter (NKCC2), the luminal, ATP-regulated, inwardly rectifying K channel (ROMK), the basolateral Cl^- channel (ClC-Kb), as well as other co-transporters and channels. Cl^- is absorbed across the luminal membrane of the TAL cell by the activity of NKCC2. The low intracellular Na^+ and Cl^- concentrations, generated by the basolateral Na^+–K^+-ATPase pump and ClC-Kb channel, drive this co-transporter. In addition, ROMK enables functioning of NKCC2 by recycling K^+ back to the renal tubular lumen. Cl^- transport in the distal convoluted tubule (DCT) occurs primarily via the luminal, thiazide-sensitive NaCl co-transporter (TSC). The exit of Cl^- to blood is also mediated via basolateral Cl^- channels.

The main nephron site where K secretion is regulated is the cortical collecting duct (CCD), mainly via the effects of aldosterone (Fig. 2). Intraluminal secretion of K in the CCD requires two elements. First, a lumen-negative voltage must be generated via electrogenic absorption of Na^+ ions. Second, 'open' K channels must be present in the luminal membrane of principal cells. Absorption of Na^+ in the CCD occurs via the epithelial Na^+ channel (ENaC) in the luminal membrane of principal cells [2] and K secretion occurs through a ROMK isoform. Aldosterone leads to an increase in Na^+ flux through the ENaC [3], which can be blocked by K-sparing diuretics such as amiloride [4] (Fig. 2). Under conditions of K^+ depletion, the intercalated cells of the CCD become a site for net K^+ absorption. The H^+-K^+-ATPase pump in these cells can be upregulated by the decrease in total body K^+, result-

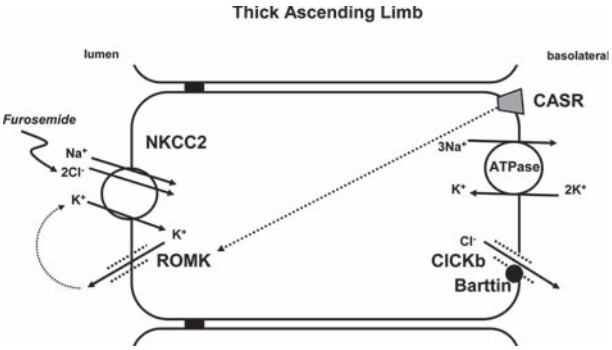

Figure 1. In the figures, the diuretic drug names (amiloride, furosemide, thiazide and aldosterone) are written in italic and point with a curved arrow to the specifically affected channel or molecule. In the thick ascending limb of Henle's loop, K absorption proceeds by electroneutral Na^+-K^+-$2Cl^-$ cotransport, the low intracellular Na^+ and Cl^- concentrations providing the driving force for transport. The apical K channel (ROMK) allows K recycling and provides substrate to the apical Na^+-K^+-$2Cl^-$ cotransporter. Loop diuretics act by competing for the Cl^- site on this carrier. Cl^- exits on the basolateral site via the CLCKb channel. Barttin acts as a subunit of CLCKb (and CLCKa). *CASR*: calcium sensing receptor.

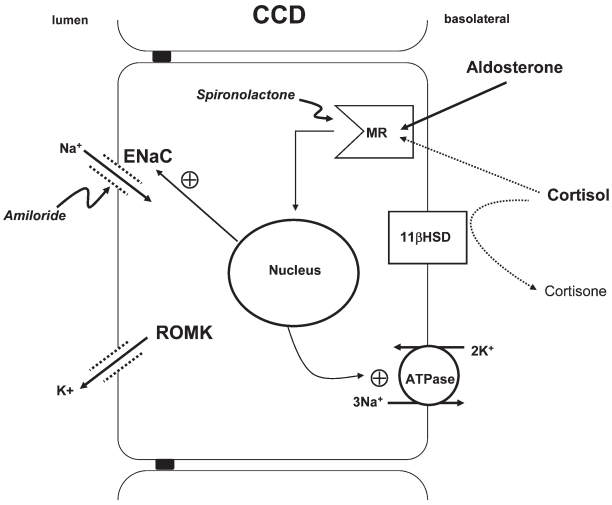

Figure 2. K^+ transport at the principal cell of the cortical collecting tubule (CCD). *MR*: mineralocorticoid receptor; *11βHSD*: 11 *β*-hydroxysteroid dehydrogenase; *ENaC*: epithelial Na channel. ROMK isoforms also exist in this tubular segment. The effects of aldosterone and cortisol through the MR at the CCD results in increased transcription of subunits of ENaC and the basolateral Na^+-K^+-ATPase pump. Cortisol and aldosterone have equal affinity for the intracellular MR. However, in aldosterone-sensitive tissues such as the kidney, the enzyme 11*β*HSD converts cortisol to inactive cortisone.

ing in enhanced K^+ absorption. This pump may be partly responsible for the maintenance of metabolic alkalosis in conditions of K^+ depletion.

There are two separate functions of aldosterone: NaCl absorption and induction of kaliuresis. Release of aldosterone in response to a low effective circulating volume is mediated via the renin-angiotensin system [5]. Hyperkalemia also causes the direct release of aldosterone from adrenal cortical cells. Hence, aldosterone can be released in response to two different stimuli. Because an open ENaC is needed to support both of the functions of aldosterone, individual responses to aldosterone could be achieved by regulation of Cl^- absorption and/or K^+ conductance in the CCD. This seems to occur by the regulation of HCO_3^- absorption to the DCT, since an alkaline luminal fluid pH may regulate the permeability for Cl^- in the CCD [6]. Cl^- absorption in the CCD takes place mostly by the paracellular pathway [7].

Bartter syndrome

Bartter syndrome (BS) was first described more than 35 years ago. Over the years, and even before the exact genetic defect was known, pathophysiological studies hinted at a basic defect in Cl^- absorption at the TAL. The syndrome is usually diagnosed based on several clinical and laboratory criteria: Cl^--resistant hypokalemic, hypochloremic metabolic alkalosis, normotensive hyperreninemic hyperaldosteronism, juxtaglomerular apparatus hyperplasia and an autosomal recessive inheritance. With time, both phenotypic and genetic heterogeneities for this syndrome were defined. The established clinical BS variants include the neonatal (or antenatal) variant, the 'classical' variant and Gitelman syndrome (Table 1).

Neonatal BS

The neonatal (or antenatal) variant of BS is characterized by polyhydramnios and prematurity, followed by postnatal polyuria, hypercalciuria and nephrocalnosis. Usually normomagnesemia is seen (contrary to the other BS variants). In addition, a high renal synthesis and urine excretion of prostaglandins exist, providing some explanation for the usual good response to prostaglandin synthesis inhibitors (such as indomethacin). A mild dysmorphism has been described for some children (prominent forehead and eyes, large ears). This variant can be ascribed to mutations in three different genes:

1. The NKCC2 gene or (*SLC12A1)* which resides on chromosome 15q [8]. This transporter is the site of action of the clinically important diuretics furosemide and bumetanide. Not surprisingly, this clinical phenotype is similar to the biochemical abnormalities induced by chronic furosemide therapy (which inhibits NKCC2).
2. The ROMK gene (*KCNJ1*), located on chromosome 11q24–25 [9]. A normal ROMK function at the luminal side of the TAL is needed for K recycling back to the luminal space, thus enabling the continuation of NKCC2 action.

3. We originally described the combination of antenatal BS and sensorineural deafness [10] and localized this disease locus to Chromosome 1p31 [11]. Subsequently, this gene has been identified as *Barttin*, a *β*-subunit for ClC-Ka and ClC-Kb Cl^- channels [12]. Barttin can be detected in basolateral membranes of the renal tubule and inner ear epithelium [13] and mediates Cl^- exit in the TAL and Cl^- recycling in K-secreting strial marginal cells in the inner ear. The expression of both ClCKa and ClCKb in the inner ear's cells explains why patients with BS due to ClCKb only (as seen in 'classical' BS) do not develop deafness. A recent case report on BS associated with deafness in a ClCKa + ClCKb double homozygote mutant patient further reiterates this point [14]. Other descriptions have correlated this BS variant with progressive renal insufficiency [15], but our original cohort did not show this complication at all [16], suggesting the possibility of differing susceptibility for renal damage in different types of mutations in this newly identified gene.

Because Cl^- absorption in the TAL is a prerequisite for the generation of medullary hypertonicity, affected BS individuals lose their ability to concentrate urine. The consequent polyuria (even during the fetal period) may be the reason for the associated polyhydramnios in pregnancies where the fetus is affected by BS. In contrast, there have been no consistent, genetically well-characterized reports on accompanying polyhydramnios for other tubulopathies, such as type I pseudohypoaldosteronism (PHA) [17] or even nephrogenic diabetes insipidus. Actually, several children who were originally reported to have PHA associated with polyhydramnios [18] are now genetically characterized as having ROMK channel defects. Thus, polyhydramnios in the absence of fetal anomalies and maternal diabetes should raise the suspicion for antenatal BS.

Classical BS

The 'classical' type of BS is an intermediate form between the neonatal type and the Gitelman syndrome, with an early childhood presentation, a mildly elevated urinary calcium excretion rate and an almost normal urine concentrating capacity. The underlying defect for this variant is usually mutations in the basolateral Cl channel (*CLCKb*) [19].

Gitelman syndrome

The Gitelman variant of hypokalemic tubulopathy is characterized clinically by its later childhood onset and the associated hypocalciuria and hypomagnesemia (the latter being sometimes more accentuated with time). The vast majority of patients with Gitelman syndrome

Table 1. Hypokalemic-related tubulopathies.

	Phenotype	Mutated gene	Tubular cell(s) involved	Heredity	Special features	
Normotensive	Neonatal BS	NKCC2	TAL	AR	Polyhydramnios, prematurity, nephrocalcinosis, normomagnesemia	
		ROMK	TAL	AR		Transient neonatal hyperkalemia. Minimal hypokalemia later
		Barttin	Distal tubule	AR		Deafness
	Classical BS	ClCKb	TAL	AR	Infancy/childhood onset, +/– hypomagnesemia*	
		CaSR	TAL	AR	Hypercalciuric hypoparathyroidism	
	Gitelman syndrome	TSC	DCT	AR	Late childhood/adolescent onset, hypomagnesemia, hypocalciuria*	
Hypertensive	Liddle	ENaC	CCD	AR	Low renin hypertension	Gain of function mutation. Response to amiloride
	GRA	CYP11B1 & CYP11B2	(Adrenal)	AD		Unequal crossing-over between genes. Hypo/normokalemia. Aldosterone synthase gain-of-function
	AME	11*β*HSD2	(Kidney, placenta)	AR		Low aldosterone. Response to spironolactone

* Families with mixed BS-Gitelman phenotypes were described.
AR: autosomal recessive; *AD*: autosomal dominant; *AME*: apparent mineralocorticoid excess; *BS*: Bartter syndrome; *CaSR*: Calcium sensing receptor; *CCD*: cortical collecting duct; *DCT*: distal convoluted tubule; *ENaC*: epithelial sodium channel; *GRA*: Glucorticoid –remediable aldosteronism; *NKCC2*: Na-K-2Cl cotransporter; *TAL*: thick ascending limb of Henle's loop; *TSC*: thiazide sensitive NaCl channel; *11βHSD*: 11 *β*-hydroxysteroid dehydrogenase.

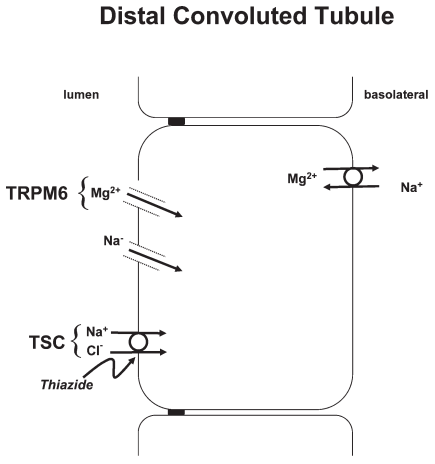

Figure 3. NaCl and Mg^{2+} luminal transport in the distal convoluted tubule. *TRPM6*: luminal magnesium channel; *TSC*: thiazide sensitive channel.

carry mutations in the TSC [20], therefore serving as an example of genetic homogeneity. This protein shows its most intense expression at the DCT (Fig. 3). Interestingly, patients taking thiazide diuretics on a chronic basis may develop hypokalemic alkalosis in association with hypocalciuria. The mechanism that leads to hypomagnesemia is being unraveled. Interesting analogies have been recently found between TRPM6, the gene causing familial hypomagnesemia with secondary hypocalcemia and Gitelman syndrome. Mutations in TRPM6 (a member of the transient receptor potential family of canonical channels) cause hypomagnesemic-hypocalcemic tetany early in life and hypocalciuria [21]. TRPM6 specifically localizes in the kidney tissue to the DCT lumen [22] and has been recently shown to be a tightly regulated magnesium apical channel in this tubular area [23]. In addition, the recent development of a knockout mouse model of Gitelman syndrome is accompanied by downregulation of TRPM6 [24], finally establishing evidence for an interplay between these two ion channels.

Recent data have suggested that the genotype–phenotype correlation is not so clear and that phenotypic overlap may occur between classical BS and Gitelman syndrome or the antenatal BS. Jeck *et al*. [25] described three patients with three different *CLCNKB* mutations whose clinical course was characterized by gradual transition from classic BS to Gitelman syndrome phenotype. A more recent study from Northen Israel also demonstrated such intrafamilial heterogeneity [26].

BS and calcium sensing receptor mutations

Recently, a fifth variant of BS, specifically associated with hypoparathyroidism, has been described, and found to be due to gain of function mutations in the calcium sensing receptor (CaSR) [27] located both at the parathyroid gland and at the renal tubular basolateral membrane. Activation of this receptor by hypercalcemia or such gain of function mutation initiates a series of intracellular events that inhibit the action of ROMK, thus leading again to inactivation of NKCC2, resulting in hypokalemic hypochloremic metabolic alkalosis. Hypomagnesemia and hypercalciuria are common in this variant. Urine calcium loss during hypocalcemia is an important laboratory sign in the differentiation of different forms of hypoparathyroidism, since the other variants of hypoparathyroidism are associated with low urine calcium excretion [28].

Neonatal BS and transient hyperkalemia

Hypokalemic alkalosis and not hyperkalemia are the common complications of BS. We have recently described a group of infants with the antenatal variant of BS, who developed hyperkalemia and hyponatremia, appearing usually at day 3 of life and normalizing by the end of the first postnatal week. All infants had mutations in exon 5 of the renal K channel ROMK. Later in life, these ROMK-defective BS children had failure-to-thrive, hypercalciuria, nephrocalcinosis and no, or minimal, hypokalemia [29].

Loss of function in ROMK channel activity at the TAL level leads to the inactivation of NKCC2, followed by reduced NaCl absorption in this nephron segment. However, ROMK has also an important role in K regulation in the CCD, in addition to its function at the TAL. In BS there is usually secondary hyperaldosteronism leading to hypokalemia. The normal K levels along childhood observed in this BS cohort may be additional evidence for defective K secretion by aldosterone action in the CCD.

During the first 72 h of postnatal life, premature neonates have a higher baseline plasma K^+ level [30]. This phenomenon (also known as nonoliguric hyperkalemia) is attributed to gestational-age-related decreased Na^+-K^+-ATPase activity, resulting in shifting of K^+ from the intracellular to the extracellular compartment [31]. This hyperkalemia is transient, due to the gradual postnatal maturation of the Na-K-ATPase activity in all body cells [32]. In the setting of premature birth seen in antenatal BS, the additional net effect of ROMK dysfunction during early postnatal life (when baseline plasma K level are increased) may be severe hyperkalemia that can resolve later, as other mechanisms reduce the plasma K^+ level.

In the human kidney, differential splicing produces five distinct, tubule-segment-specific transcripts of the ROMK gene (ROMK1, CCD, ROMK2 and –3, and TAL). Exon 5 is common to all of these isoforms and encodes the majority of the channel protein [33]. In our patients, the mutations that were found involved exon 5, again affecting all ROMK isoforms.

Treatment of the different forms of BS includes NaCl and K supplementation as well as prostaglandin synthetase

inhibitors. These measures are not always sufficient. In such cases, inhibition of the secondary hyperaldosteronism by aldosterone antagonists may be efficacious [34].

Pseudohypoaldosteronism

PHA type I is associated with a decreased response to aldosterone effects, leading to hyperkalemia and metabolic acidosis [35] (contrary to BS where appropriate tubular response to secondary hyperaldosteronism leads to hypokalemia and alkalosis). Such decreased response can be due to either mineralocorticoid receptor mutations (causing the milder and autosomal dominant variant of PHA in some affected families [36]) or to mutations in the main downstream protein involved in aldosterone signaling, the ENaC (Fig. 2). ENaC loss of function mutations cause the autosomal recessive variant of type I PHA, which is the more severe form of this disease, and which appears early in life and affects aldosterone action in many organs, including the sweat glands, the respiratory tract and the kidney. Hyperkalemia has been described for type I PHA [37]. However, contrary to the previous description on ROMK-defective BS, in type I PHA this tendency persists after birth (up to the need of chronic use for K^+-binding resins) and is always associated with metabolic acidosis.

Hypertension and K-related tubulopathies

All mentioned tubulopathies are normotensive by definition, due to the primary salt losing defect. The detection of hypertension with hypo- or hyperkalemia should raise the possibility of totally different tubulopathies, after the exclusion of primary mineralocorticoid excess, due to either primary aldosteronism, glucocorticoid-remediable aldosteronism (GRA) and apparent mineralocorticoid excess (AME), which will not be extensively discussed in this review (Tables 1, 2). The effects of aldosterone and cortisol through the mineralocorticoid receptor (MR) at the CCD results in increased transcription of subunits of the ENaC and the basolateral Na^+-K^+-ATPase pump. Cortisol and aldosterone have equal affinity for the intracellular MR. However, in aldosterone-sensitive tissues such as the kidney, the enzyme 11 β-hydroxysteroid dehydrogenase (11 β-HSD) converts cortisol to cortisone. Since cortisone has a low affinity for the MR, the enzyme 11 β-HSD serves to protect the kidney from the effects of glucocorticoids. In hereditary or acquired AME, 11 β-HSD is defective. Cortisol, which is present at concentrations approximately 1000-fold that of aldosterone, becomes then a mineralocorticoid (Fig. 2).

In the principal cells of the CCD, apical Na^+ channels (ENaC) play a key role in K^+ secretion by increasing the intracellular Na^+ available to Na^+-K^+-ATPase pumps and by creating a favorable electrical potential for K^+ secretion through a ROMK isoform. Liddle syndrome is caused by gain-of-function mutations in the ENaC [38], the same gene that causes autosomal recessive type I PHA when its function is lost. A state of 'pseudohyperaldosteronism' is the result of such hyperfunction of ENaC, leading to volume expansion and hypertension on one hand (actually suppressing renin and aldosterone secretion), but also to secondary activation of ROMK and thus increased K excretion at the CCD, resulting in hypokalemia. These patients respond well to the administration of the diuretic amiloride, a specific ENaC inhibitor.

Gordon syndrome (familial hyperkalemic hypertension or pseudohypoaldosteronism type 2; OMIM no. 145260) is an autosomal dominant disease characterized by hypertension, hyperkalemia and normal glomerular filtration rate [39]. It may be due to mutations in the WNK4 gene, encoding a serine-threonine kinase located at the DCT, causing a gain of function of TSC, leading to expansion of extracellular fluid, secondary suppression of plasma renin activity, hypoaldosteronism and hyperkalemia [40]. This unique form of hypertension responds easily to the administration of thiazide diuretics, which inhibit the TSC function. However, there is a genetic heterogeneity

Table 2. Hyperkalemic-related tubulopathies.

	Phenotype	Mutated gene	Tubular cell involved	Heredity	Special features
Normotensive	PHA type I	ENaC	CCD	AR	Loss-of-function mutation. Severe phenotype, multiorgan involvement
		Mineralocorticoid Receptor	CCD	AD	Mild/ transient phenotype, renal only
Hypertensive	Gordon syndrome (PHA type II)	WNK4 WNK1	DCT	AD	Low renin, normal aldosterone. Causes TSC gain-of-function

AR: autosomal recessive; *AD*: autosomal dominant; *CCD*: cortical collecting duct; *ENaC*: epithelial sodium channel; *PHA*: pseudohypoaldosteronism; *TSC*: thiazide-sensitive NaCl channel.

for the familial hyperkalemic hypertension syndromes [41], nowadays indicating the involvement of at least four distinct genes (Table 2).

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